Mechanisms in Group 9 Metal Catalyzed Asymmetric Olefin Hydrogenation

Tropical Seminar 12/7/2021
Outline

**Rhodium-Catalyzed Asymmetric Hydrogenation:**
- Brief history
- Mechanistic proposals: Saturated vs. Unsaturated Pathways
- Unsaturated pathways: Brown, Halpern, Landis
- Saturated pathways: Gridnev and Imamoto
- Overall picture and source of enantioselectivity

**Iridium-Catalyzed Asymmetric Hydrogenation:**
- Brief history
- Mechanistic proposals
- Mechanistic findings

**Cobalt-Catalyzed Asymmetric Hydrogenation:**
- Brief history
- Neutral catalysts: precatalysts, speciation, substrates, mechanisms
- Cations: precatalysts, speciation, substrates, mechanisms
Rhodium Catalyzed Asymmetric Hydrogenation

**Brief Overview:**

*Knowles and Horner, 1968:*

\[
\begin{align*}
\text{R} = \text{Et} & \quad 8\% \text{ ee} \\
\text{R} = \text{CO}_2 \text{H} & \quad 15\% \text{ ee}
\end{align*}
\]

*Knowles and Horner, 1975:*

\[
\begin{align*}
\text{CO}_2 \text{H} + \text{H}_2 & \quad \text{[Rh}((\text{R},\text{R})\text{-DIPAMP})(\text{COD})]\text{BF}_4 \\
\text{S/C} > 10000 & \quad 98\% \\
\text{H}_3\text{O}^+ & \quad \text{96}\% \text{ ee (100}\% \text{ ee after recrystallization)}
\end{align*}
\]

**General Scope:**

alpha- and beta-dehydroamino acid derivatives and enamides

itaconic acids

enol esters

ethenephosphonates


Mechanistic Proposals: Saturated and Unsaturated Pathways

Does $P_2Rh(S)_2$ react first with hydrogen or substrate?
Unsaturated Anti-“Lock-and-Key” Catalytic Cycle

Landis and Halpern 1987:

Unsaturated Anti-“Lock-and-Key” Catalytic Cycle

Landis and Halpern 1987:

Evidence for Unsaturated Pathways

Halpern 1977:

Solvento complexes, rather than hydrides, form when precatalysts are reacted with hydrogen in the absence of substrate.

Rapid reaction of unsaturated substrates with $\text{P}_2\text{Rh(MeOH)}_2^+$ leads to formation of stable $\text{P}_2\text{Rh(substrate)}^+$ complexes.

Formation of substrate complexes but not hydrides supports an unsaturated pathway.

Pathway starts from solvento complexes.

Unsaturated Anti-“Lock-and-Key” Catalytic Cycle

Landis and Halpern 1987:

Evidence for Unsaturated Pathways

Halpern 1979:

- [(dppe)Rh(MAC)][BF₄]⁻

  - Demonstrates two-point binding through C=C and amide carbonyl

First crystal structure of a bis(phosphine)Rh(enamide)⁺ complex

Evidence for Unsaturated Pathways

Halpern 1980:

- [(ChiraPhos)Rh(EAC)][BF₄]

- Isolated diastereomer (pro-(R)) is opposite of product stereochemistry (S)

- Substrate exchange with free EAC was rapid (found by $^{31}$P NMR line broadening)

First crystal structure of a chiral bis(phosphine)Rh(enamide)$^+$ complex

Evidence for Unsaturated Pathways

Halpern 1981:

- [(ChiraPhos)Rh(EAC)][BF₄]

- Solution CD matches solid state CD of isolated pro-(R) crystals

- Suggests that pro-(R) really is major diastereomer in solution, despite (S) product

Major diastereomer in solution corresponds to minor product

Evidence for Unsaturated Pathways

Heller 2005:

- [(DIPAMP)Rh(ename)][BF₄] (ename = L-DOPA precursor)

- Added crystals of known hand to NMR tube at low temperature to prevent interconversion and took ³¹P NMR

- Suggests that pro-(R) really is major diastereomer in solution, despite (S) product

Major diastereomer in solution corresponds to minor product

Evidence for Unsaturated Pathways

Brown 1980:

- Synthesized a variety of Rh-enamide$^+$ diastereomers with different substrates
- Studied ratio of diastereomers by $^{31}$P NMR
- Found no correlation between diastereomer ratio and product ee

**Ratio of diastereomers is not the source of eventual chirality**

Evidence for Unsaturated Pathways

Halpern 1990:

- [(DIPAMP)Rh(MPAA)][BF₄]

- Isolated diastereomer is opposite that of hydrogenation product

- Consistent major-minor concept

Anti-“Lock-and-Key” binding occurs for a variety of ligands and enamides

Evidence for Unsaturated Pathways

Brown 1993:

\[ ([\text{MeDuPhos})\text{Rh(enamide)}][\text{BF}_4] \]

- Follows major-minor concept
- DuPhos catalysts have faster reaction rates because they have lower enamide binding constants

Anti-“Lock-and-Key” binding occurs for a variety of ligands and enamides

Evidence for Unsaturated Pathways

Von Philipsborn 1993:

- [(ChiraPhos)Rh(MAC)][BF$_4$] studied by ($^{31}$P,$^{31}$P) EXSY NMR

- Both intramolecular and intermolecular interconversion occurs in all solvents

- Intermolecular exchange favored in MeOH and acetone, but intramolecular exchange is favored in DCM

Solvent participation in diastereomer interconversion mechanism

Evidence for Unsaturated Pathways

Brown 1995:

- \([\text{[(2-methoxyphenyl)-P-phenyl-P-(2'-diphenylphosphino)ethylphosphine}} \)Rh(MAC)][BF₄] studied by \(^{13}\text{C}\) and \(^{31}\text{P}\) EXSY NMR in MeOH

- Intramolecular exchange is found to be dominant

- Intramolecular mechanism dissociates and returns the C=C bond

Intramolecular conversion also occurs

Evidence for Unsaturated Pathways

Landis and Halpern 1987:

- $[(\text{DIPAMP})\text{Rh(MAC)}][\text{BF}_4]$  

- Both diastereomers observable by $^{31}\text{P}$ NMR  

- Looked at Rh-enamide diastereomer ratios at different temperatures to get an equilibrium constant  

- Titrated enamide into $[(\text{DIPAMP})\text{Rh(S)}_2][\text{BF}_4]$ and monitored by UV/vis to see total binding equilibrium constant  

- Measured MAC binding and dissociation rates by trapping with toluene in MeOH (dissociative mechanism)

Placed quantitative values of major-minor diastereomer interconversion

Evidence for Unsaturated Pathways

Heller 2005:

- [(DIPAMP)Rh(enamide)][BF₄] (enamide = 4 different beta-acylaminoacylates)
- Isolated crystal structures of catalyst substrate diastereomers
- Found that the major diastereomer in solution corresponded to the major hydrogenation product (Lock-and-Key), but that enantioselectivity was still a result of subsequent reaction steps (not diastereomer ratio)

<table>
<thead>
<tr>
<th>R</th>
<th>[Major]/[minor] ratio (T)</th>
<th>S Sel. [% ee] (e.r.)</th>
<th>kₘₐᵢ/kₘᵲ$_{ₘᵢₙ}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 C₆H₅</td>
<td>90:10 (RT) 96:4 (−87°C)</td>
<td>50 (3.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>2 p-ClC₆H₄</td>
<td>88:12 (RT) 93:7 (−87°C)</td>
<td>38 (2.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>3 m-NO₂C₆H₄</td>
<td>81:19 (RT) 86:14 (−84°C)</td>
<td>20 (1.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>4 p-MeC₆H₄</td>
<td>91:9 (RT)</td>
<td>60 (4.0)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Major diastereomer in solution corresponds to major product
Unsaturated Anti-“Lock-and-Key” Catalytic Cycle

Landis and Halpern 1987:

\[\text{Rh}^+\text{MeO}_2\text{C} = \text{NH}^+ + \text{H}_2\]

\[\text{pro-}(R)\]

RDS & EDS

k\text{major} = 1.1 M^{-1} \cdot s^{-1}

k\text{minor} = 0.15 s^{-1}

\[\text{MeO}_2\text{C} = \text{NH}^+ \quad \text{Ph} \quad \text{O} \quad \text{Rh} \quad \text{P} \quad \text{P}^* \quad \text{MeO}_2\text{C} = \text{NH}^+ \quad \text{Ph} \quad \text{O} \quad \text{Rh} \quad \text{P} \quad \text{P}^* \]

“Major” manifold

k\text{minor} = 3.2 s^{-1}

k\text{minor} = 5300 M^{-1} \cdot s^{-1}

5300 M^{-1} \cdot s^{-1}

10600 M^{-1} \cdot s^{-1}

k\text{major}

k\text{minor}

2 MeOH

- 2 MeOH

pro-\((S)\)

RDS & EDS

k\text{minor}

“Minor” manifold

k\text{minor} = 1.4

RDS & EDS

+ H2

\[\text{MeO}_2\text{C} = \text{NH}^+ \quad \text{Ph} \quad \text{O} \quad \text{Rh} \quad \text{P} \quad \text{P}^* \quad \text{MeO}_2\text{C} = \text{NH}^+ \quad \text{Ph} \quad \text{O} \quad \text{Rh} \quad \text{P} \quad \text{P}^* \]

(R)-IntA

(R)-IntB

(S)-IntA

(S)-IntB

Evidence for Unsaturated Pathways

Halpern 1980:

- Passed H₂ through MeOH solution of [(dppe)Rh(MAC)][BF₄] at -78 °C
- Monohydride alkyl, rather than dihydride alkene, is observed
- High rate of migratory insertion step

Suggests that putative dihydride alkene complex is very reactive

Evidence for Unsaturated Pathways

**Bargon 1997:**

![Chemical structure and NMR spectra](image)

- Parahydrogen-induced polarization-NMR method
- First observation of a chiral \((P_2)Rh(H)_2(alkene)\) complex
- Observed during the course of catalysis at -15 °C

**Rare observation of dihydride alkene complex**

Evidence for Unsaturated Pathways

Halpern 1980:

Resting state is wrong \([(\text{ChiraPhos})\text{Rh}(EAC)]^+\) diastereomer

Kinetics show rate law = \(k_{\text{oxidative\,addition}}[\text{H}_2][(\text{ChiraPhos})\text{Rh}(EAC)]^+\)

Minor diastereomer is sufficiently more reactive towards \(\text{H}_2\) that it dominates the enantioselectivity of the reaction

Predict that at high \(\text{H}_2\) pressures, \(ee\) should be diminished and eventually reversed

Oxidative addition of \(\text{H}_2\) is the rate determining step

Evidence for Unsaturated Pathways

Landis and Halpern 1987:

\[
\text{CO}_2\text{Me} + \text{H}_2 \rightarrow [(\text{DIPAMPs})\text{Rh(MAC)}][\text{BF}_4]\]

Low \(\text{H}_2\) pressure:

\[
\frac{\text{d}[R\text{-product}]}{\text{dt}} = \frac{k_{2}\text{maj}K_{1}\text{maj}[H_2][\text{Rh}]_{\text{tot}}}{K_{1}\text{maj} + K_{1}\text{min}} (17)
\]

\[
\frac{\text{d}[S\text{-product}]}{\text{dt}} = \frac{k_{2}\text{min}K_{1}\text{min}[H_2][\text{Rh}]_{\text{tot}}}{K_{1}\text{maj} + K_{1}\text{min}} (18)
\]

Intermediate \(\text{H}_2\) pressure:

\[
\frac{\text{d}[R\text{-product}]}{\text{dt}} = \frac{k_{2}\text{maj}[\text{Rh}]_{\text{tot}}[H_2]}{K_{1}\text{maj}(k_{-1}\text{min} + k_{2}\text{min}[H_2])} (23)
\]

\[
\frac{\text{d}[S\text{-product}]}{\text{dt}} = \frac{k_{1}\text{min}k_{2}\text{min}[H_2]}{k_{1}\text{maj}k_{-1}\text{min}} + \frac{k_{1}\text{maj}}{k_{1}\text{min}} (25)
\]

High \(\text{H}_2\) pressure:

\[
\text{rate} = -\frac{\text{d}[H_2]}{\text{dt}} = k_{1}\text{maj}[\text{Rh}]_{\text{tot}}[\text{mac}]+k_{1}\text{min}[\text{Rh}]_{\text{tot}}[\text{mac}] (21)
\]

\[
\frac{[S\text{-phenylalanine}]}{[R\text{-phenylalanine}]} = \frac{k_{1}\text{min}}{k_{1}\text{maj}} (22)
\]

Oxidative addition rate modulated by \(\text{H}_2\) pressure
Unsaturated Anti-“Lock-and-Key” Catalytic Cycle

Evidence for Unsaturated Pathways

Brown 1982:

![Chemical structure](image)

\[
\text{Ph} = \quad \text{NHCOMe} \\
\text{H}_2/\text{D}_2 \text{KIE} = 1.23 \text{ for } (Z)-\text{acetamidocinnamic acid}
\]

- Preferential deuterium incorporation in the alpha position
- Suggests "irreversible hydride step"

**Table IV. Rhodium Complex Catalyzed Additions of Hydrogen Deuteride**

<table>
<thead>
<tr>
<th>phosphine</th>
<th>substrate</th>
<th>analytical method</th>
<th>selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>diphos</td>
<td>oct-1-ene</td>
<td>(^1\text{H NMR (0.71 vs. 1.12 ppm)})</td>
<td>1.03:1(^c)</td>
</tr>
<tr>
<td>diop</td>
<td>oct-1-ene</td>
<td>(^1\text{H NMR})</td>
<td>1.00:1</td>
</tr>
<tr>
<td>diop</td>
<td>styrene</td>
<td>(^2\text{H NMR (1.20 vs. 2.35 ppm)})</td>
<td>1.01:1</td>
</tr>
<tr>
<td>diop</td>
<td>vinylacetamide</td>
<td>(^2\text{H NMR (1.11 vs. 3.21 ppm)})</td>
<td>1.02:1</td>
</tr>
<tr>
<td>diphos</td>
<td>(Z)-PhCH=\text{C(}\text{CO}_2\text{H}) \text{ NHAc}</td>
<td>(^1\text{H NMR})</td>
<td>1.37:1</td>
</tr>
<tr>
<td>diop</td>
<td>(Z)-PhCH=\text{C(}\text{CO}_2\text{H}) \text{ NHAc}</td>
<td>(^1\text{H NMR})</td>
<td>1.36:1</td>
</tr>
<tr>
<td>dipamp</td>
<td>(Z)-PhCH=\text{C(}\text{CO}_2\text{H}) \text{ NHAc}</td>
<td>(^1\text{H NMR})</td>
<td>1.33:1</td>
</tr>
</tbody>
</table>

**Directional specificity for migratory insertion**

Evidence for Unsaturated Pathways

**Landis 1998:**

\[ \text{CO}_2\text{Me} \]
\[ \text{NHCOMe} \] 

\[ \text{Ph} \]
\[ \text{CO}_2\text{Me} \]
\[ \text{NHCOMe} \]

\[ \text{[Rh(DIPHOS)NBD][BF}_4\text{]} \]

**HD (1 atm), THF, 25 °C**

\[ \text{HCO}_2\text{Me} \]
\[ \text{DCOMe} \]
\[ \text{NHCOMe} \]

\[ \text{1.33 : 1.00} \]

\[ \text{HCO}_2\text{Me} \]
\[ \text{DCOMe} \]
\[ \text{NHCOMe} \]

\[ \text{Ph} \]
\[ \text{HCO}_2\text{Me} \]
\[ \text{DCOMe} \]
\[ \text{NHCOMe} \]

\[ \text{1.21 : 1.00} \]

- $H_2/D_2$ KIE = 1.04 for MAA
- Preferential deuterium incorporation in the alpha position
- Larger HD partitioning ratio than KIE suggests control by two different transition states
- Lack of H/D scrambling with $D_2$ hydrogenation suggests irreversible insertion
- Irreversible oxidative addition and irreversible migratory insertion

**Irreversible oxidative addition and irreversible migratory insertion**

Evidence for Unsaturated Pathways

Landis 2000:

- Only A pathways are kinetically active
- Major diastereomer is more stable because alpha-carbon lies closest to the coordination plane
- Reaction of $H_2$ with minor is favored because MAJ would have disfavored motion of nitrile group across hindered quadrant

Computational confirmation

Unsaturated Anti-“Lock-and-Key” Catalytic Cycle


Landis and Halpern 1987:

RDS & EDS

k₂²minor
1.1 M⁻¹ • s⁻¹

k₁²minor
0.15 s⁻¹

k₂¹major
1.1 M⁻¹ • s⁻¹

k₁¹major
5.6 (0.8)

“Major” manifold

pro-(R)

k₂¹minor
3.2 s⁻¹

pro-(S)

5300 M⁻¹ • s⁻¹

10600 M⁻¹ • s⁻¹

“Minor” manifold

- 2 MeOH

k₁²minor
0.15 s⁻¹

k-1²minor
3.2 s⁻¹

RDS & EDS

Gridnev and Imamoto 2000:
Saturated “Dihydride” Catalytic Cycle

Gridnev and Imamoto 2000:

Evidence for Saturated Pathways

Gridnev and Imamoto 2000:

Addition of \( \text{H}_2 \) to \([(\text{BisP}^*)\text{Rh(S)}_2]^+\) at -90 °C reversibly generates two diastereomeric dihydride complexes

Addition of HD demonstrates a 1.3:1 preference deuterium in the axial position

Observed by NMR

\[
(\text{[10a}^d1 + \text{10b}^d1]) : (\text{10a}^d2 + \text{10b}^d2) = 1.3 : 1
\]

\(\text{Observed dihydride complex at low temperature}\)

Evidence for Saturated Pathways

Gridnev and Imamoto 2001:

- Monomeric dihydride complexes form at low temperatures
- Warming to room temperature generates a stable bridging tetrahydride dimer
- Observed by NMR

Dihydride complex persists at room temperature

Evidence for Saturated Pathways

Gridnev and Imamoto 2001:

- MiniPhos ligand maintains bis(ligand) even under H_2 pressure

- Cis-dihydride formed at -90°C, isomerizes to trans-dihydride at 0 °C

- Observed by NMR

Dihydride complexes can be formed with multiple ligands

Evidence for Saturated Pathways

Gridnev and Imamoto 2006:

- Tethered BisP* complex forms at -70 °C (stable up to 0 °C when it loses H₂)
- Four possible diastereomers can form
- Observed by NMR

Dihydride complexes can be formed with multiple ligands

Saturated “Dihydride” Catalytic Cycle

Gridnev and Imamoto 2000:

Evidence for Saturated Pathways

Gridnev and Imamoto 2001:

- Reaction of dihydride complex with MAC at low temperature gives observable monohydride alkyls, which are stable to 0 °C.
- Four monohydride alkyl diastereomers are observable by NMR —> three lead to (R) and one leads to (S).
- Dihydride substrate complexes are not observed due to very low barriers for migratory insertion.
- Above 0 °C, reductive elimination generates hydrogenated products and dihydride complex.

Dihydride complex competent for enamide insertion

Evidence for Saturated Pathways

Gridnev and Imamoto 2000:

- Simulated saturated and unsaturated pathways at low temperature, faster rate and slightly higher ee for saturated pathway
- Simulated insertion replicates catalytic HD partitioning ratio

Simulation of saturated pathway supports role in catalysis

Evidence for Saturated Pathways

Gridnev and Imamoto 2006:

- MAC addition to tetrahydride tethered species gives observable dihydride substrate complex with dissociated C=C bond
- Insertion gives observable monohydride alkyl
- Excess MAC induces reductive elimination

Evidence for Saturated Pathways

Gridnev and Imamoto 2008:

- Computations show low-energy isomerization dihydride substrate complexes through C=C dissociation prior to migratory insertion
- Placement of chelate in less hindered quadrant of dihydride substrate complex is source of enantioselectivity
- Methanol assists double bond dissociation

Enantioselection in saturated pathway

Saturated “Dihydridc” Catalytic Cycle

Gridnev and Imamoto 2000:

Consolidating Saturated and Unsaturated Pathways

Gridnev and Imamoto 2004:

Consolidating Saturated and Unsaturated Pathways

Gridnev and Imamoto 2009:

Chelate coordination is kinetically hindered and does not occur

Fast interconversion via pseudo-rotation

IRREVERSIBLE STEP
Fixes the results of enantioselection

ENANTIOSELECTIVE STAGE
Chelate coordination takes place in the less-hindered quadrant

Consolidating Saturated and Unsaturated Pathways

**Gridnev and Imamoto 2009:**

- Bulky substituents on the phosphorus atoms in the top-left and bottom-right quadrants give \( R \)-hydrogenation products and vice versa.

**New quadrant model consolidates all known examples**

Consolidating Saturated and Unsaturated Pathways

Imamoto 2003:

Old empirical rule for backbone chirality:

\[
\begin{array}{cc}
\text{δ-conformer} & \text{λ-conformer} \\
\text{75a} & \text{75b}
\end{array}
\]

\[
\begin{array}{c}
(\text{R)}\text{-amino acids} \\
(\text{S)}\text{-amino acids}
\end{array}
\]

Old quadrant diagram for P-chirality:

New quadrant diagrams:

\[
\begin{array}{cc}
L & S \\
S & L
\end{array}
\]

L/S = group presenting the larger/smaller steric hindrance

Conclusions and Outlook

- Saturated mechanism does not have kinetic support, likely does not carry a large amount of the catalytic flux with any ligand at reasonably low hydrogen pressures.

- Simulation of both pathways suggests enantioselection at migratory insertion, not oxidative addition.

- No such thing as a “solved problem” in chemistry!!
**Iridium Catalyzed Asymmetric Hydrogenation**

**Brief Overview:**

**Crabtree 1977:**

\[
\text{IrN(o-Tol)_2POTBu}^+ \text{PF}_6^- \rightarrow \text{H}_2, \text{DCM}
\]

\[
\text{H}_2, \text{DCM, rt}
\]

- Unfunctionalized olefins
- Furans
- Alcohols
- Esters
- Carboxylic acids
- Phosphates

**Pfaltz 1998:**

\[
\text{(o-Tol)}_2\text{P}_2\text{IrN}^+ \text{BAR}_{4}^- \rightarrow \text{H}_2, \text{DCM}
\]

\[
\text{H}_2, \text{DCM, rt}
\]

- >99% conv., 98% ee

**General Scope:**


Mechanistic Proposals

Three Pathways Considered:

Path I: Insertion with oxidative addition Ir$^{III}$-Ir$^{V}$ catalytic cycle

Path II: Metathesis-insertion-type Ir$^{III}$-Ir$^{V}$ catalytic cycle

Path III: Insertion-reductive elimination Ir$^{I}$-Ir$^{III}$ catalytic cycle

Mainly explored computationally
**Experimental Results**

**Pfaltz 2007:**

- Characterized by NMR
- $\text{H}_2$ adds to the more sterically encumbered face of the starting complex
- Formation of an Ir-H bond *trans* to the N ligand is electronically favored
- Oxidative addition to iridium is rapid at low temperature, with migratory insertion being a slower step

"Dihydride route" could play a major role in Ir-catalyzed hydrogenation

Experimental Results

Dietker 2004:

- Using mass spectrometry to study reaction intermediates
- Hydrogen pressure is maintained in the capillary
- Addition of styrene and H\textsubscript{2} to [(PHOX)Ir(COD)][BAR\textsubscript{4}] generates 3 new peaks corresponding to: [(PHOX)Ir(styrene)(H\textsubscript{2})\textsubscript{2}]\textsuperscript{+}, [(PHOX)Ir(styrene)(H\textsubscript{2})]\textsuperscript{+} (species I-IV), and [(PHOX)Ir(styrene)]\textsuperscript{+} (species V)
- Preformed IV loses H\textsubscript{2} to form V, which reacts reversibly with H\textsubscript{2}
- It is very unclear to me why this suggests a I-III cycle!!!

Suggests Ir\textsuperscript{I}-Ir\textsuperscript{III} cycle (Path III)

Dietker, R.; Chen, P. Gas-phase reactions of the [(PHOX)Ir\textsubscript{L\textsubscript{2}}]\textsuperscript{+} ion olefin-hydrogenation catalyst support an Ir\textsuperscript{I}/Ir\textsuperscript{III} cycle. Angew. Chem. Int. Ed. 2004, 43, 5513–5516.
Experimental Results

Pfaltz 2014:

- [(C,N or P,N)Ir(H)(alkene)][BARF₄] complexes characterized by NMR
- Additional H₂ required to induce migratory insertion, suggesting an Ir<sup>III</sup>/Ir<sup>V</sup> cycle via an [Ir<sup>III</sup>(H)₂(alkene)(H₂)(L)]<sup>+</sup> intermediate
- Rapid equilibration of isomeric dihydride alkene intermediates with subsequent slow enantioselectivity-determining step
- Minor, less stable intermediate is converted to major product enantiomer

Suggests Ir<sup>III</sup>-Ir<sup>V</sup> cycle (Path I or II)

Experimental Results

Andersson 2003:

![Chemical reaction diagram]

- Kinetics show first order dependence on catalyst and \( \text{H}_2 \) pressure, zero order dependence on substrate

*Suggests \( \text{Ir}^{\text{III}}-\text{Ir}^{\text{V}} \) cycle (Path I)*

Zhou 2017:

SIPHOX and SpiroBAP ligands are used (PHOX ligands have tendency to form inactive trimeric aggregates under hydrogen atmosphere with carboxylic acids)

- Iridium dihydride disolvento species was prepared

- Addition of substrate generated a monohydride alkyl complex (different than Pfaltz because didn’t require additional H₂)

*Suggests Ir^{III}-Ir^{V} cycle (Path l)*

**Experimental Results**

**Zhou 2017:**

- Heating monohydride alkyl in absence of substrate generates bridging bimetallic tetrahydride substrate complex.

- Addition of D$_2$ to the monohydride alkyl generates product with 50% D incorporation into beta-position (suggests Ir(III/V)).

- Addition of H$_2$ to the monohydride alkyl generates a bridging dimeric tetrahydride product complex.

Suggests Ir$^{III}$-Ir$^{V}$ cycle (Path I)

**Experimental Results**

**Zhou 2017:**

Suggests $\text{Ir}^\text{III}$-$\text{Ir}^\text{V}$ cycle (Path I)

Supported by experiments and DFT

**Computational Results**

**Hopmann 2011:**

- PHOX ligand and *trans* and methyl *trans* stilbene as representative substrates

- Calculated all three pathways:
  - Mechanism A = Ir$^I$-Ir$^{III}$ cycle (Path III)
  - Mechanism B = Ir$^{III}$-Ir$^{V}$ with oxidative addition of H$_2$ (Path I)
  - Mechanism C = Ir$^{III}$-Ir$^{V}$ with insertion into coordinated H$_2$ (Path II)

- Found mechanism B to be the most feasible

**Suggests Ir$^{III}$-Ir$^{V}$ cycle (Path I)**


### Computational Results

**Hall 2004:**

- **Carbene-oxazole ligand**
- **Metathesis-insertion type Ir$^{III}$-Ir$^{V}$ catalytic cycle is favored (Path II)**

**Suggests Ir$^{III}$-Ir$^{V}$ cycle (Path II)**
Computational Results

Andersson 2003:

- PHOX ligand
- $\text{Ir}^{\text{III}}$-$\text{Ir}^{\text{V}}$ catalytic cycle facilitated by coordination of a second equivalent of dihydrogen ($\text{Ir}^{\text{I}}$-$\text{Ir}^{\text{III}}$ cycle ruled out)
- Rate-determining migratory insertion into Ir-H with simultaneous oxidative addition of bound dihydrogen

Suggests $\text{Ir}^{\text{III}}$-$\text{Ir}^{\text{V}}$ cycle (Path I)

Computational Results

Bohm 2016:

- Phosphine sulfoximine ligand and alpha,beta-unsaturated ketone substrate
- Coordination of carbonyl group facilitates all Ir$^{III}$ pathway (complex assisted metathesis)

**All Ir$^{III}$ Mechanism**
Experimental and computational results point to an Ir$^{\text{III}}$-Ir$^{\text{V}}$ cycle for most substrates for both C,N and P,N systems.

Most studies support path I, although some support path II in certain examples.

Pathway is dependent on ligand, as well as substrate.
Cobalt Catalyzed Asymmetric Hydrogenation

Brief Overview:

Friedfeld and Chirik 2013:

R<sub>1</sub> R<sub>2</sub> R<sub>3</sub> → R<sub>1</sub> R<sub>2</sub> R<sub>3</sub>

10 mol% (py)<sub>2</sub>Co(CH<sub>2</sub>SiMe<sub>3</sub>)<sub>2</sub>
10 mol% bisphosphine
THF, 500 psi H<sub>2</sub>, 23 °C, 20 h

P<sub>2</sub> = (S,S)<sub>2</sub>BPE
>99% conv., 95.3% ee (R)

P<sub>2</sub> = (S,S)<sub>2</sub>BPE
>99% conv., 92.7% ee (S)

P<sub>2</sub> = (R,R)<sub>2</sub>iPrDuPhos
>99% conv., 82.0% ee (R)

P<sub>2</sub> = SL-A109-2
83.1% conv., 93.8% ee (R)

Precatalysts in multiple oxidation states:

Precatalysts in multiple oxidation states:
**Mechanism**

*Key questions:*

- Does cobalt react with hydrogen or substrate first?
- Does cobalt redox cycling occur?
- What is the effect of changing oxidation states?
- How do various substrates change the mechanism?
- What is the source of enantioselectivity?

*Does cobalt act similarly to rhodium or iridium?*
Mechanistic Proposals: Neutral Cobalt with Carboxylic Acids

Chirik 2020:

- Low temp EPR freeze quench experiments show only biscarboxylate compounds
- $\text{P}_2\text{Co(OPiv)}_2$ complexes could hydrogenate carboxylic acids, but with poor ee, suggests different enantioinduction mechanism than for Co(0) precursors
- Deuterium labeling experiments show that hydrogen comes from gas (homolytic $\text{H}_2$ cleavage)
- Suggests dihydride mechanism

**Mechanistic Proposals: Neutral Cobalt with Carboxylic Acids**

**Zhang 2020:**

![Mechanistic diagram](image)

- Esters do not get hydrogenated
- Zn was not required
- Deuterium labeling showed that hydrogen comes from gas
- EPR experiments show that coordination of ligand and exchange between acac and substrate occur

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Mechanistic Proposals: Neutral Cobalt with Carboxylic Acids

Zhang 2021:

- Esters do not get hydrogenated
- Zn had no effect on asymmetric hydrogenation
- D$_2$ gave >98% deuterium incorporation (none from alcohol)
- Hydrogenation with H$_2$/D$_2$ gave some mono-deuterated product
- EPR of solids after hydrogenation reaction showed that a paramagnetic Co(II) species could be involved in the catalytic cycle
- DFT calculations of complete cycle

Mechanistic Proposals: Cationic Cobalt with Enynes

Zhang 2021:

- Rh can’t do this because of large atomic radius and strong electron transport capacity

- Using CoCl(PPh₃)₃ with QuinoxP* gave no product unless ZnCl₂ was added, in which case it nearly replicated results with CoCl₂

- Suggests cationic Co(I) species generated from reduction of Co(II) to Co(I) followed by the abstraction of the coordinated halide on Co(I) by the ZnCl₂ activator

- Deuterium-labeling gave exclusive 1,2-d₂ incorporated product

Mechanistic Proposals: Neutral Cobalt with Enamides

Chirik:

\[
\text{Co(0)-Sub-H}_2\text{-pro-(R)} \quad 12.3
\]

\[
\text{TS-H}_2\text{-pro-(R)} \quad 19.3
\]

\[
\text{Co(0)-Sub-H}_2\text{-pro-(R)} \quad 12.3
\]

\[
\text{TS-Hyd-pro-(R)} \quad 27.7
\]

\[
\text{Proton transfer (RE)}
\]

\[
\text{TS_Pr-pro-(R)} \quad 21.2
\]

\[
\text{(R)-pathway}
\]

\[
\text{Chelate-pro-(R)} \quad 4.1
\]

\[
\text{TS_Pr-pro-(S)} \quad 21.6
\]

\[
\text{(S)-pathway}
\]

Oxidative hydride transfer on beta-carbon.
Rate determining step

\[
\text{Proton transfer (RE)}
\]

\[
\text{TS-Hyd-pro-(S)} \quad 25.0
\]

\[
\text{Co(0)-Sub-H}_2\text{-pro-(S)} \quad 12.4
\]

\[
\text{TS-H}_2\text{-pro-(S)} \quad 19.5
\]

Unsaturated, Co(0/II) Redox-Cycling Pathway
Cobalt-Catalyzed Asymmetric Hydrogenation

Conclusions and Outlook

- Mechanism seems to be highly substrate and oxidation state dependent

- Cobalt redox cycling may occur, but is disfavored with certain substrates that can undergo formal X-H addition

- Cation mechanism still needs to be studied more carefully

- Surprisingly rhodium-like mechanism and stereoinduction for enamides

A lot more left to explore!