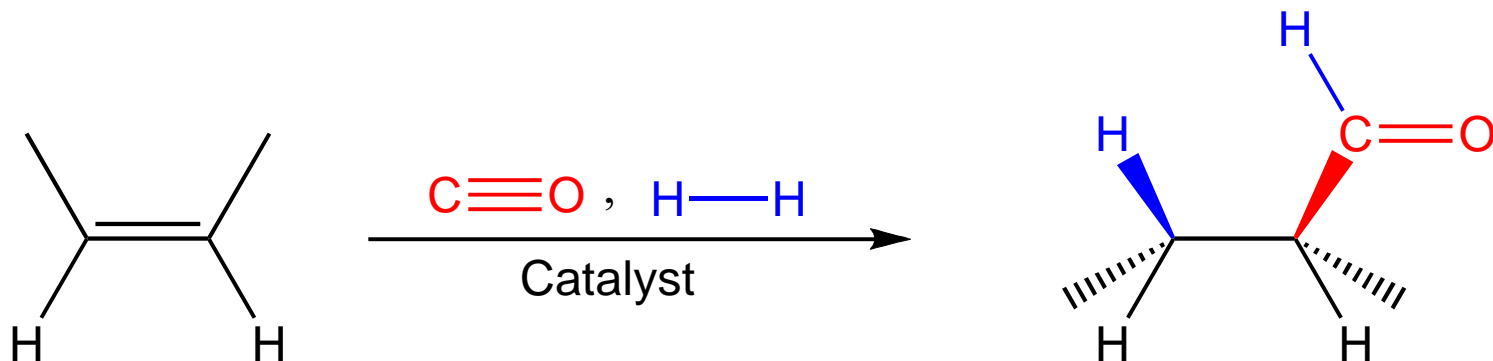


The Hydroformylation Reaction



It is a **three component** reaction: three bonds are cleaved and three bonds are formed;

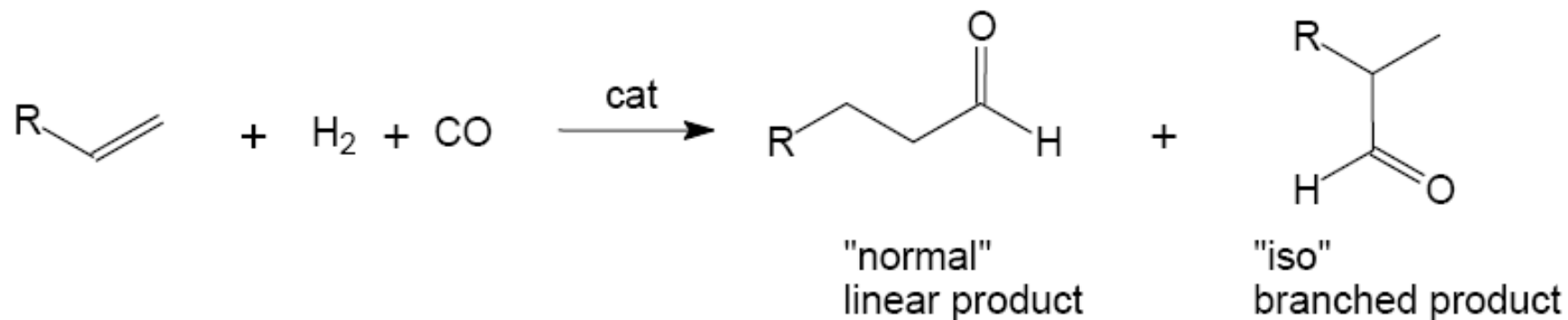
It consists in the **addition of CO and H₂** to a **C-C double bond**, moving from an alkene to an aldehyde with **one carbon atom more** than the starting alkene;

The **CO/H₂** mixture is called **syngas** (or synthesis gas);

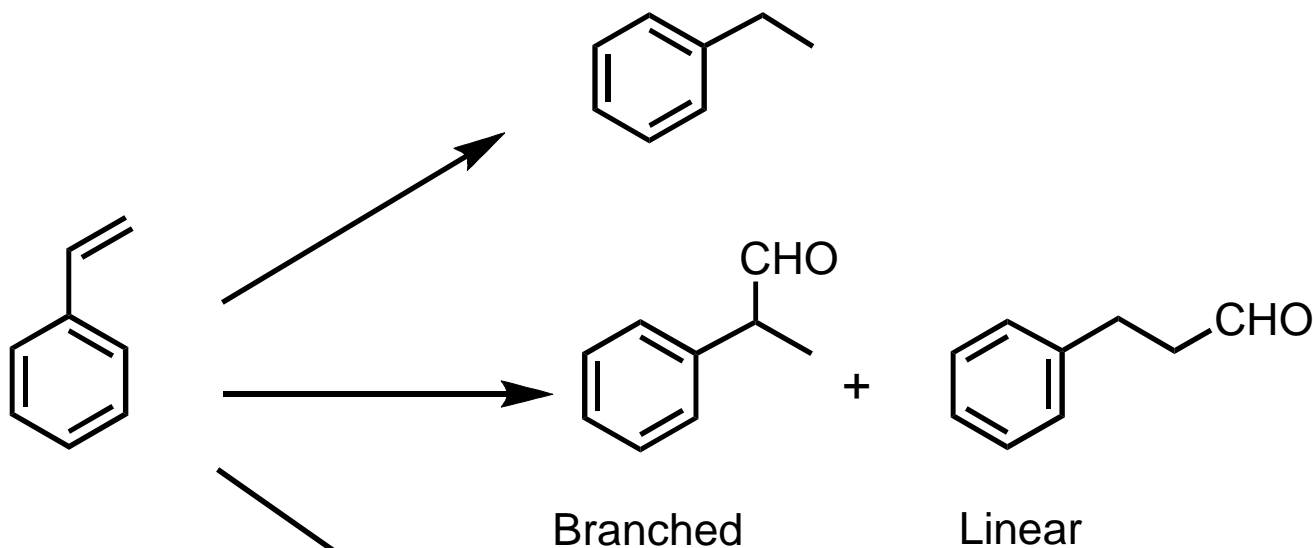
It was introduced by Otto Roelen in 1938 and it is known as **oxo-synthesis**, today is a large scale industrial process, dominated by the conversion of propene to ***n*-butanal**; in 2008 the worldwide production of aldehydes was about **10.4 millions of metric tons**.

The catalysts are based on organometallic complexes of **Co** or **Rh**.

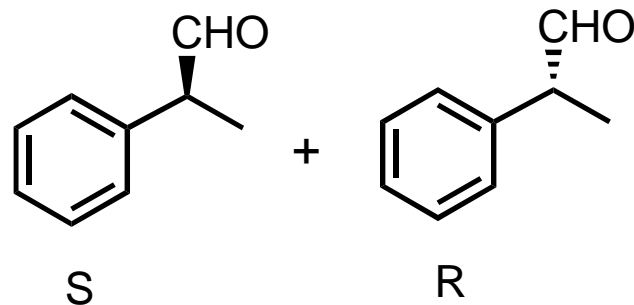
Selectivity in hydroformylation reactions



Chemoselectivity

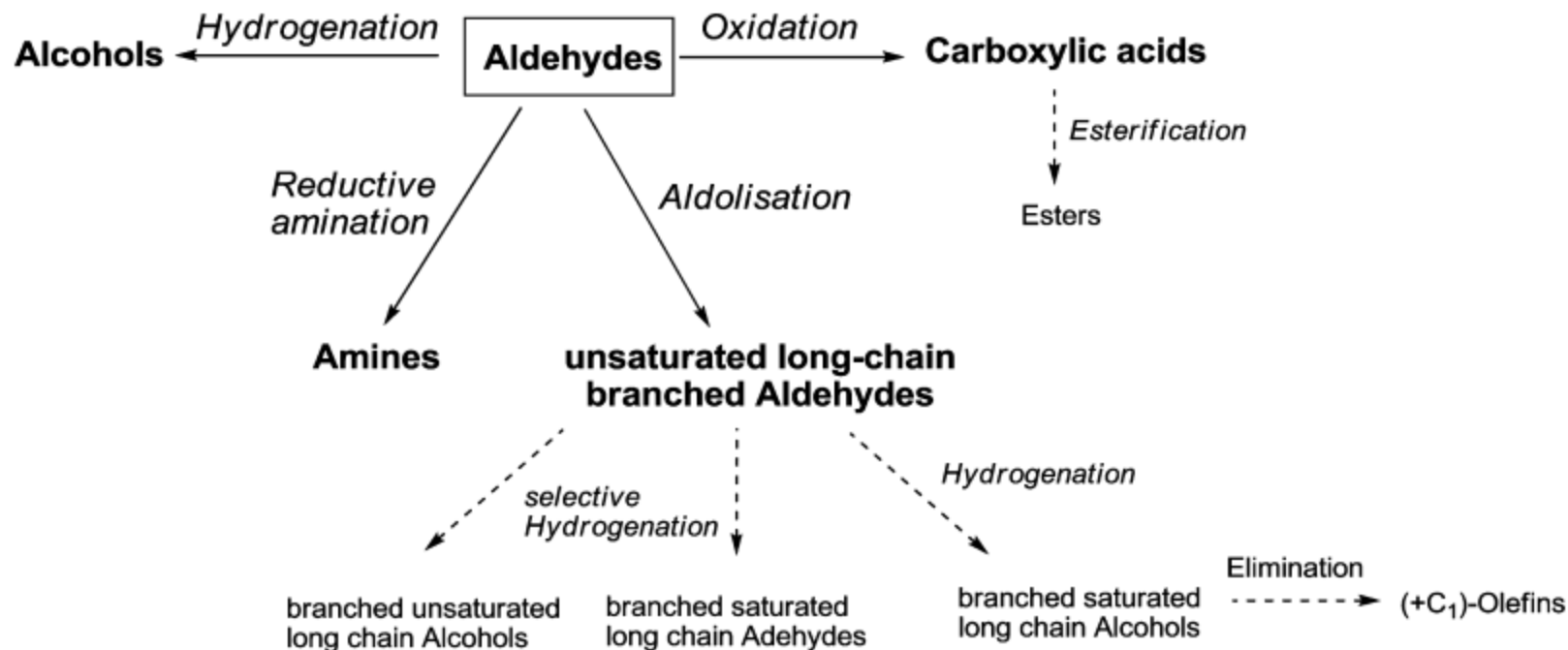


Regioselectivity



Stereoselectivity

Products obtained from aldehydes



Hydroformylation vs ***Hydrogenation***

Bulk chemicals

Fine chemicals

Asymmetric catalysis?

Asymmetric catalysis

Historical Evolution of industrial processes for hydroformylation

1950's HCo(CO)_x catalysts; Oxo-alcohols

1960's Shell-catalyst; HCo(CO)_x + PPh₃

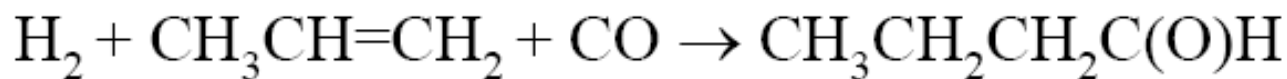
1970's Rh-catalysts; low pressure process

1980's Aqueous-biphasic hydroformylation

1990's Up to 99% linear aldehyde

2000's Asymmetric hydroformylation

Thermodynamics of hydroformylation and hydrogenation



$$\Delta G \quad 63 \quad \quad \quad -138 \quad \quad \quad -117 \text{ (l)} = -42 \text{ kJ.mol}^{-1}$$

$$\Delta H \quad 21 \quad \quad \quad -109 \quad \quad \quad -238 = -150 \text{ kJ.mol}^{-1}$$



$$\Delta G \quad 63 \quad \quad \quad -25 = -88 \text{ kJ.mol}^{-1}$$

$$\Delta H \quad 21 \quad \quad \quad -105 = -126 \text{ kJ.mol}^{-1}$$

Cobalt catalysed processes

Homogeneous Catalyst: $[\text{CoH}(\text{CO})_4]$

Reaction conditions: $T = 100 - 200 \text{ }^\circ\text{C}$

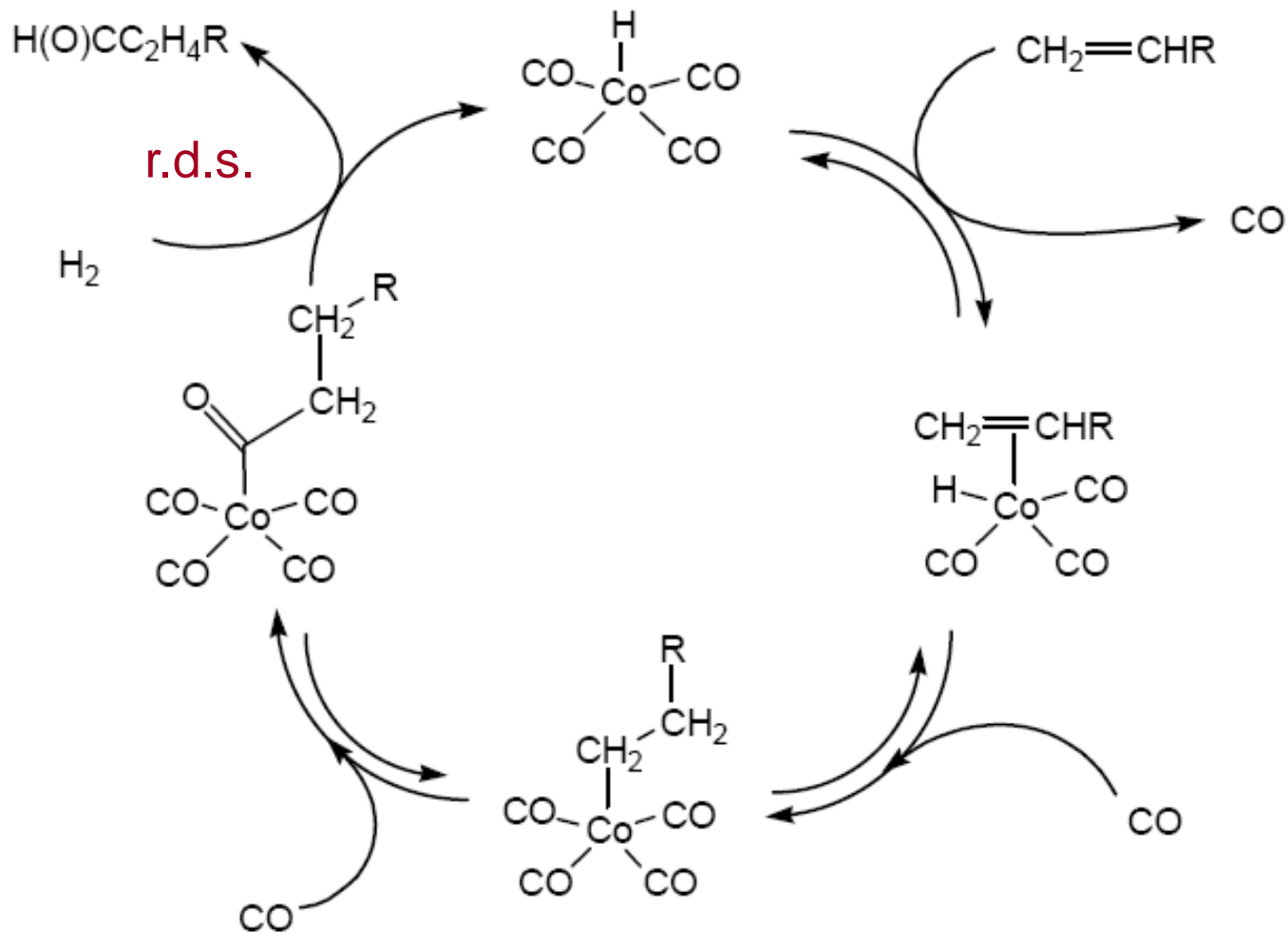
$P_{\text{tot}} = 200 - 300 \text{ atm}$

$$v = k [\text{Co}][\text{alkene}][\text{H}_2][\text{CO}]^{-1}$$

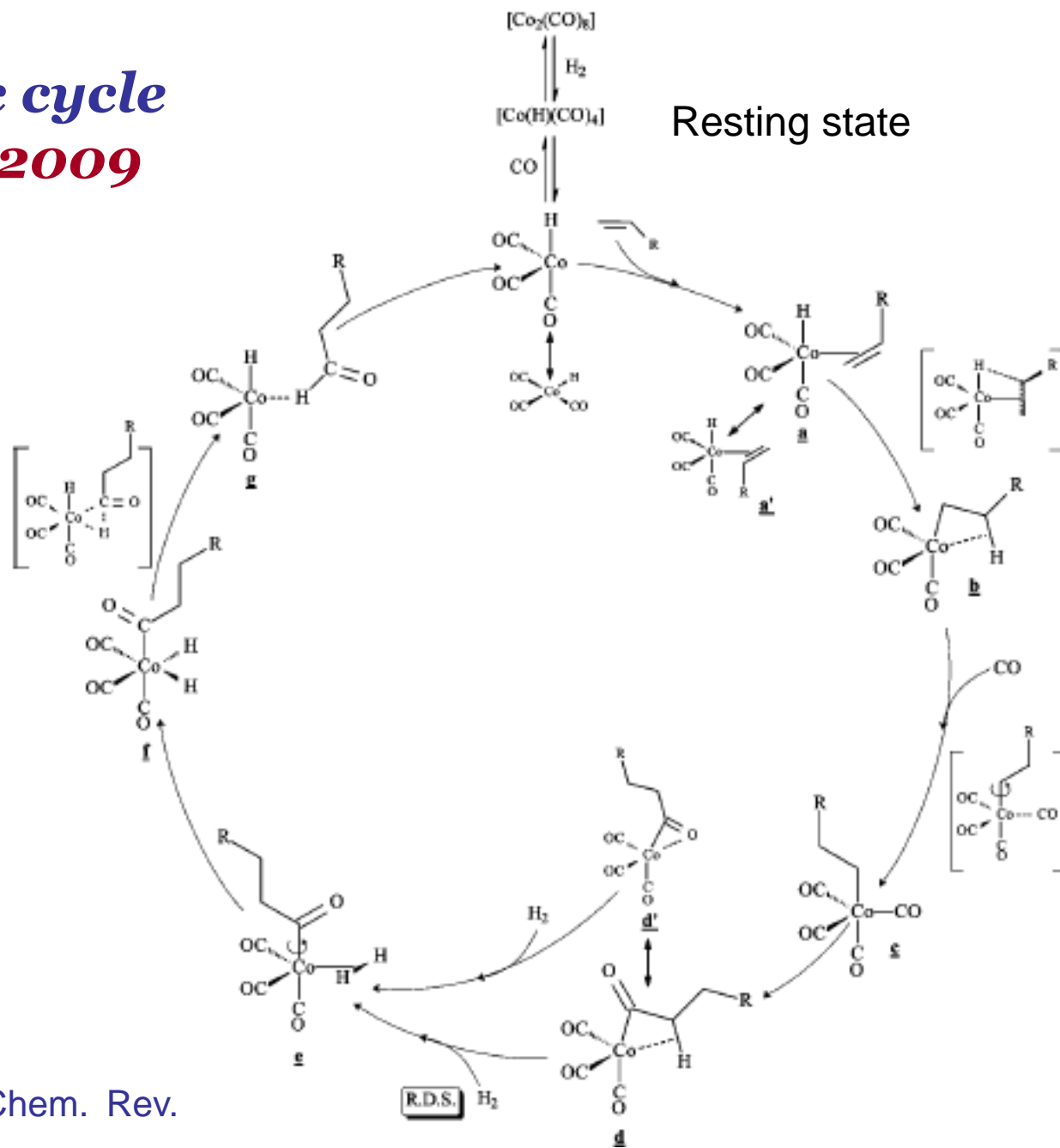
Scientifically it is interesting to understand how the ratio of linear and branched product can be influenced and maximised by varying the ancillary ligands and the kinetic of the reaction.

$[\text{CoH}(\text{CO})_4]$ is an excellent catalyst for isomerisation reaction of internal alkenes to terminal alkenes.

The catalytic cycle reported in 1953



The catalytic cycle reported in 2009



Selectivity in linear aldehyde is 81%.

F. Hebrard, P. Kalck Chem. Rev. 2009, 109, 4272.

Hydroformylation of higher alkenes

$[\text{CoH}(\text{CO})_4]$ is the catalyst industrially applied.

Remarks:

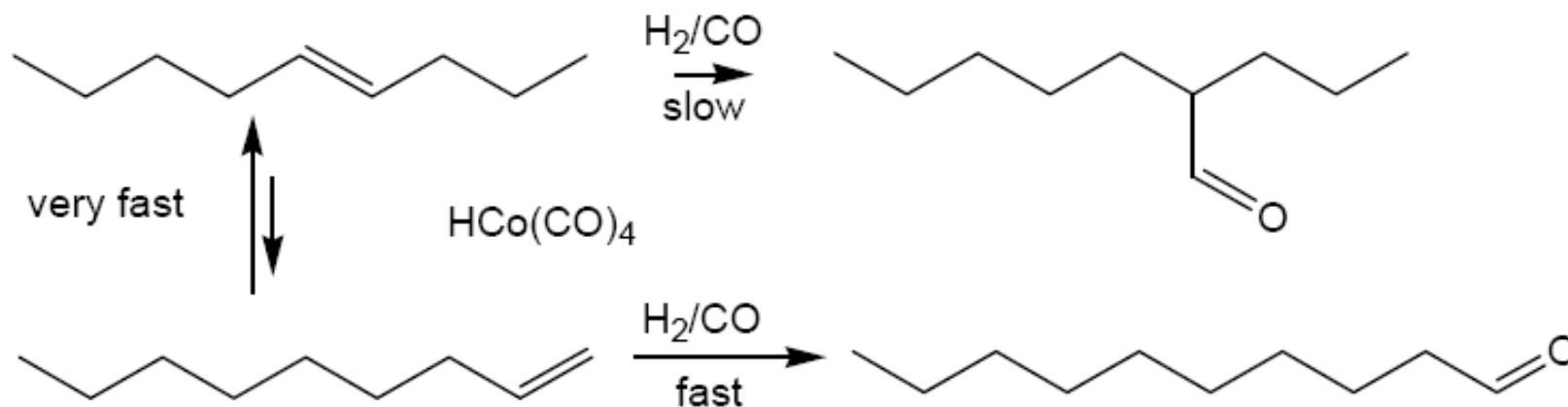
1. The higher alkene feed C_{10-14} is essentially made of internal alkenes;
2. The linear aldehyde is the desired product with an acceptable selectivity around 60 – 80%.

Experimental data:

1. $[\text{CoH}(\text{CO})_4]$ is an excellent catalyst for isomerisation reaction of internal alkenes to terminal alkenes;
2. $[\text{CoH}(\text{CO})_4]$ has a high preference for hydroformylation of terminal alkenes: the hydroformylation rate is 1000 times faster than on internal alkenes.

Hydroformylation of *higher alkenes*

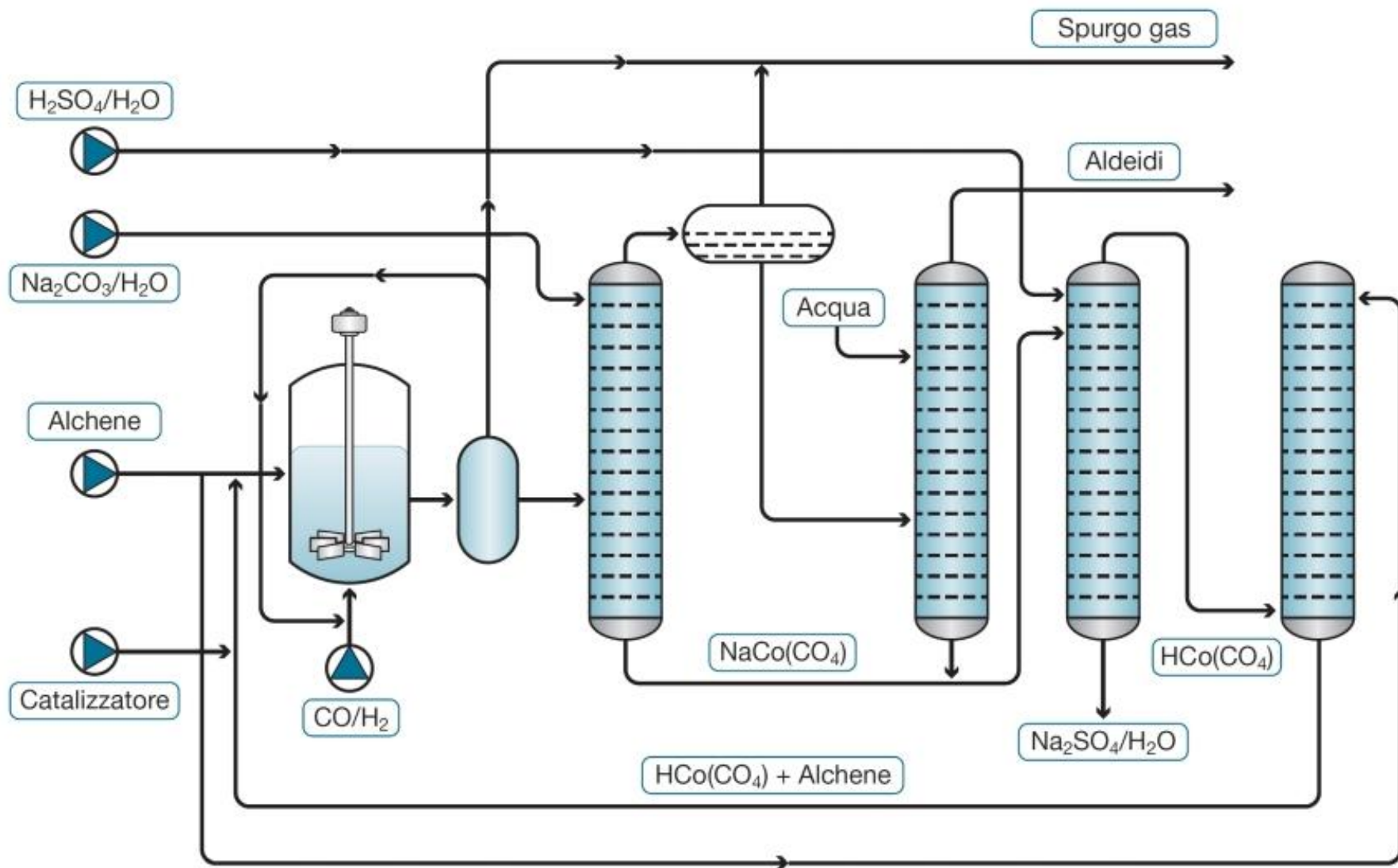
[CoH(CO)₄] is the catalyst industrially applied.



Rate constants for the hydroformylation of *selected alkenes*

Alkene	$k / \times 10^{-5} \text{ s}^{-1}$
Hex-1-ene	110
Hex-2-ene	30
Cyclohexene	10
Oct-1-ene	109
Oct-2-ene	31
2-Methylpent-2-ene	8

The *Kuhlmann process*: the flow scheme and the catalyst recycling



The Shell process

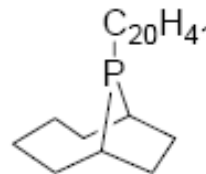
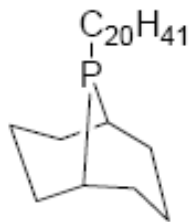
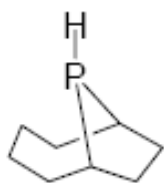
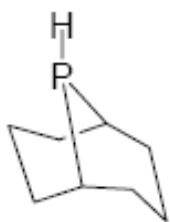
Introduction of catalysts based on phosphines:
 $[\text{CoH}(\text{CO})_3(\text{PR}_3)]$.

The introduction of monophosphines resulted in:

1. the reaction is a **hundred times slower**;
2. the selectivity to **linear aldehyde increases**;
3. The carbonyl compound formed, $[\text{CoH}(\text{CO})_3(\text{PR}_3)]$, is much more stable than $[\text{CoH}(\text{CO})_4]$;
4. The catalyst results to be **active** also in the **hydrogenation** reaction.

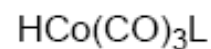
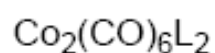
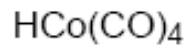
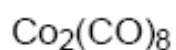
Cat. Prec.	P (bar)	T (°C)	Pr.	lin. (%)	Cat. act.	alkanes (%)
$[\text{CoH}(\text{CO})_4]$	200 – 300	100 – 180	ald.	70	5 (145°C)	1
$[\text{CoH}(\text{CO})_3(\text{PR}_3)]$	25 – 100	100 – 200	alc.	90	1 (185°C)	15

Examples of tested monophosphines

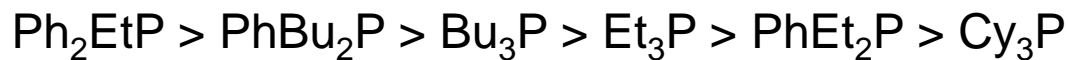


phobane mixture

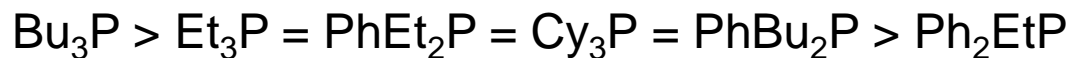
Examples of applied cobalt complexes



*Effect of the phosphine on **activity***



*Effect of the phosphine on **linear/branched ratio (5.5 – 3)***

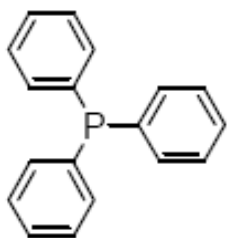


The catalytic system based on **Rhodium** **LPO** (Low Pressure Oxo process)

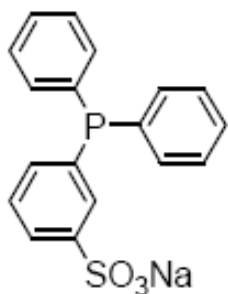
General features:

1. Catalysts are **100 - 10000 times faster** than those based on Co;
2. High catalytic activity in isomerization reactions;
3. **They do not** catalyze the **hydrogenation** reaction of aldehydes;
4. Rh is much more **expensive** than Co.

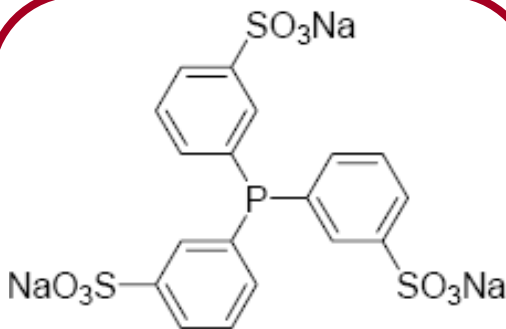
Examples of tested monophosphines and phosphites



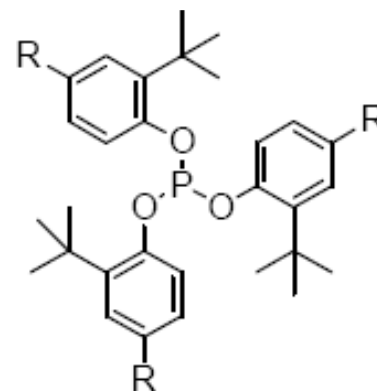
tpp



tppms



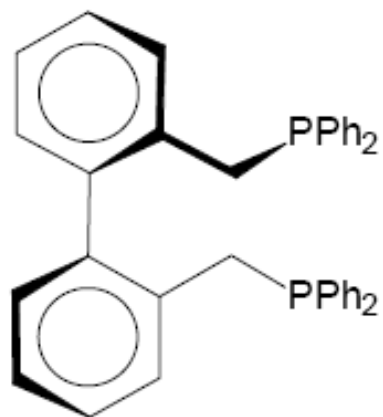
tppts



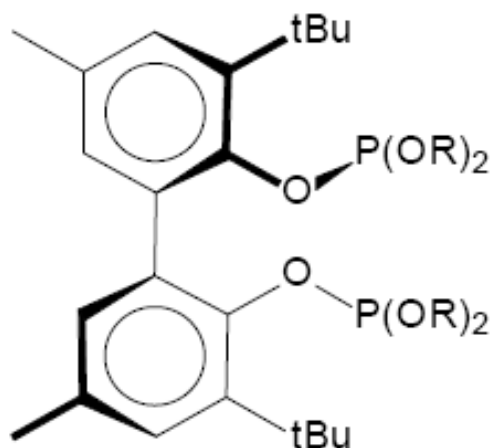
"bulky" phosphite

Cone angle = 195°

Examples of diphosphines and diphosphites

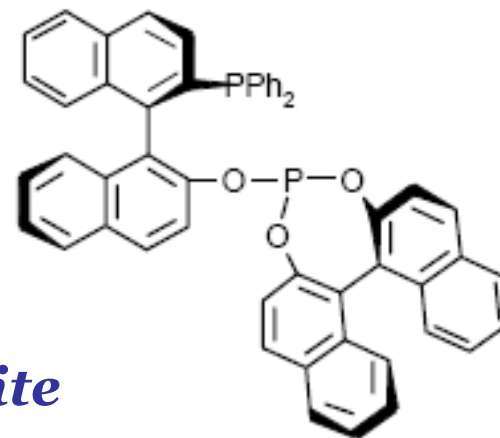


"BISBI"



general formula of diphosphite

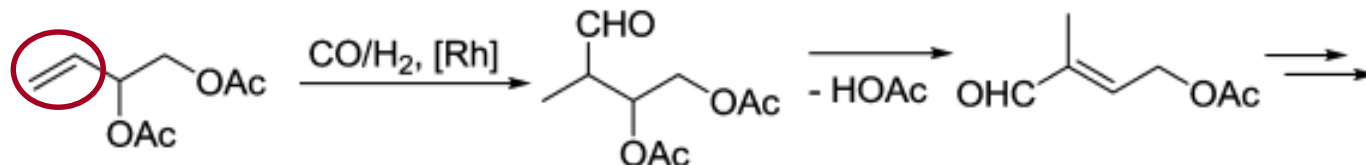
Union Carbide 1997



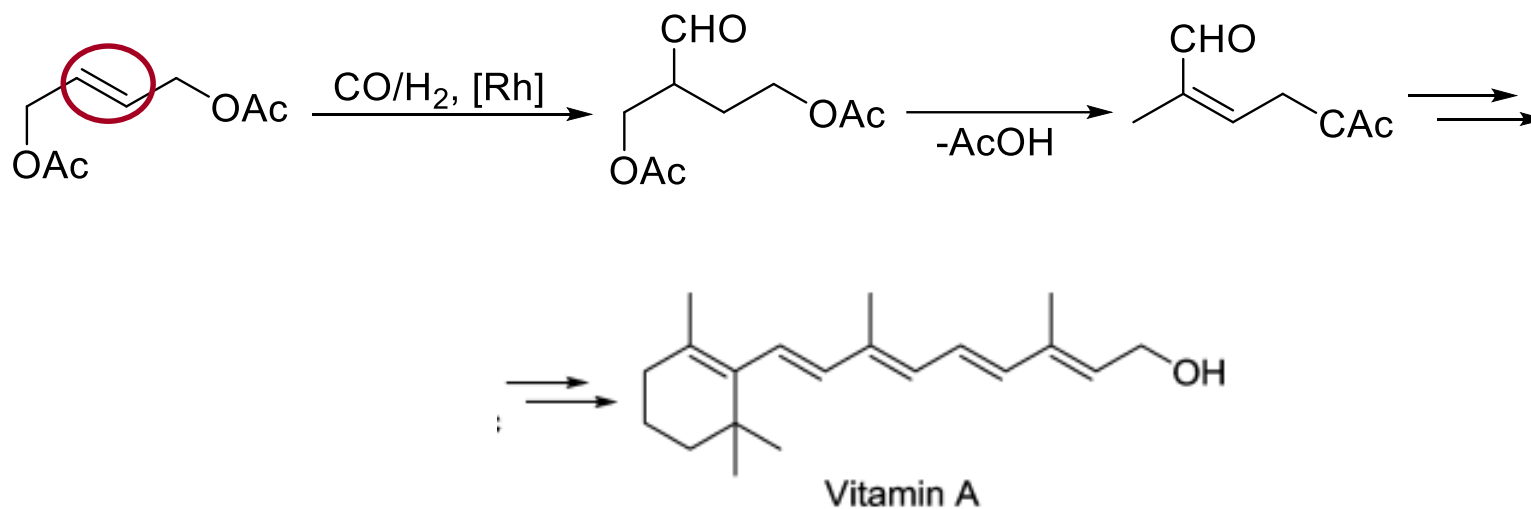
BINAPHOS:
a chiral phosphino-phosphite

Synthetic technology for the production of **Vitamin A**

The **BASF** process

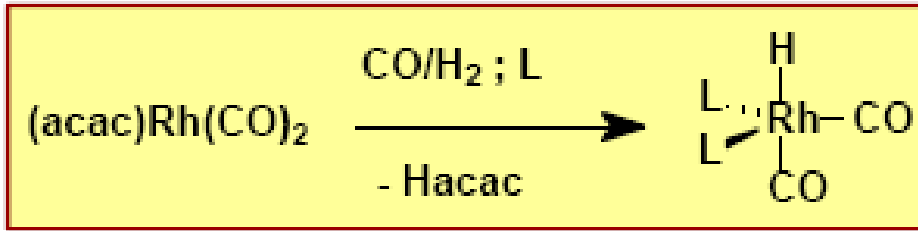


The **Hoffmann-La Roche** process

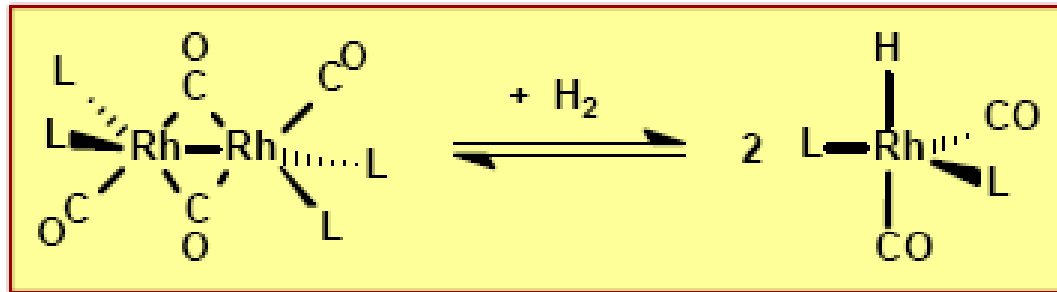


The *Rh/tpp* system

in situ catalytic system



Inactive species



The **kinetic** law

$$v = k [\text{alkene}]^1 [\text{Rh}]^1 [\text{H}_2]^1 [\text{PPh}_3]^{-1} [\text{CO}]^{-1}$$

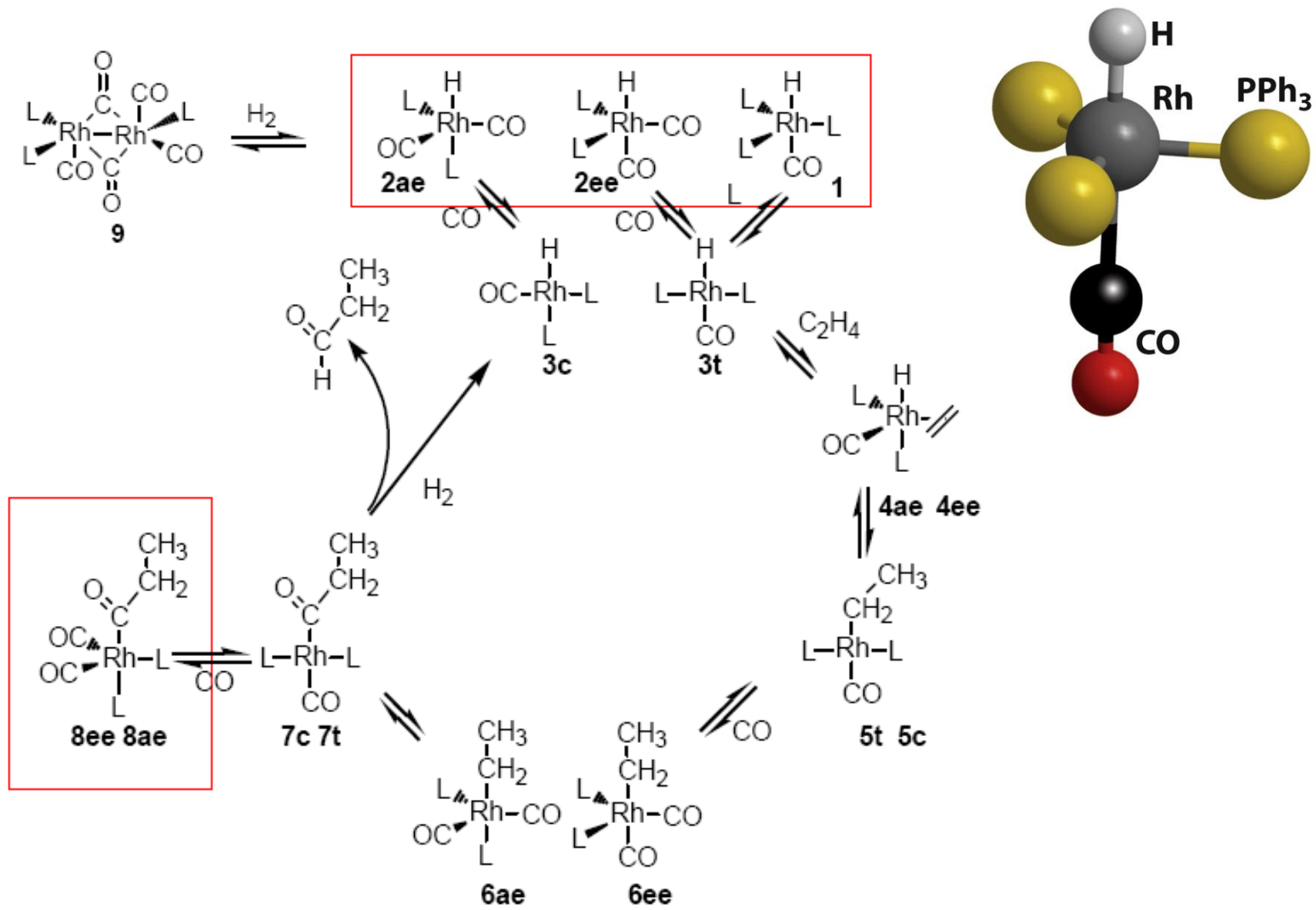
The **kinetic** law for the industrial synthesis of butanal

d'Oro's equation

$$V = k [\text{C}_3\text{H}_6]^{0.6} [\text{Rh}]^1 [\text{H}_2]^0 [\text{PPh}_3]^{-0.7} [\text{CO}]^{-0.1}$$

(conditions 90-110°C, 1-25 bar CO, 1-45 bar H₂, PPh₃/Rh ratio 300:1 to 7:1)

Simplified mechanism for hydroformylation of ethene with *Rh*/tpp



*Simplified mechanism for hydroformylation of ethene with **Rh/tpp***

The catalyst resting state:

1. At high concentration of phosphine: the catalyst resting state is $[\text{RhH}(\text{PPh}_3)_3\text{CO}]$;
2. At low concentration of phosphine: the catalyst resting state is $[\text{RhH}(\text{PPh}_3)_2(\text{CO})_2]$.

The rate determining step:

- a. At high concentration of phosphine: the catalyst resting state is $[\text{RhH}(\text{PPh}_3)_3\text{CO}]$ and rds is alkene coordination and its migratory insertion;
- b. At high concentration of CO: the catalyst resting state is the Rh-acyle intermediate and rds is the reaction with H_2 .

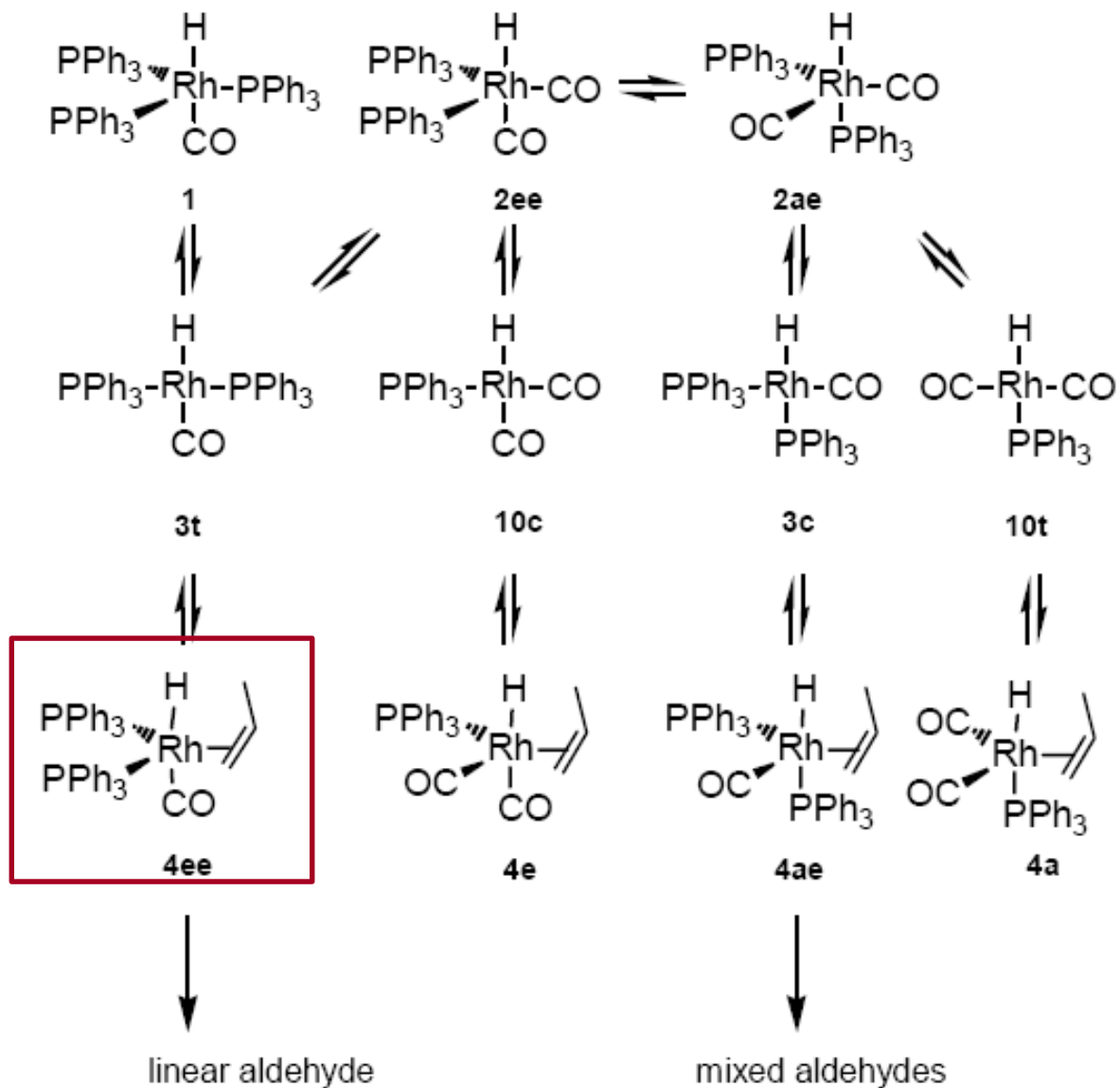
Activity: electronic effects

Ligands with **electron-withdrawing substituents** increase the rate of reactions leading to intermediates 3 and 7, and increase their concentration at equilibrium; they decrease the rate of oxidative addition;

Phosphines **with a Lewis basicity higher** than tpp lead to slower catalysts;

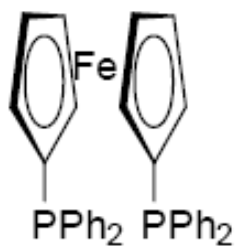
In general, **phosphites** lead to **faster catalysts**.

Regioselectivity

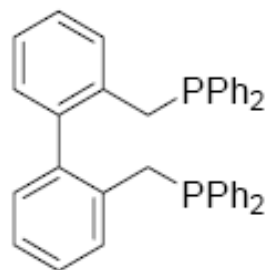


Hydroformylation with diphosphines

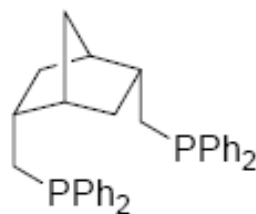
Ligand	Bite angle	Rate $\text{m.m}^{-1}.\text{h}^{-1}$	Ratio I:b
12	126	2550	2.6–4.3
BISBI, 11	113/120	3650	25
13	107	3200	4.4–12
DIOP [also 56]	102	3250	4.0–8.5
dppf [also 33]	99	3800	3.6–5
dppp	91	600	0.8–2.6
dppe	85		2.1
PPh_3^{a}		6000	2.4



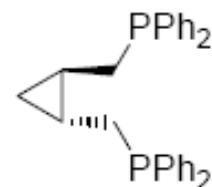
dppf



11

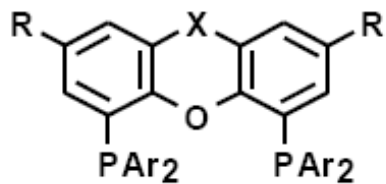


12



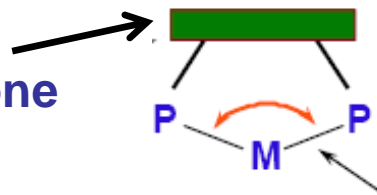
13

Hydroformylation with diphosphines

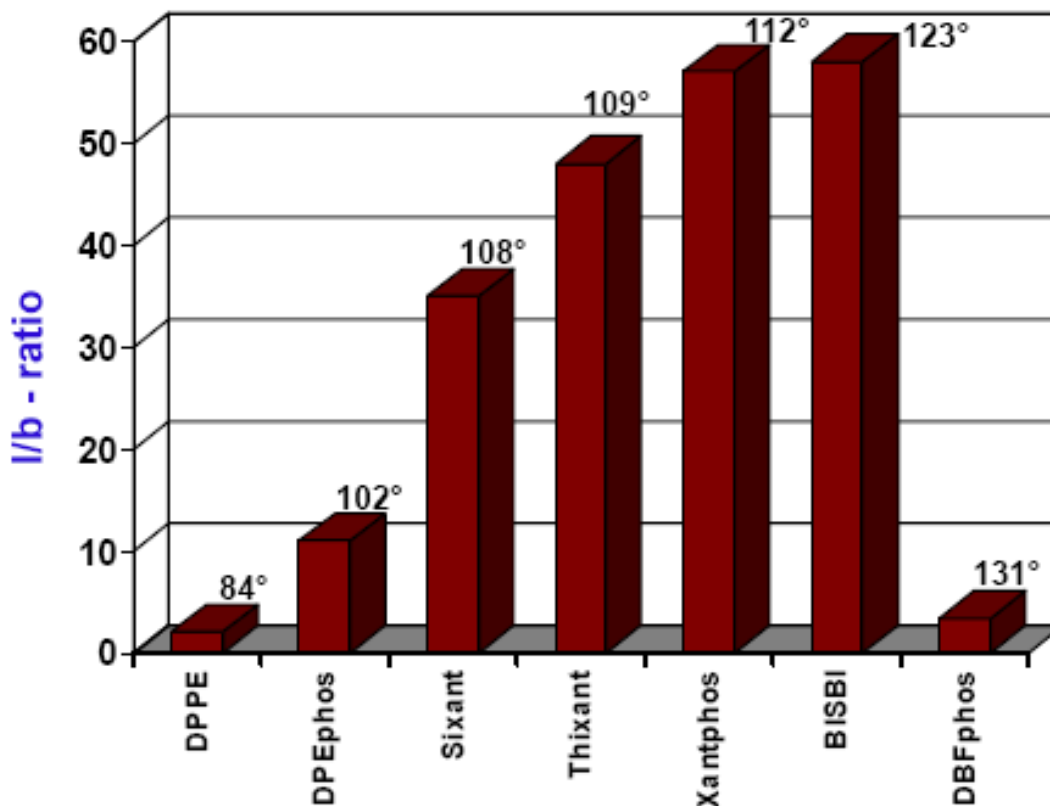
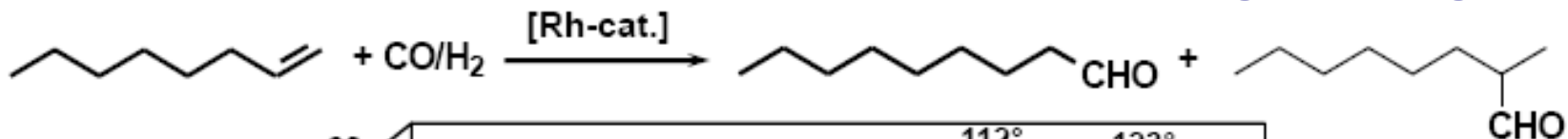


Xantphos ligands

Rigid backbone



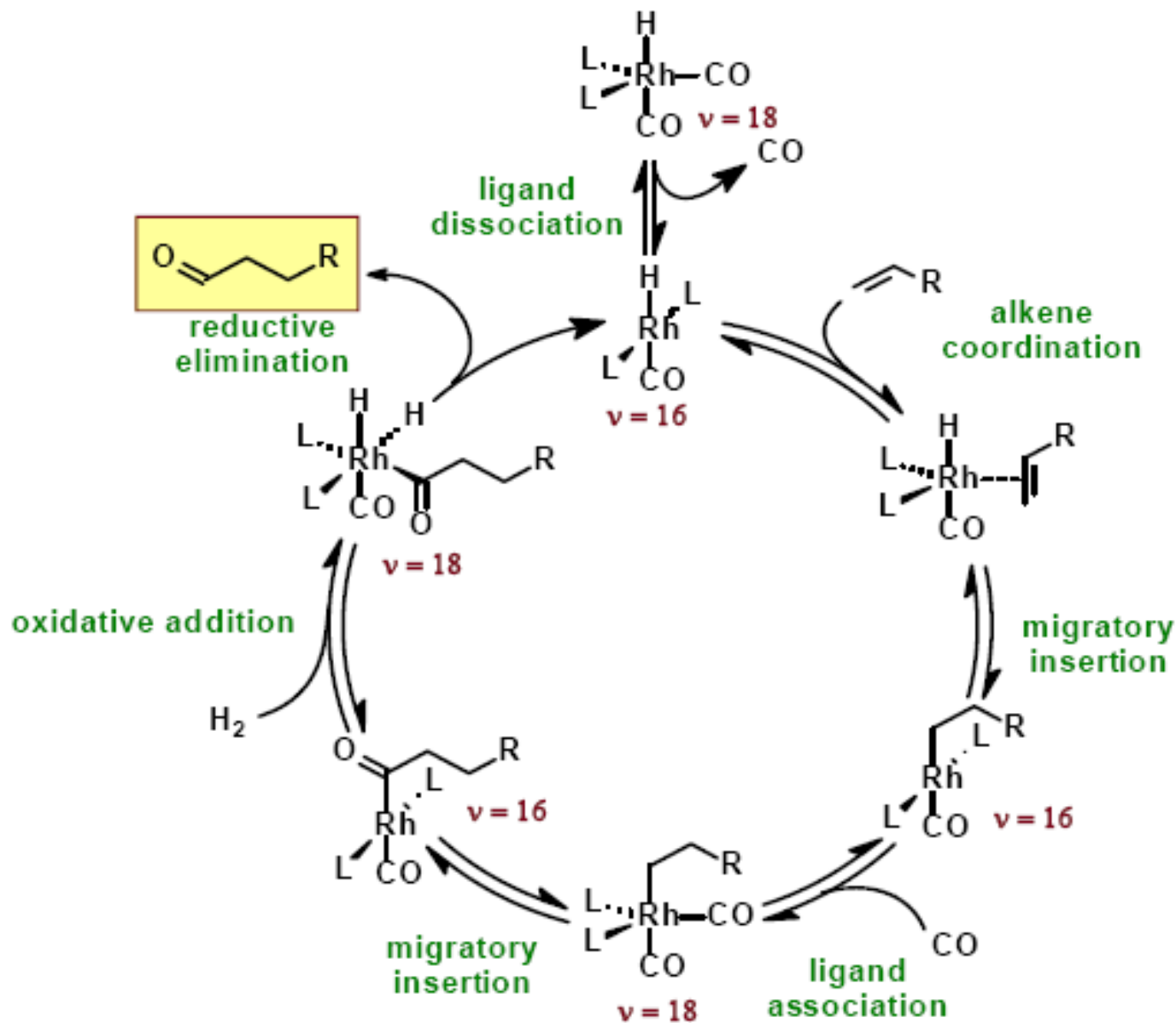
large bite angle



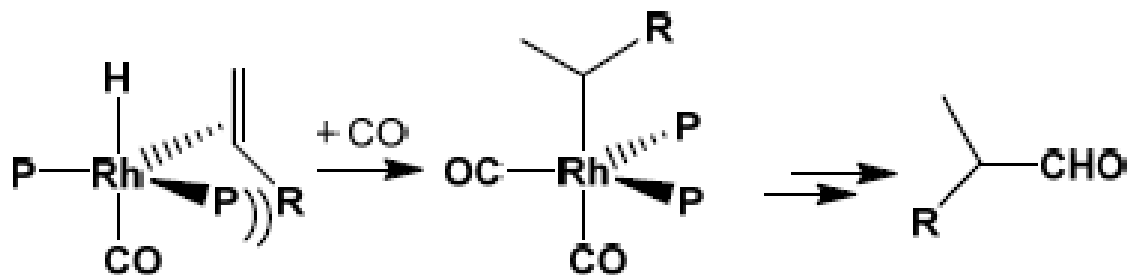
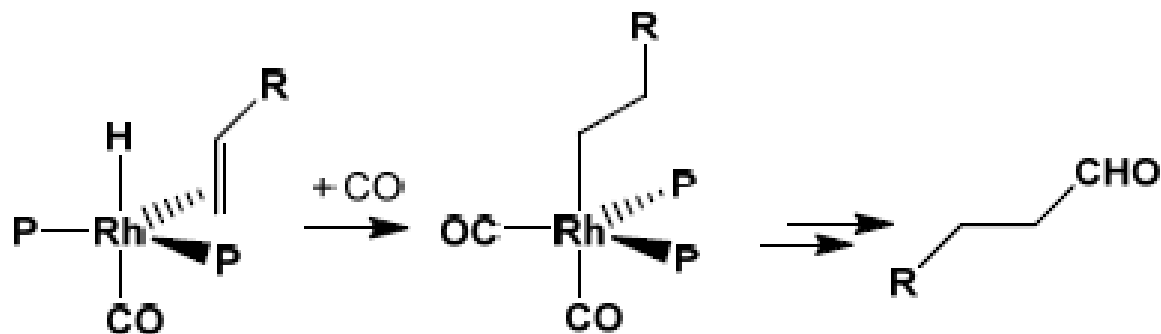
Piet van Leeuwen

T = 40°C, p = 10 bar CO/H₂ (1:1), substrate/Rh = 674, L/Rh = 2.2, [Rh] = 1.78 mM

Simplified mechanism for hydroformylation with *Rh/tpp*



Regioselectivity: steric effects



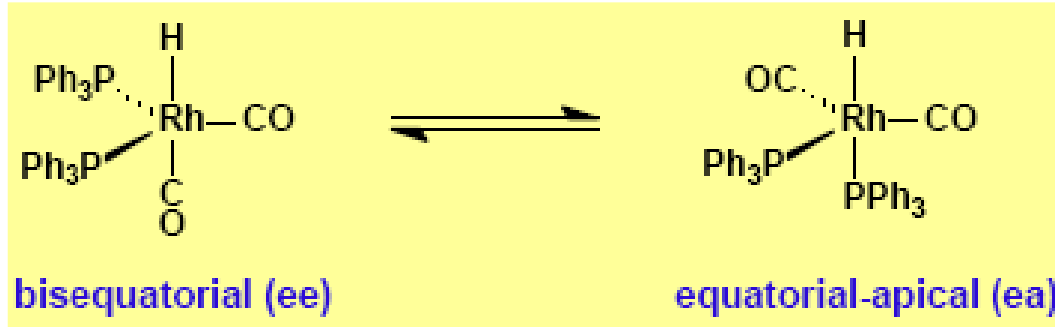
Selectivity in linear aldehyde increases:

- on increasing the Tolman cone-angle of phosphine;
- moving from phosphines to bulky phosphites.

If the Tolman cone-angle is too large, only one P is on Rh: the reaction is fast, but isomerization takes place.

Rhodium-phosphine

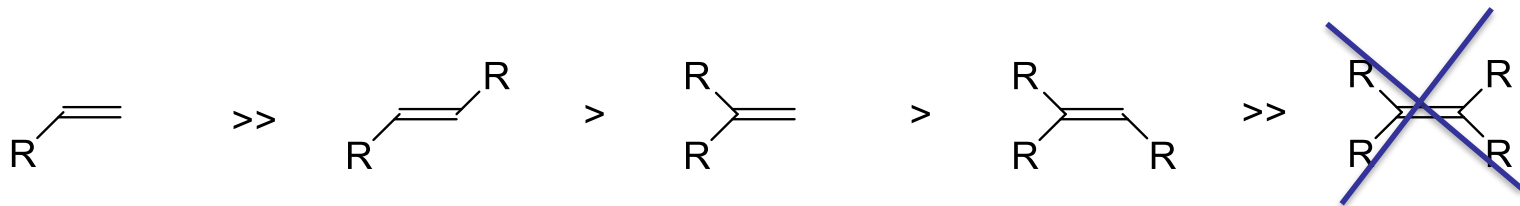
Alkylphosphines: stronger donors, stabilize Rh-CO bond, very SLOW reactions.



Smaller arylphosphines give more stable catalysts, which are less reactive and give less linear product (equil. hand side);

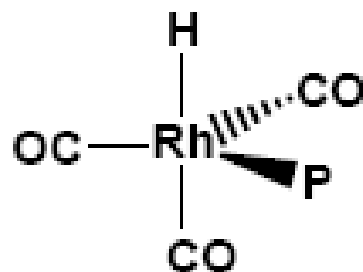
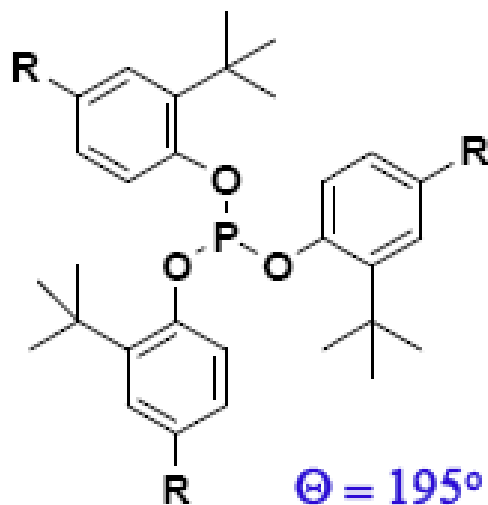
Larger arylphosphines give more linear product (equil. left hand side);

Effect of the alkene



Rhodium-phosphite

Large acceptor-type ligands: lead to unstable catalysts $[\text{RhH}(\text{CO})_3(\text{P})]$, which are highly reactive. Only one phosphite on Rh due to space limitation.



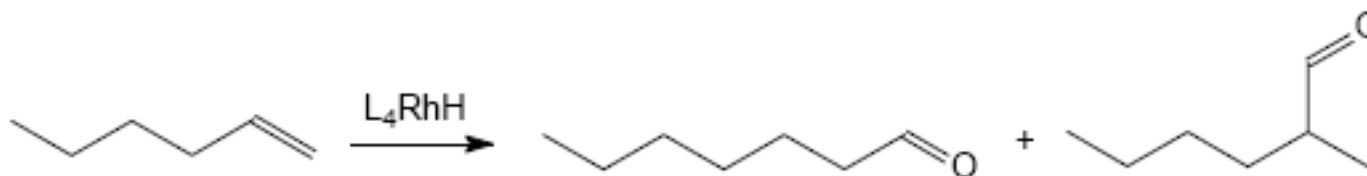
**This complex may
easy loose CO.**

Effect of the alkene

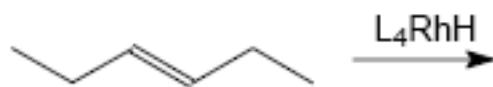
Extremely fast hydroformylation for **1-alkenes** with high selectivity in the linear product;

Fast hydroformylation of **2-alkenes** and **other internal alkenes**.

Other examples of hydroformylations catalysed from Rh: effect of phosphine

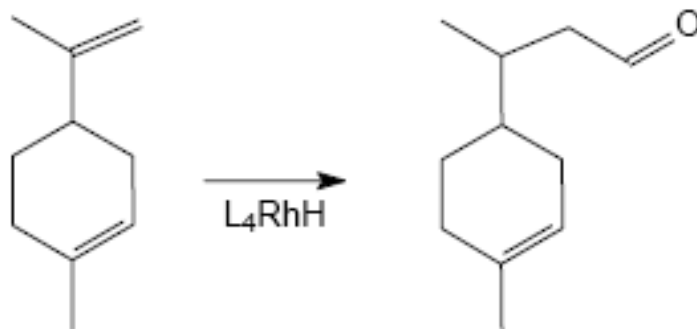


Linearity 40-96% depending on L



8% linear if L = $P(OEt)_3$

62% linear if L = $P(OCH_2CF_3)_3$



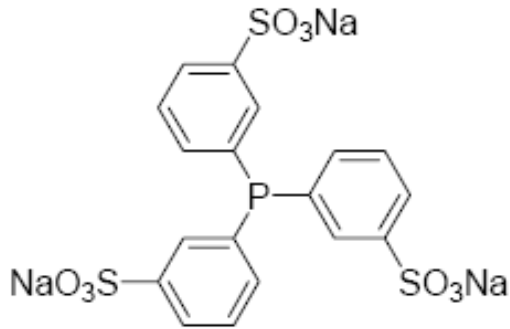
BASF, L = PPh_3

700 bar, 120 °C

L = bulky phosphite,

10 bar, 80 °C

The Ruhrchemie/Rhone-Poulenc process



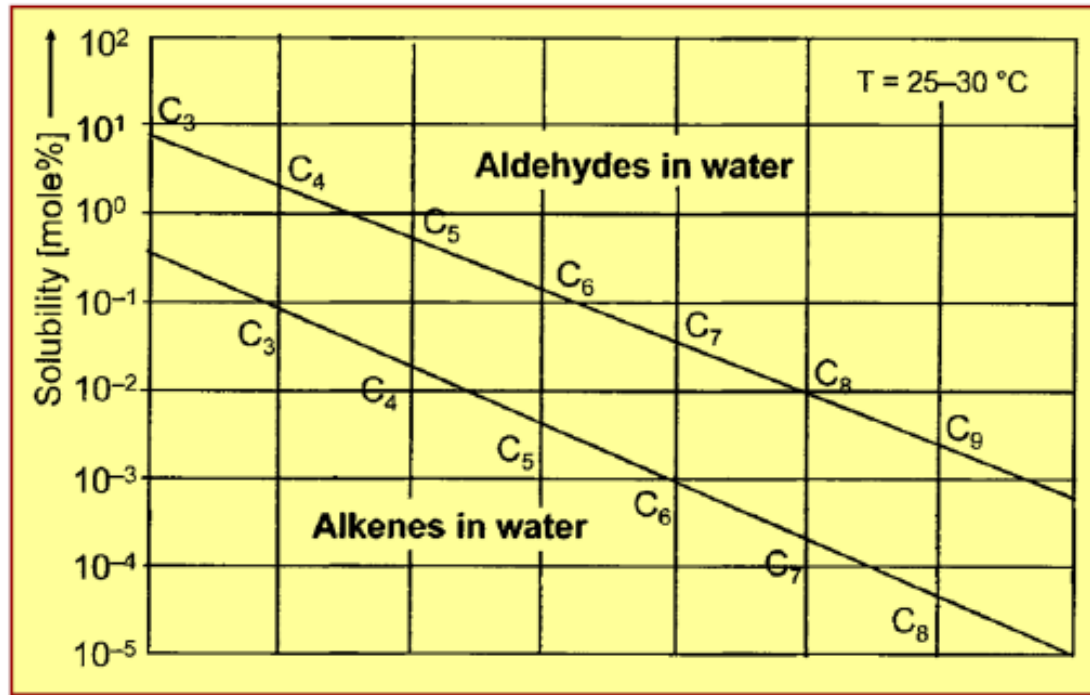
Ruhrchemie-Rhone Poulenc 1986

Propene and 1-butene

Same chemistry as tpp

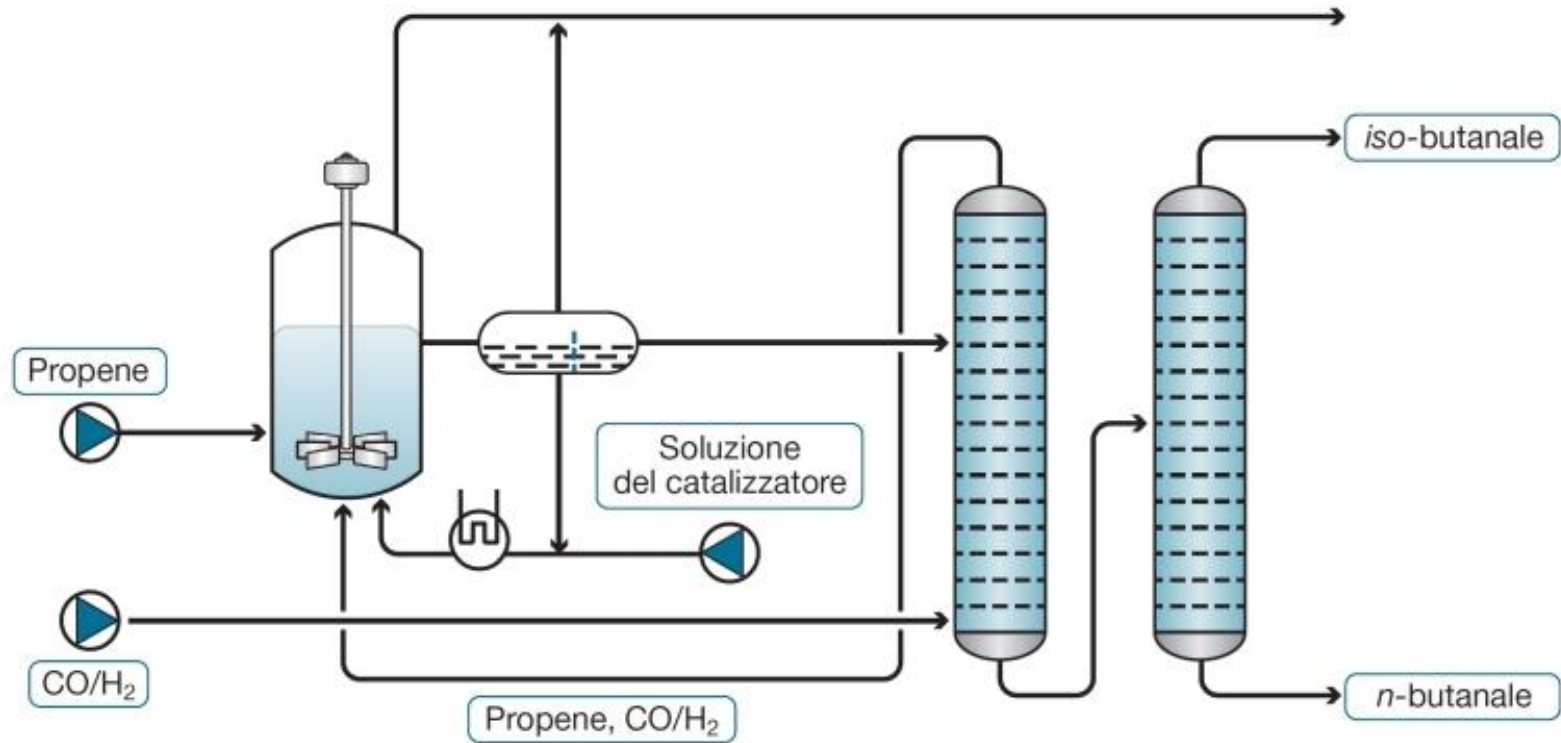
Solubility: 1 kg of ligand in 1 kg of water!

Solubility of alkenes and aldehydes in water

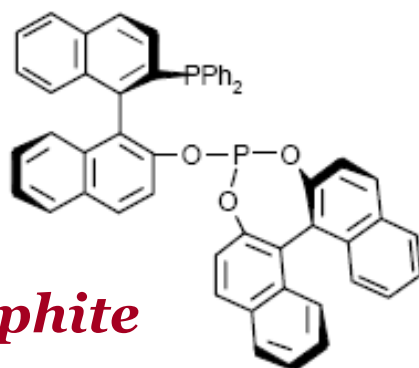
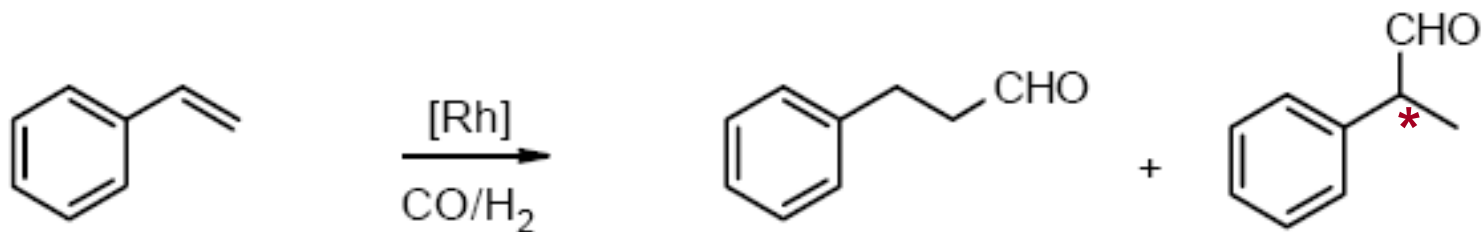


Solubility of higher alkenes is too low for efficient conversion in water .

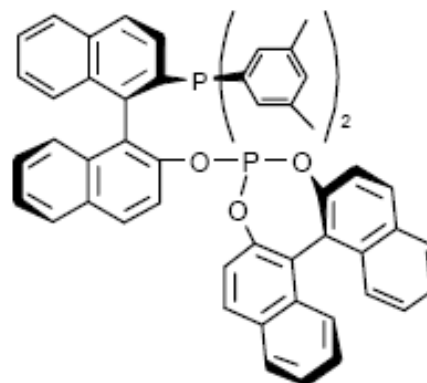
Flow-scheme for *Ruhrchemie/Rhone-Poulenc process*



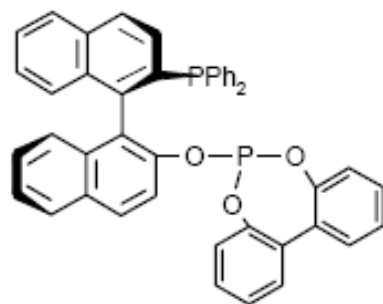
Asymmetric hydroformylation



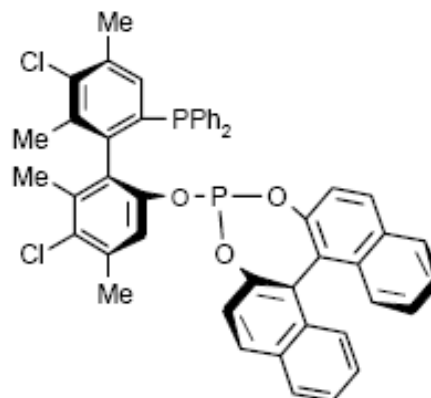
46 (R,S)-BINAPHOS



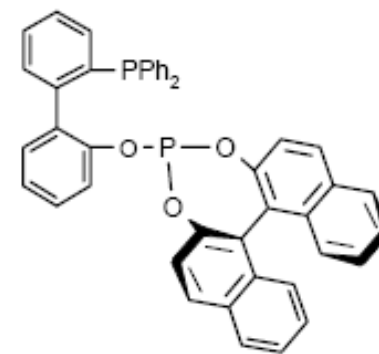
47 (R,S)



48(R)



49a (S,R)
49b (R,R)



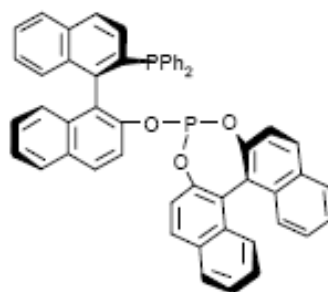
50 (R)

Phosphine-phosphite ligands

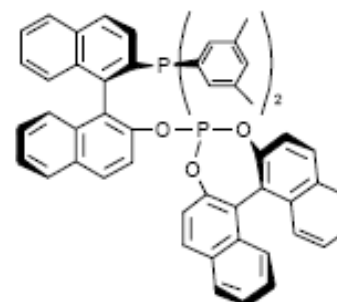
Phosphine-phosphite ligands

Reaction conditions: $T = 60 - 80\text{ }^{\circ}\text{C}$, $P_{\text{TOT}} = 100\text{ bar}$.
Conversion $> 99\%$; b/l : $86 - 92\%$.

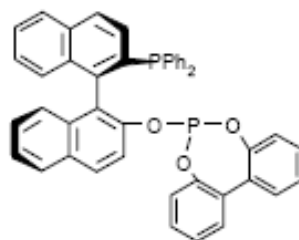
Ligand	% e.e.
46 (S,R)	94 (S)
46 (R,R)	25 (R)
47 (R,S)	85 (R)
48 (R,--)	83 (R)
49 (S,R)	94 (S)
49 (R,R)	16 (R)
50 (--,R)	69 (S)



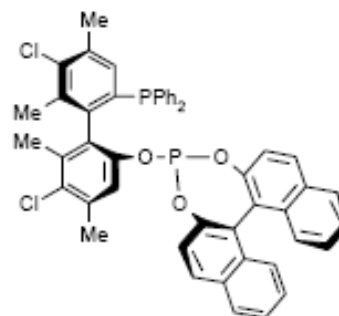
46 (R,S)-BINAPHOS



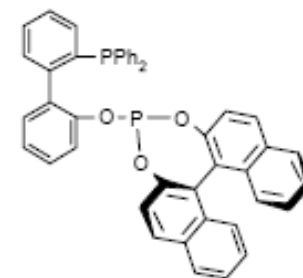
47 (R,S)



48(R)

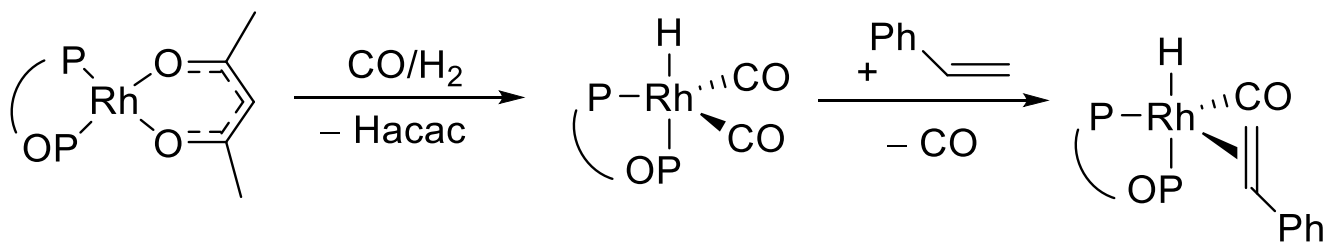
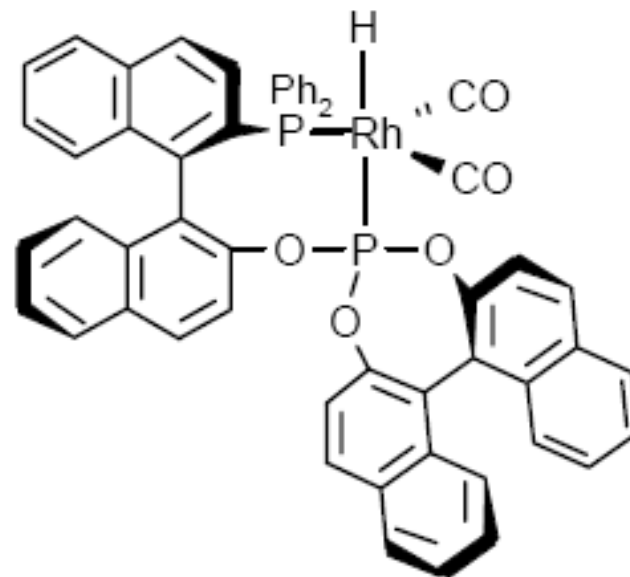


49a (S,R)
49b (R,R)

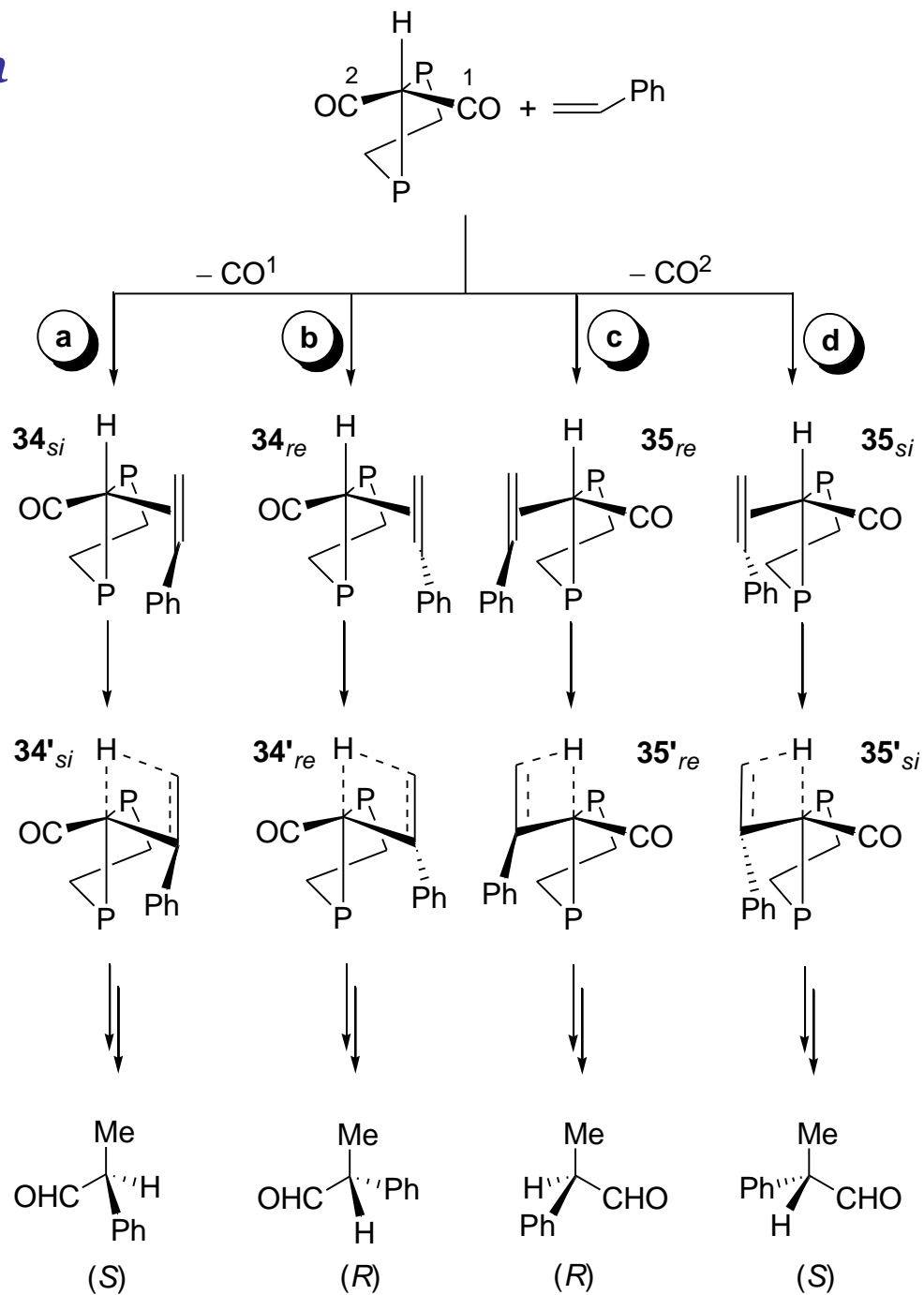


50 (R)

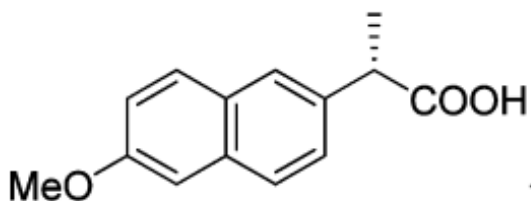
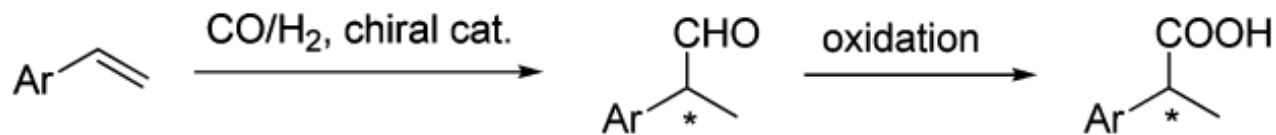
The catalytic active complex in asymmetric hydroformylation achieving high e.e.: equatorial-apical ligand coordination!



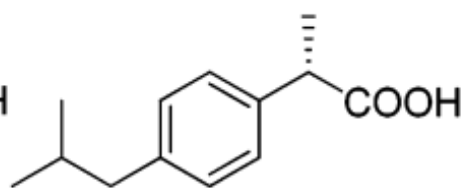
Stereodifferentiation in trigonal-bipyramidal rhodium complexes



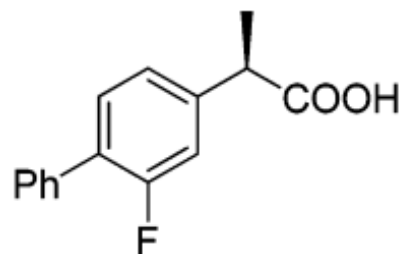
One of the possible applications of *asymmetric hydroformylation*



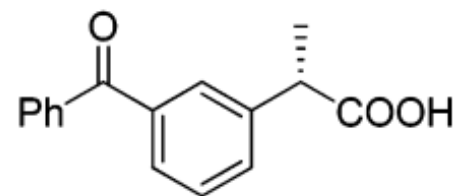
(S)-Naproxen



(S)-Ibuprofen



(R)-Flurbiprofen



(S)-Ketoprofen

Hydroformylation: Application in the synthesis of fragrances

