Advanced Synthesis and Catalysis — Hydrogenation and Hydrofunctionalization

Homogeneous vs. heterogeneous hydrogenation

Olefin hydrogenation is a thermodynamically favored process but the activation energy is high as the concerted addition of a hydrogen molecule to an olefin is a symmetrically forbidden reaction. However, transition metals can react with molecular hydrogen to generate metal hydrides that react with olefins without violating symmetry rules.

Hydrogenation can be catalyzed by either a homogenous or a heterogeneous metal catalyst. In classic hydrogenation reactions, metal hydride is the key species that reacts with olefin. Monohydrides and dihydrides have different reactivities. For example, HRh(PPh₃)₃(CO) is specific for terminal alkenes and promotes olefin isomerization. In contrast, H₂Rh(PPh₃)₂Cl has broader, predictable olefin selectivities and does not promote olefin isomerization under neutral conditions.

Homogenous catalyst is generally more reactive, selective for a single product, and easier to modify. However, catalyst poison is a more serious issue and it is more difficult to separate from the product. Therefore, most chemical processes use heterogeneous catalysts. Homogenous catalysts are used when the selectivity is critical and product-catalyst separation problems can be solved.

Heterogeneous catalysis occurs on catalyst surface. Substrate haptophilicity refers to the functional group affinity to catalyst surface in directed hydrogenation. Blocking or poisoning active sites reduces activity and increases selectivity. Metal cations, halides, sulfides, amines and phosphines are good poisons.

Mechanistically, hydrogenation occurs with syn addition, but olefin isomerization on the catalyst surface leads to apparent anti-addition products. Isomerization usually occurs with Pd but not Pt catalysts that bind to olefin irreversibly. Pt catalysts typically favor C=O over C=C reduction, especially when poisoned. Lindlar catalyst (Pd/CaCO₃/PbO) has deactivated surface that provides no over-reduction and cis/trans isomerization. The general order of reactivity is:

- Pt: C=O >> C=C > C-X > Ar
- Pd: C=C > C-X > C=O > Ar
- Ru: C=O > C=C > Ar > C-X

Heterogeneous asymmetric hydrogenation can be realized with PdCl₂ adsorbed on silk fibroin. Modification of Raney nickel with chiral acids allows for asymmetric reduction of imines and ketones. However, the enantioselectivity is usually moderate. In contrast, there are many highly effective homogeneous catalysts for asymmetric hydrogenation.
Metal hydrides

In classic hydrogenation, M-H is the active species that reacts with olefins. Hydrogen ligands on transition metals, acidic or hydridic, are always referred to as “hydrides”. The name of metal “hydrides” originates from the observation of upfield-shift of hydrogen ligands in $^1$H NMR. However, the shift arises from the shielding effect of the partially filled $d$ orbitals on the transition metal leading to mixing of low-lying electronic excited states into the ground state. The typical value for $\delta_{M-H}$ ranges from $-5$ to $-25$ ppm for $d^6$ to $d^9$ metal hydrides, but $>0$ ppm for $d^0$ and $d^{10}$ metal hydrides.

$$
\begin{align*}
\text{HMn(CO)}_5 & \quad d^6 \quad \delta -7.5 \quad pK_a 7.1 \\
\text{H}_2\text{Fe(CO)}_4 & \quad d^6 \quad pK_a 4.0 \\
\text{HCo(CO)}_4 & \quad d^6 \quad \delta -10.7 \quad pK_a \approx \text{HCl, HNO}_3 \\
\text{HCo(CO)}_3\text{P(OPh)}_3 & \quad d^8 \quad pK_a 5.0 \\
\text{HCo(CO)}_3\text{PPh}_3 & \quad d^8 \quad pK_a 7.0 \\
\text{H}_2\text{ZrCp}^*_2 & \quad d^0 \quad \delta 7.46 \\
\text{HCo(P-Tol)}_3 & \quad d^{10} \quad \delta 3.50
\end{align*}
$$

Both the thermodynamic and kinetic acidity decrease going down the column of periodic table, with Cr>Mo>W, Fe>Ru>Os, but Pd<Ni<Pt, and increase from left to right across a row of the periodic table, with Zr-H and Ti-H being the most hydridic. In terms of the kinetic acidity, M-H is more similar to C-H (carbon acid) and the deprotonation rate is significantly slower than that of O-H or N-H.

Although the $^1$H chemical shift of HCo(CO)$_4$ occurs at $\delta -10.7$ in NMR, this metal “hydride” is highly acidic. It is somewhat weaker than HBr and H$_2$SO$_4$ and approximately equal to HCl and HNO$_3$. The hydride ligand normally occupies a normal coordination site, and the M-H bond distance is the sum of the covalent radii of M and H. However, the hydride coordination site can be hard to find when the ligands are too big. For example, the phosphine ligands of complex HRh(PPh$_3$)$_4$ take the four corners of a tetrahedron.
Hydride can also exist as a bridged ligand by forming a three-center two-electron bond. Nearly all \(\mu_2\)-H-M structures adopt a non-linear geometry. As many as four bridging hydrides between two metals have been observed.

In addition to forming a \(\mu_2\)-H structure, the hydride can also bridge multiple metal atoms to give \(\mu_3\)-H, \(\mu_4\)-H, \(\mu_5\)-H and \(\mu_6\)-H structures.
Molecular hydrogen can also coordinate to metal centers through a $\sigma_{H-H} \rightarrow d_\pi$ orbital interaction. Backbonding of metal center to the ligand though a $d_\pi \rightarrow \sigma^*_{H-H}$ orbital interaction further weakens the H-H bond. Groups 6–9 metals tend to form the L-type M(H$_2$) complexes whereas the more electron-rich group 10–12 metals having strong backbonding favor oxidative addition to form the X-type M(H)$_2$ complexes.

Elongation of the H-H distance upon coordination of H$_2$ to a metal indicates a weakening of the H-H bond. The energy barrier for moving the H-H distance from 1.00 Å to 1.60 Å, is only about 4 kcal/mol, readily tunable by ligands.

The dissociation energy for M-H is generally 60 kcal/mol, regardless of the nature of the metal or ligands. However, the dissociation energy of Os-H is greater than 78 kcal/mol. The interaction energy of Fe(\(\mu\)-H)Fe is 81–85 kcal/mol. The stretching vibration of M-H in IR occurs at 2200–1600 cm$^{-1}$ while that for bridging hydride occurs at 1600–800 cm$^{-1}$.

Metal hydrides can be generated from homolytic or heterolytic cleavage of H-H. Oxidative addition of hydrogen to metals gives metal hydrides with homolytic cleavage of H-H. Two-electron oxidative addition gives metal dihydrides while one-electron oxidative addition provides metal monohydrides. Hydrogenolysis of a M-M or M=$\equiv$M bond gives metal hydrides with one hydride per metal.
Because oxidative addition requires a vacant coordination site, coordinatively saturated complexes usually react slower than coordinatively unsaturated complexes.

\[
\text{IrCl(PPh}_3\text{)}_3 + \text{H}_2 \xrightarrow{1 \text{ atm} \atop 25 \text{ °C}} \text{H}_2\text{IrCl(PPh}_3\text{)}_3
\]

\[
\text{Os(CO)}_4(\text{PPh}_3) + \text{H}_2 \xrightarrow{80 \text{ atm} \atop 100 \text{ °C}} \text{H}_2\text{Os(CO)}_3(\text{PPh}_3)
\]

Reaction of Ir(cod)(PPh\textsubscript{3})\textsuperscript{+} with 8-methylquinoline gave a complex with an agostic C-H that non-dissociatively bound to Ir via a 2-electron 3-centre C-H-Ir bridge. For 7,8-benzoquinoline, the C-H bond is dissociatively bound to Ir giving a metal hydride. The water molecule of iridium complex H(H\textsubscript{2}O)Ir(bq)(PPh\textsubscript{3})\textsubscript{2}\textsuperscript{+} is readily replaced by a hydrogen molecule. Based on HD isotope labeling experiments, there is also an exchange of the hydrogen atom between the Ir-H and Ir(H\textsubscript{2}) ligands through a trihydride intermediate.

Heterolytic cleavage of H-H gives metal monohydrides without changing the oxidation state of the metals. Same with oxidative addition, the metal center needs to have an empty orbital for H\textsubscript{2}-binding. The only way that early transition metals with a σ\textsuperscript{0} configuration react with hydrogen is through hydrogenolysis. Lanthanides and actinides also favor hydrogenolysis.

The hydrogen ligand is acidified (ΔpK\textsubscript{a} up to 30 units) by the σ-binding of M-(H\textsubscript{2}). Metal hydrides can thus be produced by heterolytic cleavage of H-H through deprotonation with an external base. Protonation of the alkyl or halide ligand by the hydrogen ligand is referred to as hydrogenolysis. Conversely, protonation of a basic metal hydride, e.g., HRe(CO)\textsubscript{2}(PMe\textsubscript{2}Ph)\textsubscript{3} provides M-(H\textsubscript{2}) σ-complex (H\textsubscript{2})Re(CO)\textsubscript{2}(PMe\textsubscript{2}Ph)\textsubscript{3}\textsuperscript{+}.

Heterolytic cleavage of H-H is favored over homolytic cleavage in polar environments commonly used for electrochemical or enzymatic reactions. Hydrogenase enzymes use bifunctional interaction to facilitate the heterolysis of H-H.
The Wilkinson’s catalyst and Schrock–Osborn catalyst

Iguchi discovered in 1930s that catalytic hydrogenation can be achieved with RhCl$_3$, [Rh(NH$_3$)$_5$(H$_2$O)]Cl$_3$, or [Rh(NH$_3$)$_4$Cl$_2$]Cl. Vaska reported in 1963 the synthesis of HRh(CO)(PPh$_3$)$_3$ and Wilkinson studied in detail the activity of this monohydride. As a coordinatively saturated 18-electron complex, dissociation of a phosphine ligand is needed to generate the real catalyst. Because of the reversibility of the initial steps, internal olefins isomerize to terminal olefin without hydrogenation.

Wilkinson, Coffey, Vaska, and Bennett reported in 1965 the synthesis of the first practical hydrogenation catalyst Rh(PPh$_3$)$_3$Cl. Because of Wilkinson’s extensive work on its catalytic activity, this complex is commonly known as Wilkinson’s catalyst.

Unconjugated olefins and acetylenes can rapidly hydrogenated by Wilkinson’s catalyst in benzene. The use of a polar co-solvent facilitate the rate-limiting migratory insertion step. Hydrogenation of terminal acetylene is faster than terminal olefin due to better binding and easier insertion especially when carried out with trifluoroethanol as a co-solvent.

The reactivity of olefins negatively correlates with the steric hindrance for binding. However, ethylene and 1,3-butadiene react very slowly because the binding is too strong. Higher hydrogenation rate is observed for substrates bearing polar functional groups that facilitate binding. The reactivity of different types of olefin varies by more than 50 times, making selective hydrogenation of polyenes by Wilkinson’s catalyst possible.
The relative rate of hydrogenation for many substrates has been determined. Addition of a co-solvent can dramatically change the selective index, and pyridine, nitromethane, acetonitrile, and acetic acid significantly suppress the reaction.

Unlike HRh(CO)(PPh$_3$)$_3$, olefin isomerization is not often observed with the Wilkinson’s catalyst. The two hydrogen atoms are added in a syn fashion from the less hindered face.

Remarkably, olefin hydrogenation can be carried out without reducing aldehyde, ketone, carboxylic acid, ester, nitrile, and nitro groups. However, the selectivity is substrate- and solvent-sensitive.
Mechanistically, the reaction can proceed via the 16-electron complex Rh(PPh$_3$)$_2$Cl or the 14-electron Rh(PPh$_3$)$_2$Cl complex after dissociation of a phosphine ligand, but Rh(PPh$_3$)$_2$Cl is at least 10,000 times more reactive than Rh(PPh$_3$)$_3$Cl. In the absence of hydrogen, Rh(PPh$_3$)$_2$Cl forms a Cl-bridged dimer (PPh$_3$)$_2$Rh($\mu$-Cl)$_2$Rh(PPh$_3$)$_2$, which can be prevented by addition of a small amount of phosphine. The rate-limiting step is the migratory insertion. Same as the monohydride-catalyzed hydrogenation, the reaction goes through a Rh(I)/Rh(III) catalytic cycle.

The reactivity of the catalyst can be tuned by its ligand. Higher rate is observed with electron-rich phosphines. However, alkylphosphine ligands are too basic.

\[
\begin{align*}
\text{PET}_3 & \quad \text{PPhEt}_2 & \quad P(p\text{-Cl-Ph})_3 & \quad \text{PPPh}_3 & \quad P(p\text{-Me-Ph})_3 & \quad P(p\text{-MeO-Ph})_3 \\
\sim 0 & \quad \sim 0 & \quad 1.8 & \quad 41 & \quad 86 & \quad 100
\end{align*}
\]

The synthesis of cationic rhodium catalysts [Rh(diene)L$_n$]$^+$ (diene=nbd or cod; $n=2$ or $3$; L=PR$_3$, P(OR)$_3$, or AsR$_3$) was first reported by Osborn and others in 1969. Generally known as the Schrock–Osborn catalyst, [Rh(cod)(PPh$_3$)$_2$]PF$_6$ is much more reactive than the Wilkinson’s catalyst as the cationic metal center is more favored for olefin binding. The diene ligand is quickly hydrogenated upon exposure to hydrogen, giving a dihydride that is in equilibrium with the monohydride.

\[ [\text{Rh(diene)L}_n]^+ + 2\text{H}_2 \rightarrow \text{alkane} + [\text{RhL}_n\text{S}_2]^+ \]
\[ [\text{RhL}_n\text{S}_2]^+ + \text{H}_2 \rightleftharpoons [\text{RhH}_2\text{L}_n\text{S}_2]^+ \]
\[ [\text{RhH}_2\text{L}_n\text{S}_2]^+ + \text{H}^+ \rightarrow \text{RhHL}_n\text{S}_2 \]

The activity of monohydride and dihydride depends strongly on the nature of L. The dihydride is a good olefin hydrogenation catalyst and a poor olefin isomerization catalyst, whereas the monohydride is an excellent olefin hydrogenation and isomerization catalyst. Both the monohydride and dihydride are present under normal conditions, and selectively reduce alkynes to cis olefins at comparable rates. Addition of an acid favors the formation of dihydride and addition of a base favors monohydride.
Three different paths are operative for the Schrock–Osborn catalyst. The neutral monohydride species $\text{HRhL}_n$ in path A hydrogenates at least two times faster than the dihydride species $[\text{H}_2\text{RhL}_n]^+$ in path B, but it also isomerizes olefin. This undesired pathway can be suppressed by addition of an acid.

Under acidic conditions, path B that resembles the Wilkinson’s catalytic pathway is operative. Selective reduction of internal and terminal acetylenes to (cis) olefins can be achieved with electron-rich ligands such as $\text{PPhMe}_2$. For the reduction of ethyl phenylpropiolate, $[\text{Rh(dbn)}(\text{PPhMe}_2)_3]^+\text{PF}_6$ gives 96% yield of cis-ethyl cinnamate while Lindlar’s catalyst primarily the over-reduction product.

For strongly coordinating diene substrates, path C is operative and $[\text{Rh(diene)}L_2]^+$ predominates in solution when chelating phosphines or arsines were used as the stabilizing ligands. The complex reacts rapidly with hydrogen and catalyzes the selective 1,2- and 1,4-reduction of dienes to monoenes.

Directed hydrogenation can also be achieved with Wilkinson’s catalyst; however, the hydroxyl group needs to be deprotonated to generate an alkoxide that can displace the chloride ligand. In contrast, cationic rhodium complexes that readily accept an additional ligand are more effective for directed hydrogenation. In addition to the hydroxyl group, ether, ester, and amide are all effectively directing groups. The chelating bisphosphine dppb (DIPHOS-4) is a particularly successful ligand for this reaction.
Evans has summarized and rationalized the stereochemistry of directed hydrogenation as well as a variety of other directed transformations \((Chem. \ Rev. \ 1993, \ 93, \ 1307)\). Stereochemical models for allylic and homoallylic alcohol of cyclic systems involving an axial hydroxyl group have also been proposed.

For the acyclic allylic systems, the stereochemical outcomes can be predicted by minimizing the allylic interactions of the metal-substrate complex. However, olefin isomerization complicates the issue when low hydrogen pressure is applied.

\[
\begin{align*}
\text{Disubstituted alkene} & \quad 15 \quad 1 \times 2 \quad 25 \div 8 \div 67 \\
\text{Disubstituted alkene} & \quad 515 \quad 9 \div 1 \quad 100 \div 0 \div 0 \\
\text{Trisubstituted alkene} & \quad 15 \quad 1 \div 6 \quad 10 \div 10 \div 80 \\
\text{Trisubstituted alkene} & \quad 515 \quad 1 \div 9 \quad 0 \div 10 \div 90
\end{align*}
\]
Minimization of the A\textsuperscript{1,3} strains accounts for the stereochemical outcomes of acyclic trisubstituted homoallylic alcohols.

For 1,1-disubstituted olefins, the proposed stereochemical model involves minimization of syn-pentane or 1,3-diaxial interactions.
The Crabtree catalyst

The high metal-ligand bond strength of the third-row transition metals makes \( \text{Ir}(\text{PPh}_3)_3\text{Cl} \) an inactive hydrogenation catalyst. The olefin substrate cannot coordinate to the metal although \( \text{H}_2\text{Ir}(\text{PPh}_3)_3\text{Cl} \) can be formed. The cationic \([\text{Ir}(\text{cod})(\text{PPh}_3)_2]\text{PF}_6\) complex forms inactive precipitates in common hydrogenation solvents such as benzene, toluene, and hexane. Although \( \text{CHCl}_3 \), and to some extent, \( \text{CH}_2\text{Cl}_2 \), normally oxidize and deactivate low valent catalysts toward hydrogenation, Crabtree observed catalytic activities in chlorinated solvents \( \text{CHCl}_3 \), \( \text{C}_6\text{H}_5\text{Cl} \), and, best of all, \( \text{CH}_2\text{Cl}_2 \). Changing the ligands to \( \text{PPh}_2\text{Me} \) or \( \text{PCy}_3/\text{py} \) further improves the activity. The Crabtree catalyst \([\text{Ir}(\text{cod})(\text{py})(\text{PCy}_3)]\text{PF}_6\) is highly active and can catalyze hydrogenation of tetrasubstituted olefins presumably due to a less crowded metal center. However, this catalyst is sensitive to extraneous proton-bearing impurities, and tends to form an inactive trimeric heptahydride irreversibly at low alkene concentration.

The Crabtree catalyst is much more reactive than the Schrock–Osborn catalyst and generally has stronger directing effects. However, the cationic rhodium catalysts are used more often for hydrogenation of acyclic substrates.
**Asymmetric hydrogenation**

Knowles and Horner have demonstrated in 1968 that rhodium-catalyzed asymmetric hydrogenation can be achieved by using $P$-chiral phosphine ligand ($^n$Pr)P(Me)Ph despite low ee values. Later, Morrison found neomethyldiphenylphosphine (NMDPP) a significantly better chiral ligand, and Kagan introduced the $C_2$-symmetric chiral diphosphine ligand 2,3-0-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP).

Meanwhile, Knowles developed improved $P$-chiral ligands for the hydrogenation of $\alpha$-acylaminoacrylic acids.

Knowles at Monsanto established an industrial protocol for the synthesis of L-DOPA, a drug for Parkinson’s disease, using asymmetric hydrogenation in 1975. This is the first example of an industrial application of homogeneous asymmetric catalysis. He also demonstrated that for the hydrogenation of $\alpha$-acylaminoacrylic acids, the ($Z$)-isomer reacts much faster than the ($E$)-isomer and gives products with much higher ee values. Interestingly, the ($Z$)- and ($E$)-isomers give the same enantiomeric products.
A wide variety of chiral ligands has been developed since then. The most notable ones include 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl (BINAP), bis(phospholanyl)ethanes (BPE) and bis(phospholanyl)benzenes (DuPHOS). Some examples are given below.

Halpern and Brown have carefully studied the mechanism of Schrock–Osborn-type hydrogenation. Detailed kinetic studies revealed that complexation of methyl α-acetamidocinnamate (MAC) to Rh(DIPPHOS)⁺ is reversible. Oxidative addition of hydrogen is the rate-limiting (and ee-determining for chiral ligands) step at room temperature.
Surprisingly, for the asymmetric hydrogenation of MAC/EAC catalyzed by [Rh(DIPAMP)]^+, the major intermediate observed by NMR and isolated and characterized by X-ray analysis corresponds to the minor product. At ambient temperatures, the interconversion of the two isomeric Rh/olefin complexes occurs rapidly. Oxidative addition of hydrogen is irreversible, and the minor isomer reacts much faster than the major isomer. The kinetic behavior of this reaction can be explained by Curtin–Hammett principle. At low temperatures, the enantioselectivity is significantly reduced because the interconversion of the diastereomeric intermediates is slow. Increase of hydrogen pressure also leads to reduced ee values.

The mechanism of this “unsaturated pathway” is shown below.
The Noyori catalysts

The cationic Rh(I)/BINAP catalyst system introduced by Noyori in 1980 catalyzes the hydrogenation of α-(acylamino)acrylates to give amino acid derivatives with excellent optical purities. Because this catalyst system also operates under the Halpern–Brown mechanistic manifold, a careful choice of the reaction parameters to balance the stability and reactivity of the catalyst-olefin complex is needed for high enantioselectivity.

The atropoisomeric backbone of BINAP transmit the chiral information by gearing the phenyl rings to occupy two diagonal quadrants. The $^{31}$P-NMR spectrum of a 6:1 mixture of (R)-BINAP–Rh catalyst and (Z)-α-(benzamido)cinnamic acid in methanol showed a single signal for the Si-complex and the minor Re-complex was not detectable. Thermodynamically favored Si-intermediate is only weakly reactive.
Rhodium catalysts with electron-rich phosphine ligands such as DuPhos and BPE display very high enantioselectivity in the hydrogenation of many dehydroamino acids and enamides because the “dihydride pathway” is favored over the canonical “unsaturated pathway”.

The trichickenfootphos developed by researchers at Pfizer provides extremely high reactivity and selectivity for asymmetric hydrogenation. The methanol solvent coordinates to rhodium and dissociates olefin, promoting interconversion of the two pseudo-enantiomeric intermediates. Researchers at Merck found that hindered tetrasubstituted enamide are less prone to E/Z isomerization. Replacing the aryl nitrile group in the substrate with an amide group prevented catalyst deactivation.

<table>
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<tr>
<th>ligand</th>
<th>S/C</th>
<th>H₂</th>
<th>temp</th>
<th>time</th>
<th>ee</th>
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<tr>
<td>(R)-trichickenfootphos</td>
<td>27,000</td>
<td>50 psi</td>
<td>23 °C</td>
<td>40 h</td>
<td>98%</td>
</tr>
<tr>
<td>(R,R)-Me-DuPhos</td>
<td>2,700</td>
<td>45 psi</td>
<td>55 °C</td>
<td>4 h</td>
<td>97%</td>
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<tr>
<td>(R)-Trichickenfootphos</td>
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<tr>
<td>Josiphos SL-J505-1</td>
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</table>

H₂ (150 psi)
0.05 mol % [Rh(nbd)L]BF₄
L=Josiphos SL-J505-1
TFE, 40 °C, 17 h
90% yield, 99.7% ee
Noyori found a mechanistically different type of hydrogenation reaction in 1988 when replacing the metal center from rhodium to ruthenium. Ru(BINAP)(OAc)$_2$ catalyzed hydrogenation of MAC with high efficiency and selectivity; however, the sense of the asymmetric induction is opposite to that induced by [Rh(nbd)(BINAP)]ClO$_4$.

The Ru(II)/BINAP-catalyzed hydrogenation proceeds through a monohydride pathway. First, heterolytic cleavage of hydrogen by Ru(BINAP)(OAc)$_2$ gives HRu(BINAP)(OAc) that serves as the active catalyst. The rate-limiting and ee-determining step is the cleavage of Ru–C. The major diastereomeric intermediate is directly converted into the major product. The two hydrogen atoms incorporated into the substrate come from two different hydrogen molecules.

In the hydrogenation of enamides, the Ru–C bond is cleaved mainly by hydrogen. However, protonolysis by the methanol solvent or the carboxylic acid substrate can also be operative. The structure of the substrates and the hydrogen pressure significantly influence the sense and degree of the asymmetric induction because of multiple reaction pathways.

\[
\begin{align*}
\text{COOH} & \quad 84\% \ D \\
\text{COOH} & \quad 71\% \ H \\
\text{COOH} & \quad 68\% \ H \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Conversion</th>
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<tr>
<td>D$_2$ (4 atm) CH$_3$OH</td>
<td>95% H</td>
<td>106% D</td>
</tr>
<tr>
<td>H$_2$ (4 atm) CH$_3$OD</td>
<td>71% H</td>
<td>62% D</td>
</tr>
<tr>
<td>H$_2$ (100 atm) CH$_3$OD</td>
<td>84% D</td>
<td>68% H</td>
</tr>
</tbody>
</table>
Whereas ketone is usually inert to hydrogenation, Ojima reported in 1978 a synthesis of vitamin B complexes using an enantioselective reduction of a cyclic α-keto ester by a rhodium complex derived from [Rh(cod)Cl]₂ and (2S,4S)-N-tert-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphino-methyl-pyrrolidine ((S,S)-BPPM).

![Chemical structure](image)

Markó reported in 1979 the first rhodium-catalyzed asymmetric reduction of unfunctionalized ketones. A neutral rhodium complex prepared from [Rh(nbd)Cl]₂ and DIOP effectively catalyzes the reduction of aryl ketones in the presence of NEt₃.

Later, Zhang discovered that the catalyst prepared in situ from [Rh(cod)Cl]₂ and \( P,P^-1,2\)-phenylenebis(endo-2,5-dialkyl-7-phosphabicyclo-[2.2.1]heptanes (PennPhos) effectively reduced aryl and alkyl ketones.

![Chemical structure](image)

Noyori found in 1988 that replacing the acetate ligands of Ru(BINAP)(OAc)₂ to halides turns on the activity toward β-keto esters due to the protonation of the coordinated ketone group by the HCl generated in catalyst activation process.

![Chemical structure](image)
The Ru-BINAP complex catalyze the reduction of a wide variety of functionalized ketones with a coordinating group. The ability of this catalyst to reduce α-disubstituted-β-keto esters indicates that the reduction proceeds through the keto form. Reduction of β-diketones gives mostly (pseudo) C2-diols; reduction of α-diketones provides mainly meso products; and reduction of γ-ketoesters yields γ-lactones.

Researchers at Merck have found that [Ru(BINAP)Cl₂]₂•NET₃ effectively catalyzes the reduction of ketones in the presence of a small amount of HCl at lower temperature. Addition of NET₃ inhibits the reaction and addition of more HCl resumes the reaction.

A dynamic kinetic resolution of α-substituted β-keto esters can be achieved by in situ epimerization of the α-stereocenter in methylene chloride to give essentially a single diastereomeric product. The diastereoselectivity drops to nearly 1:1 when the reaction was carried out in methanol, although the ee values of the products remains the same.
Although Ru(II)-phosphine complexes are normally not very active as catalysts for hydrogenation of unfunctionalized ketones, addition of ethylenediamine and KOH leads to a more than 1,000-fold increase of turnover frequency of Ru(PPh$_3$)$_3$Cl$_2$ in 2-propanol. Without KOH, addition of ethylenediamine retards the reaction. The combined effects of ethylenediamine and KOH decelerate olefin hydrogenation and accelerate carbonyl hydrogenation, changing the selectivity profile by a factor of 375,000.

The use of ruthenium dichloride complexed with BINAP and a chiral 1,2-diamine allows for asymmetric hydrogenation of various ketones in isopropanol containing an alkaline base cocatalyst such as KOH, iPrOK, and tBuOK. The presence of an NH$_2$ moiety in the diamine ligand is crucial to high catalytic activity. The high reaction rate and carbonyl selectivity originate from an outer sphere hydrogenation mechanism. The hydridic RuH and protic NH react with ketone without the formation of a Ru-ketone complex in this non-classical metal-ligand bifunctional catalysis.
The outer sphere hydrogenation is highly selective for carbonyl reduction. Isolated and conjugated olefin, acetylene, halogen, trifluoromethyl, carboxylic ester, acetal, nitro group, amide, and amine can all be tolerated. This new catalyst system also allows for dynamic kinetic resolution of α-substituted ketones. Hydrogenation of racemic 2-isopropylcyclohexanone at 4 atm with a catalytic amount of Ru[(S)-BINAP]Cl₂•(dmf)ₙ, KOH, and 1,2-diphenylethylenediamine (DPEN) afforded quantitatively a 500:1 mixture of the cis and trans alcohols with 93% and 28% ee, respectively.

Later, Noyori developed a new, stable hydrogenation catalyst Ru[(S)-BINAP][(S)-DIAPEN]Cl₂. By avoiding the in situ generation of the metal-amine complex, this well-defined complex is a significantly better pre-catalyst, giving higher turnover number and rate.

Mikami found that the chiral BINAP ligand can be replaced by achiral 2,2'-bis(3,5-dimethylphenyl)phosphino-1,1'-biphenyl (DM-BIPHEP). This conformationally flexible ligand together with (S,S)-DPEN, gives a 3:1 diastereomeric mixture of ruthenium complex Ru(DM-BIPHEP) [(S,S)-DPEN]Cl₂. The major S/S,S complex is more reactive in the hydrogenation of aromatic ketones.

Ding found that the chiral induction is even better with benzophenone. Coordination of the carbonyl group to the cationic Ru center provides a higher thermodynamic and kinetic rotation barrier for the flexible bisphosphane ligand, resulting in the preferential formation of only one diastereomer and thus higher enantioselectivity.
Transfer hydrogenation reactions

The Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation are classic transfer hydrogenation reactions via the hydride route. Performing these reactions under chelation-controlled conditions provides very high diastereoselectivities. 3-Nitrobenzaldehyde and 2,6-dinitrobenzaldehyde are excellent hydride acceptors.

Kagan reported in 1984 that lanthanide iodo alkoxides, in particular tBuOSmI, display good reactivity in Meerwein–Ponndorf–Verley–Oppenauer reactions. Evans later developed an asymmetric samarium catalyst for this reaction, in addition to studying samarium-catalyzed diastereoselective Tishchenko reduction (Cannizzaro reaction).

Group 8–11 transition metals are highly effective transfer hydrogenation catalysts. Bäckvall found in 1991 that, with NaOH co-catalyst, RuCl₂(PPh₃)₃ effectively catalyzes transfer hydrogenation of ketones using isopropanol as the hydride donor. No hydrogenation occurs in the absence of sodium hydroxide. Noyori reported in 1995 a highly enantioselective transfer hydrogenation catalyst. Replacing isopropanol with the formic acid-triethylamine azeotropic mixture (5:2) solved the reversibility issue. The use of formic acid as the hydrogen donor was originally developed by Blum.
The classic hydride mechanism with a Meerwein–Ponndorf–Verley transition state does not explain the observation that the presence of an NH or NH$_2$ group in the ligand is crucial for catalytic activity. Additionally, the sulfonyl group enhances the acidity of NH to stabilize the Ru complex. The corresponding dialkylamine, diamine, and diol analogues are all ineffective ligands, but the NHTs group of the ligand can be switched to OH. Various chiral amino alcohols can be used for asymmetric reduction of aromatic ketones.

Kinetic studies with isolated complexes showed that the interconversion between the 16-electron intermediate and the 18-electron true catalyst takes place either directly or via a very short-lived intermediate. Hydrogen transfer occurs even in the absence of base when isolated complexes were used. The enantioselectivity is explained by the CH–π interaction between the catalyst and the substrate.

**Frustrated Lewis pair**

Stephan found in 2006 that bulky phosphine and bulky borane that are not able to form an adduct can react with hydrogen reversibly. The unquenched Lewis acidity and basicity of this “frustrated” Lewis pair polarize hydrogen to facilitate H–H cleavage and forms a transit ion pair [A–H]/[H–B]$^+$ that transfers H$^+$ and H$^-$ to olefins or carbonyl groups through a concerted mechanism. Both side-on and end-on coordination of hydrogen to borane have been proposed. In addition to splitting hydrogen, frustrated Lewis pair can also add to olefin, acetylene, and carbon dioxide.

![Diagram of Frustrated Lewis pair mechanism]

- **Mes$_2$HP**
  - $^{150 \degree C}$
  - $^{25 \degree C}$
  - Mes$_2$P

- **PR$_3$ + B(C$_6$F$_5$)$_3$ + H$_2$**
  - $^{150 \degree C}$
  - $^{25 \degree C}$
  - [R$_3$PH][HB(C$_6$F$_5$)$_3$]
  - $R = ^1$Bu or Mes

- **Mes$_2$P – B(C$_6$F$_5$)$_2$**
  - $^{25 \degree C}$
  - Mes$_2$P

- **P$^3$Bu$_3$ + B(C$_6$F$_5$)$_3$ + RCH=CH$_2$**
  - $^{25 \degree C}$
  - $^{1}$Bu$_3$P

Advanced Synthesis and Catalysis — Hydrogenation and Hydrofunctionalization  
Chen

24
Hydroformylation (oxo process)

Transition metal catalyzes the reaction between olefin and synthesis gas (CO + H₂). As the largest homogeneous catalytic process, hydroformylation is used to produce over 15 billion pounds of aldehydes/alcohols per year. Cobalt catalysts were mostly used in early days but rhodium catalysts predominate nowadays, in particular, for lower hydrocarbons. The reaction was first discovered by Roelen in 1938 during the study of cobalt carbonyl-catalyzed Fischer–Tropsch reaction. Both linear and branched products can be produced. Heck and DS Breslow established the mechanism of this reaction in 1960.

\[
\text{Co}_2(\text{CO})_8 + \text{H}_2 \rightarrow \text{HCo(CO)}_4
\]

The subsequent dissociation of a CO ligand and migratory insertion of olefin into Co–H is the regioselectivity-determining step. Next, CO inserts into Co–R and another CO is incorporated into the complex. The rate-determining step is the dissociation of a CO ligand and oxidative addition of hydrogen to give a dihydride complex. Subsequent reductive elimination gives the aldehyde. Product formation may also proceed through a dinuclear mechanism. The 16 e⁻ complex \( \text{RC(O)Co(CO)}_3 \) can react with \( \text{HCo(CO)}_4 \) to give the aldehyde and \( \text{Co}_2(\text{CO})_7 \) that reenters the catalytic cycle upon reacting with hydrogen. The mononuclear pathway plays a more important role for simple substrates.

With a rate law of \( k\text{[cat]}\text{[alkene]}\text{[H}_2\text{]}\text{[CO]}^{-1} \), the reaction rate is independent of the pressure of synthesis gas (1:1 H₂/CO) because of the opposing orders of H₂ and CO. Higher CO pressure is needed to prevent the formation of inactive metallic cobalt at higher temperature. Additionally, increasing the pressure of CO, whereas slowing the reaction, suppresses olefin isomerization and hydrogen exchange, and improves the linear/branched product ratio.

Reduction of aldehyde to alcohol is a desired side-reaction. Higher H₂/CO ratio can be used to compensate the consumed hydrogen. Increasing reaction temperature improves rate but promotes the formation of byproducts from aldol condensation, aldol reaction, trimerization, and Guerbet dimerization. These heavy byproducts become the solvent of the reaction over time. The catalyst HCo(CO)_4 can be extracted directly by base or after oxidation, and recycled for use again after activation.
The trialkylphosphine-modified cobalt catalyst introduced by Shell provides higher yield of the desirable linear aldehydes despite lower reaction rate. Treatment of Co$_2$(CO)$_8$ with P$_n$Bu$_3$ at 150 °C under H$_2$/CO gives [Co(P$_n$Bu$_3$)(CO)$_3$]$_2$ along with [Co(P$_n$Bu$_3$)$_2$(CO)$_3$][Co(CO)$_4$] that, under hydroformylation conditions, converts to [Co(P$_n$Bu$_3$)(CO)$_3$]$_2$, the principle Co complex recovered from the hydroformylation products.

Replacement of a CO with a phosphine ligand leads to stronger Co–CO binding and thus higher catalyst stability. Despite lower rate, the linear/branched ratio is better. The higher hydritic property of Co–H leads to some olefin hydrogenation, but the aldehyde product is also reduced to alcohol, eliminating the heavy-product issues derived from aldehyde condensation.

<table>
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<th>aldehyde</th>
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Coupling with Shell higher olefin process (SHOP), C$_{13}$–C$_{19}$ fatty alcohols are produced for the use of plasticizer and detergent syntheses. The specific trialkylphosphine used is not publicly known outside of Shell. The key reaction of SHOP is the nickel-catalyzed ethylene polymerization. The nickel hydride with an unusual bidentate phosphine carboxylate ligand is extremely selective for ethylene in the presence of other olefins, allowing for the formation of a statistical (Flory–Schultz) mixture of linear terminal olefins. After distillation, the lighter and heavier fractions are isomerized to a mixture of internal olefins and subjected to metathesis using MoO$_3$/Al$_2$O$_3$ to give C$_8$–C$_{18}$ products.
Reaction of the tetrameric and hexameric rhodium carbonyl with $\text{H}_2/\text{CO}$ gives highly active HRh(CO)$_4$ that catalyzes hydroformylation with lower linear/branched ratio as well as olefin hydrogenation and isomerization. Both Rh(acac)(CO)$_2$ and HRh(CO)$_2$(PPh$_3$)$_3$ are commonly used catalysts.

<table>
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<tr>
<td>Co</td>
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<tr>
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<tr>
<td>Fe</td>
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<tr>
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</tr>
<tr>
<td>Ni, Pt</td>
<td></td>
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</tr>
</tbody>
</table>

Relative reactivity

Hydroformylation with modified rhodium catalysts was first reported by Wilkinson in 1965. They showed that Rh(PPh$_3$)$_3$Cl$_3$ catalyzes hydroformylation of olefins under conditions milder than those required for cobalt carbonyl catalysts. Later, they found that addition of hydrogen halide acceptors eliminates the induction period for trans-RhCl(CO)(PPh$_3$)$_2$ and the active catalyst is HRh(CO)$_2$(PPh$_3$)$_2$.

Addition of excess phosphine or phosphite ligands improves the catalyst stability and the linear/branched ratios, and suppresses olefin hydrogenation/isomerization without affecting hydroformylation turnover frequencies. Hydroformylation of propene has even been run in molten triphenylphosphine (mp. 79 ºC) as the solvent in a commercial process.

The detailed mechanism of rhodium-catalyzed hydroformylation is not clear, although it is generally believed to be similar to that of the cobalt-catalyzed process. Multiple active species may be involved, with HRh(PPh$_3$)$_2$(CO) being the most selective yet highly reactive one. There is no clear rate-limiting step and several elementary reactions have similar rate.

Very high linear/branched ratio can be achieved when using rhodium catalysts with a bidentate ligand that has large bite angles. 2,2’-Bis[(diphenylphosphino)methyl]-1,1’-biphenyl (BISBI), 6,6’-[(3,3’-di-tert-butyl-5,5'-dimethoxy-1,1’-biphenyl-2,2’-diyl)bis(oxy)]bis(dibenzo[d,f][1,3,2]dioxaphosphepin) (BIPHEPHOS), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS) are among the best ligands for linear products. There are not many examples of asymmetric hydroformylation giving branched products with high enantioselectivity. Takaya found that Rh(acac)(CO)$_2$ when complexed with BINAPHOS catalyzes enantioselective hydroformylation with good selectivity and reactivity.
Hydrosilylation

Speier reported in 1957 that \([\text{H}_2\text{PtCl}_6] \cdot \text{H}_2\text{O}\) is a highly active catalyst for hydrosilylation of olefins. Other effective catalysts include Pt/C, K_2PtCl_4, Pt-black, RuCl_3, and IrCl_3. Karstedt later developed a Pt-vinylsiloxane complex that has improved reactivity and selectivity. Chalk reported in 1970 that RhCl(PPh_3)_3, RhCl(CO)(PPh_3)_2 and HRh(CO)(PPh_3)_3 are also effective catalysts.

For the reaction between PhMe_2SiH and ethylene, the relative reactivity is \(\text{H}_2\text{PtCl}_2 : \text{Rh(PPh}_3)_3\text{Cl} : \text{Co}_2(\text{CO})_8 = 4,000 : 200 : 1\). Linear products are usually formed for steric reasons. Internal olefins can isomerize under reaction conditions to give linear products.

Hydrosilylation of alkynes proceeds with cis-addition of H and Si to afford trans-products that can isomerize to cis-vinylicsilanes via migratory insertion/β-hydride elimination. Platinum and rhodium complexes catalyze hydrosilylation of terminal alkynes to give trans-β-vinylicsilanes, whereas ruthenium complexes, for example, \([\text{Ru(benzene)}\text{Cl}_2]_2\) and \([\text{Ru(p-cymene)}\text{Cl}_2]_2\) are selective for cis-products. The Wilkinson’s catalyst gives trans-products in polar solvents and cis-products in non-polar solvents. The regio and stereoselectivity of Grubbs’ 1st generation catalyst is highly dependent on the alkyne, silane, and solvent.

The platinum and rhodium complexes catalyze hydrosilylation following the classic Chalk–Harrod mechanism. The reaction likely operates with an “olefin” rather than “hydride” pathway. The oxidative addition of metal into Si–H and the subsequent migratory insertion are reversible based on isotopic labeling experiments. Both steps proceed with retention of the silicon configuration.

The cationic complex \([\text{Cp}^*(\text{P}^\text{tBu}_3)\text{H})_2\text{Ru=Si(H)Ph}]^+\) promotes the reaction between alkynes and primary silanes to give terminal silanes through an outer sphere mechanism.
Trost reported in 2001 that [Cp*Ru(MeCN)\(_2\)]PF\(_6\) catalyze the hydrosilylation of terminal alkynes to give α-vinylsilanes, and the hydrosilylation of internal alkynes to yield (Z)-alkenes. Polar functional groups can be used as directing groups.

Asymmetric hydrosilylation has also been achieved by Hayashi using palladium as the catalyst and monophosphine 2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl as the ligand.

Nesmeyanov discovered in 1962 that iron pentacarbonyl catalyzes hydrosilylation of terminal olefin. However, activation of iron complexes typically requires elevated temperature or photolysis. Chirik reported in 2004 that high spin iron complex (PDI)Fe(N\(_2\))\(_2\) loses a nitrogen ligand in solution to form [(PDI)Fe(N\(_2\))]\(_2\). Both the monomer and dimer are highly effective catalysts for hydrogenation and hydrosilylation of olefins and alkynes.
Hydroboration

Brown found in 1956 that the borane reagent generated from sodium borohydride and aluminum chloride reacts directly with olefins to give trialkylborane. Catecholborane (HBcat) and pinacolborane (HBpin) react only at elevated temperatures.

Kono found in 1975 that Wilkinson’s catalyst undergoes oxidative addition with HBcat or HBpin to give metalloboranes. Nöth reported in 1985 the catalytic hydroboration of olefins by Wilkinson’s catalyst. Nickel, palladium, ruthenium, iridium, samarium, titanium, and zirconium also catalyze hydroboration, but rhodium has remained the metal of choice. Labeling studies suggest that the degree of reversibility of the elementary steps in the catalytic cycle is highly substrate-dependent. Whether the reaction proceeds through a 16-electron dissociative or a 18-electron associative mechanism is debatable.

Whereas HB(OR)₂ reduces ketone preferentially in the presence of olefin, the chemoselectivity is reversed in the presence of Wilkinson’s catalyst. Both Markovnikov and anti-Markovnikov products can be obtained from metal-catalyzed hydroboration, depending on the ligands of the metal and the stereoelectronic properties of the olefins. In general, chiral P,N-ligands perform better than P,P-ligands in enantioselective hydroboration.