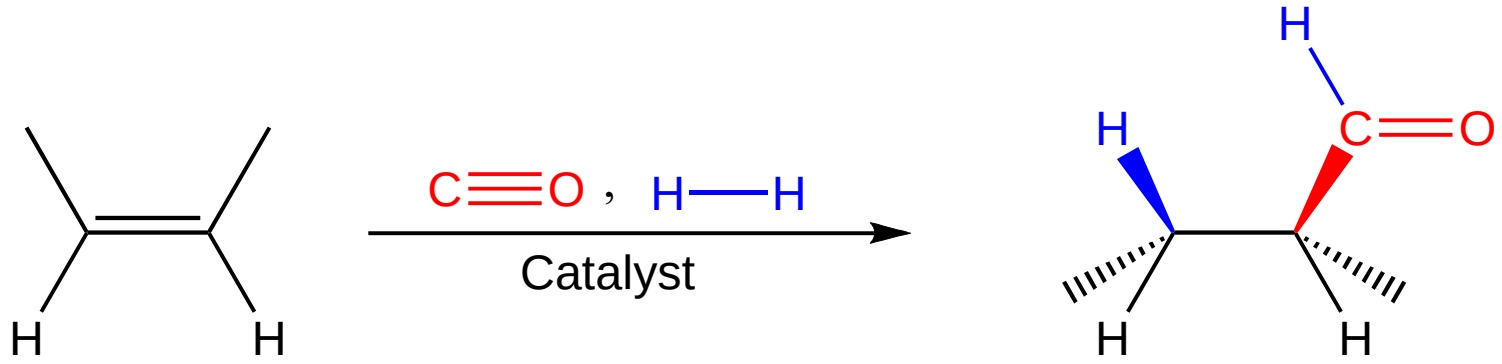
The Hydroformylation Reaction



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

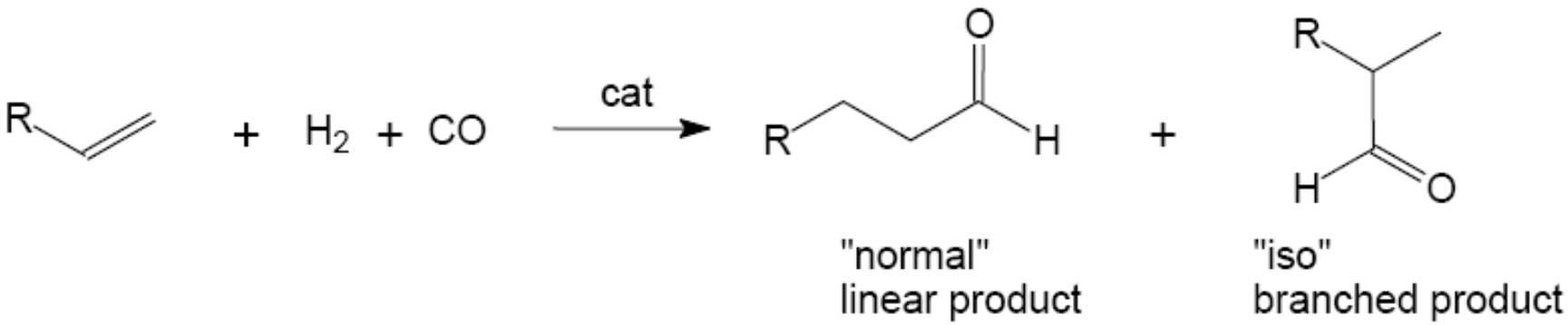
It consists in the addition of CO and H_2 to a C-C double bond, moving from an alkene to an aldehyde with one carbon atom more than the starting alkene;

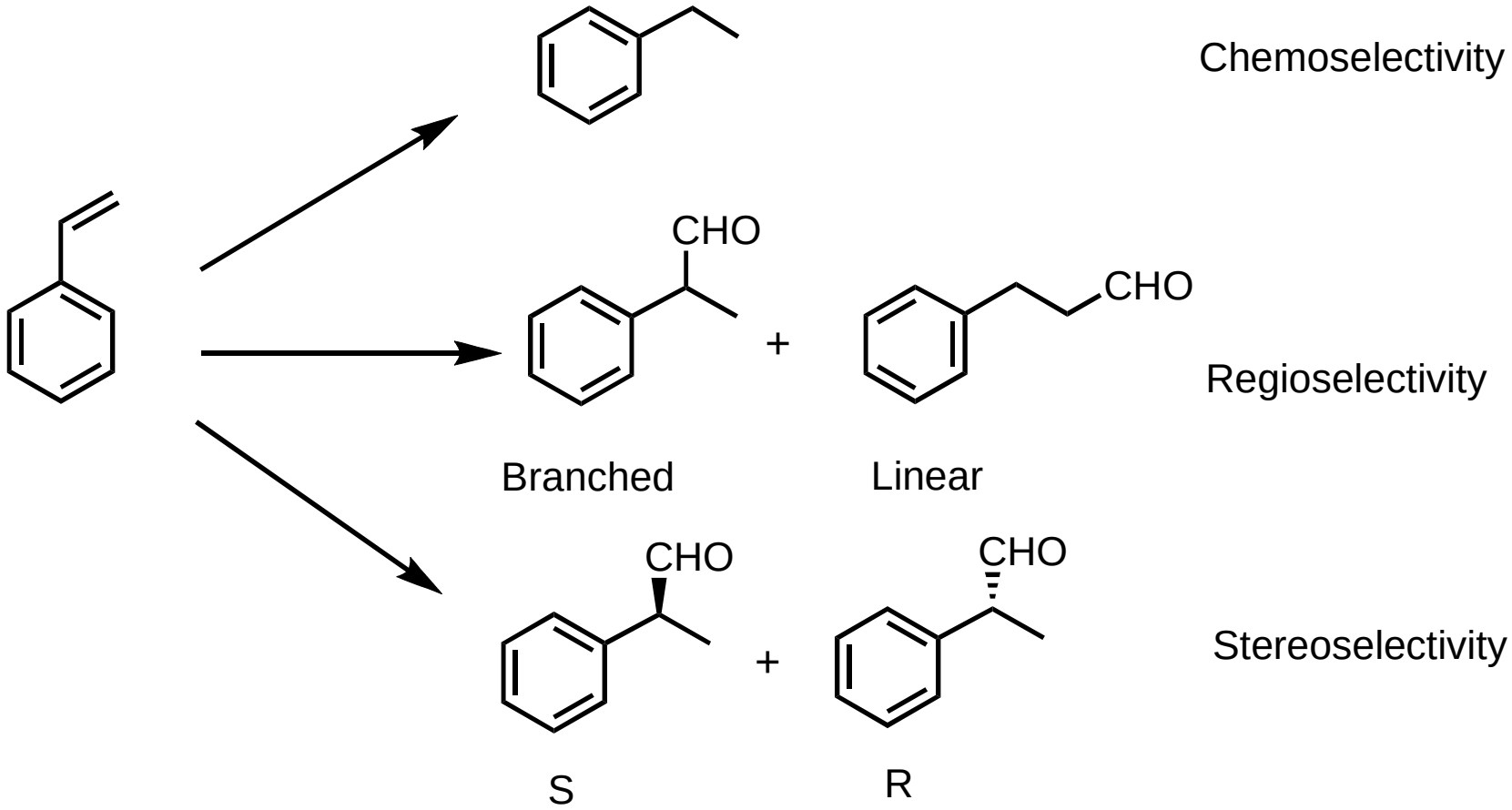
The CO/H_2 mixture is called syngas (or synthesis gas);

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 worlwide production of aldehydes was about 10.4 milions of metric tons.

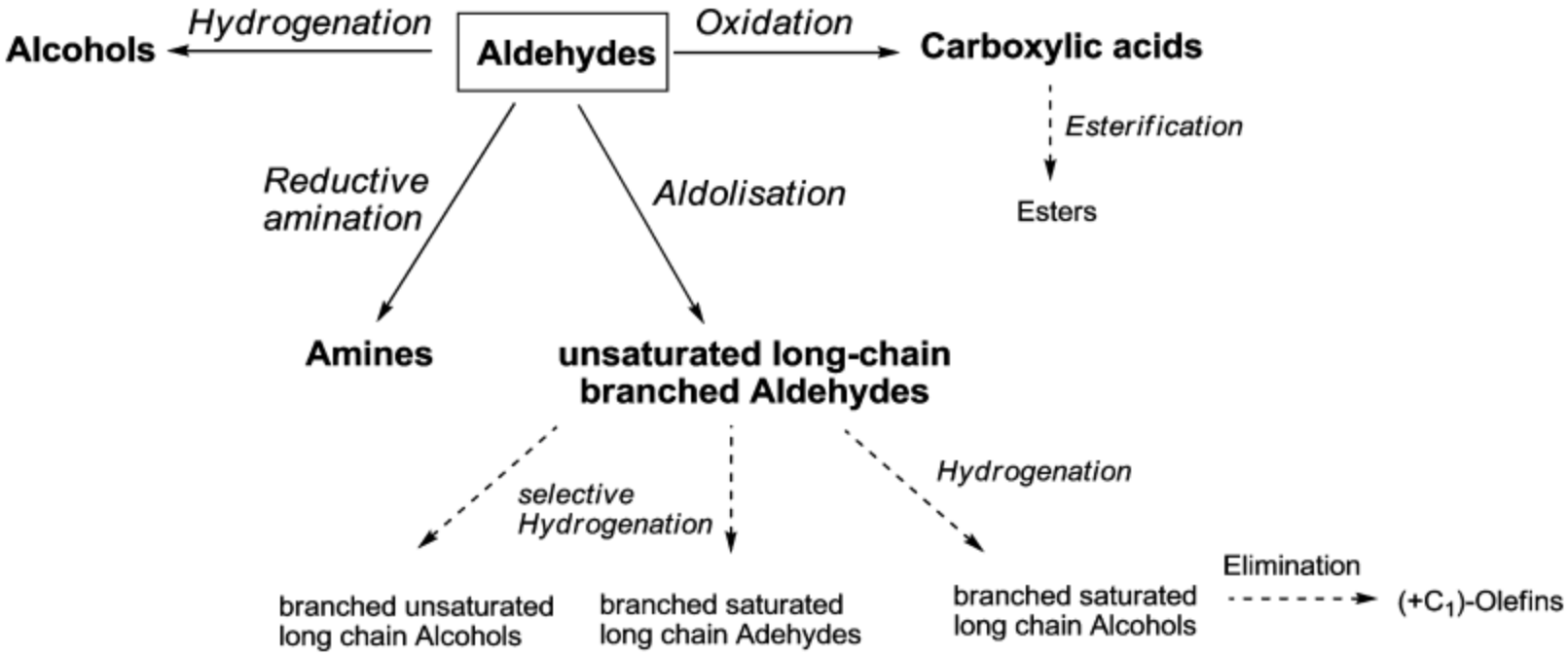
The catalysts are based on organometallic complexes of Co or Rh.

Selectivity in hydroformylation reactions





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; $HCo(CO)_x + PPh_3$
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

$H_2 + CH_3CH{=}CH_2 + CO \rightarrow CH_3CH_2CH_2C(O)H$

ΔG	63	-138	-117 (l) =	-42 kJ.mol^{-1}
ΔH	21	-109	-238 =	-150 kJ.mol^{-1}

$H_2 + CH_3CH{=}CH_2 \rightarrow CH_3CH_2CH_3$

ΔG	63	-25	= -88 kJ.mol^{-1}
ΔH	21	-105	= -126 kJ.mol^{-1}

Cobalt catalysed processes

Homogeneous Catalyst: $[CoH(CO)_4]$

Reaction conditions: T = 100 – 200 °C

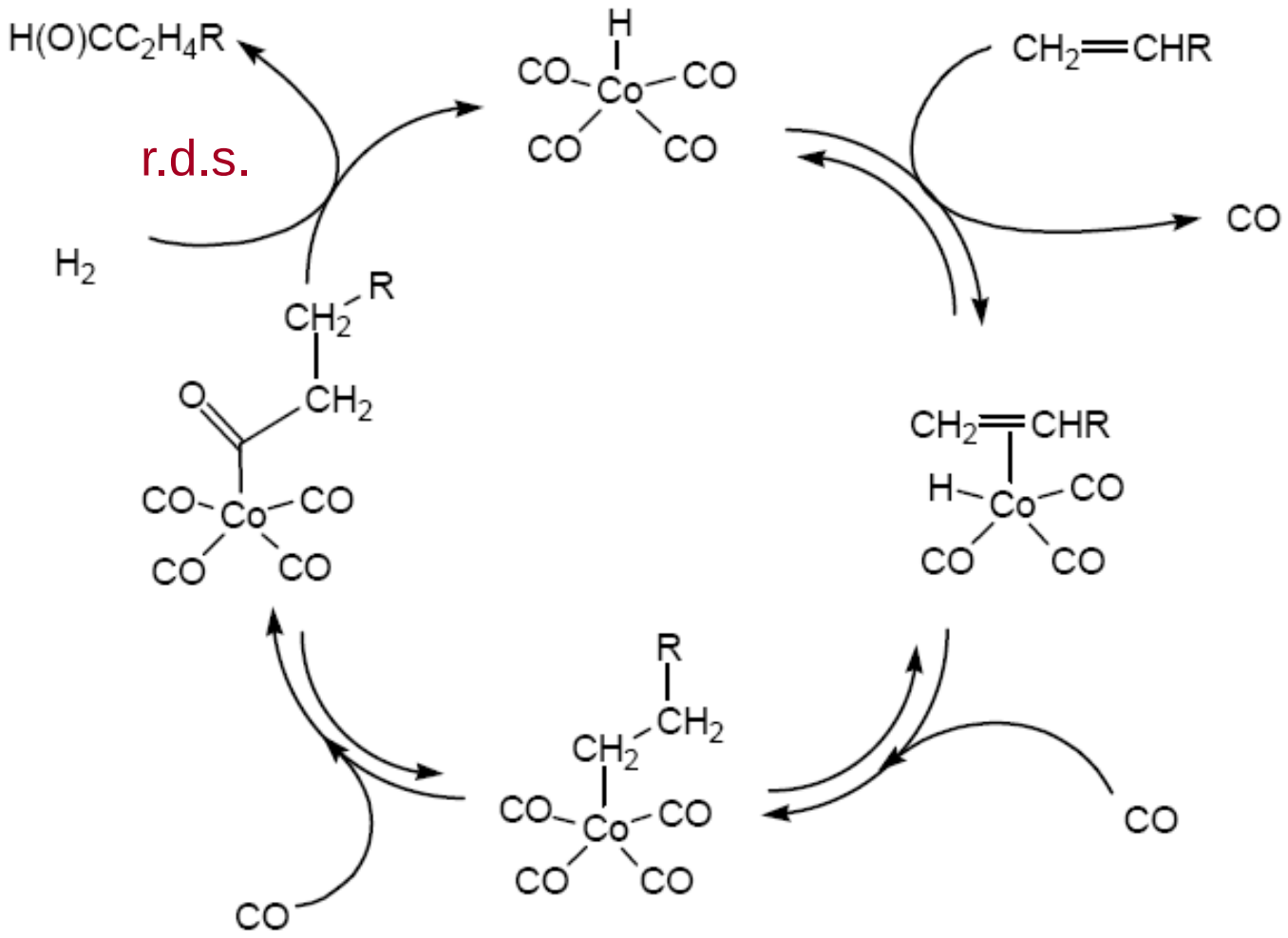
P_{tot} = 200 – 300 atm

$$v = k\,[Co][alkene][H_2][CO]^{-1}$$

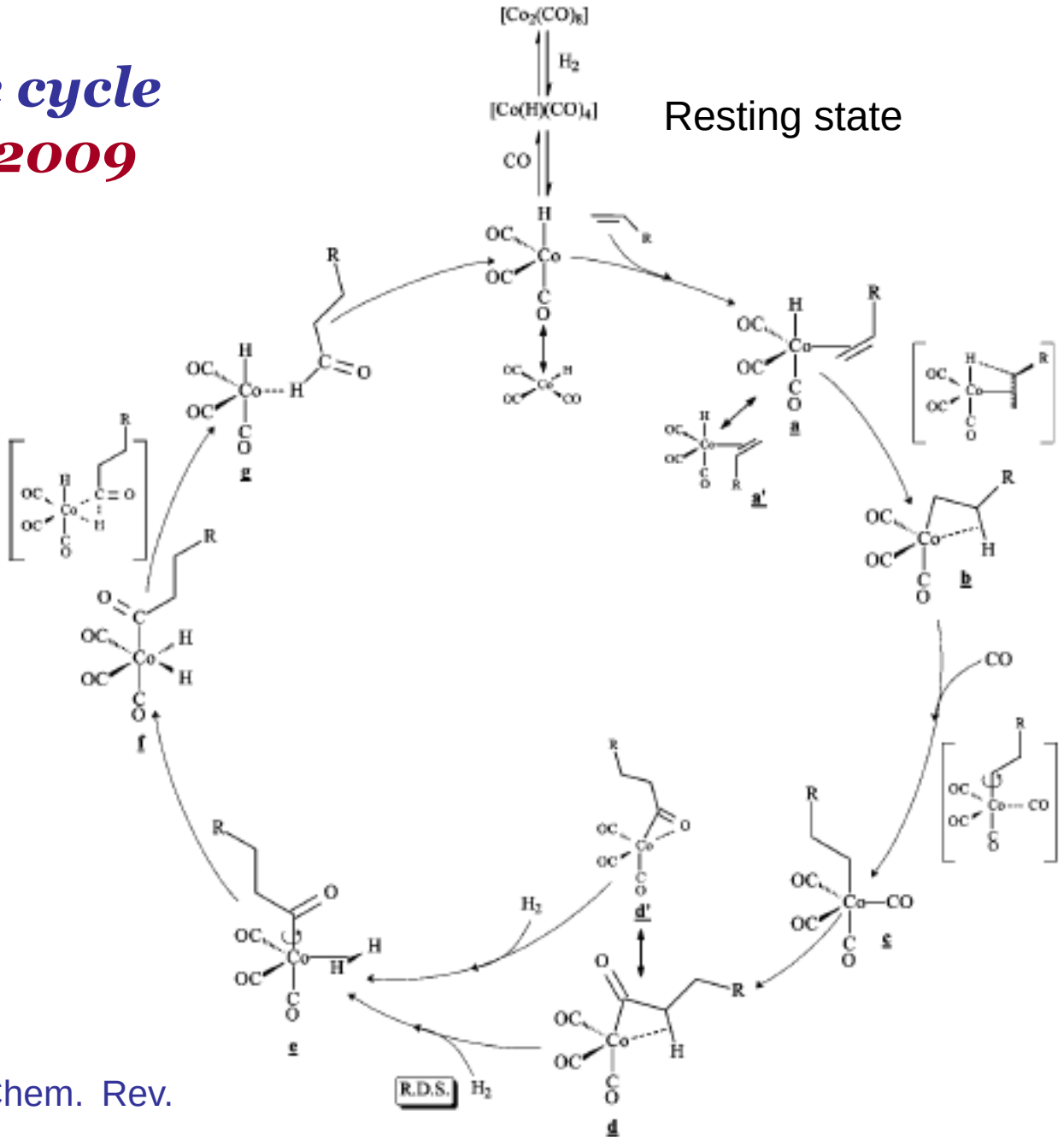
Scientifically it is interesting to understand how the ratio of linear and branched product can be influenced and maximised by varying the ancillary ligands and the kinetic of the reaction.

$[CoH(CO)_4]$ 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

$[CoH(CO)_4]$ is the catalyst industrially applied.

Remarks:

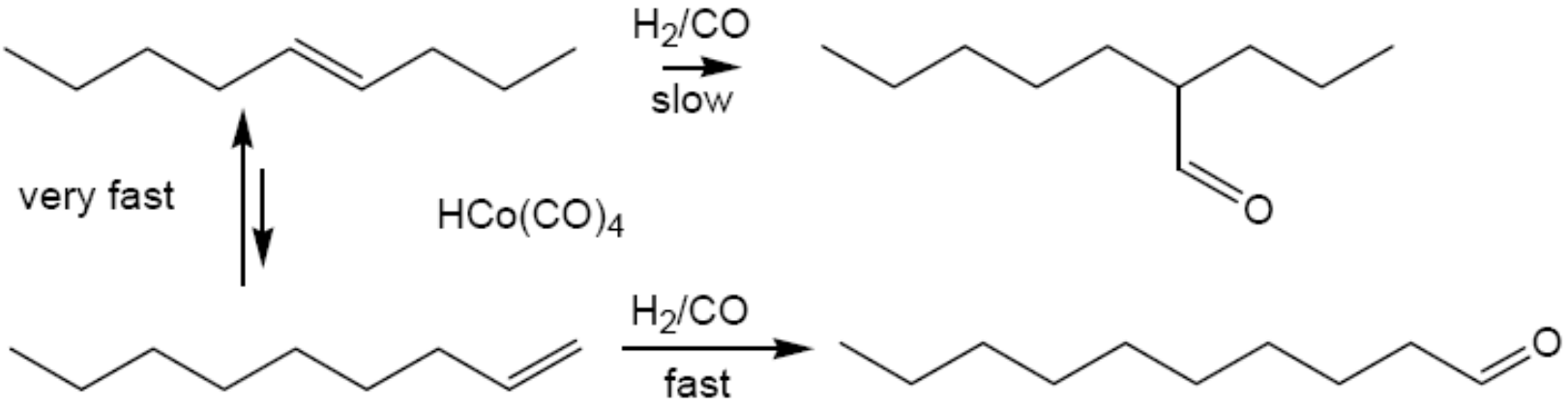
1. The higher alkene feed C_{10-14} is essentially made of internal alkenes;
2. The linear aldehyde is the desired product with an acceptable selectivity around 60 – 80%.

Experimental data:

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

Hydroformylation of higher alkenes

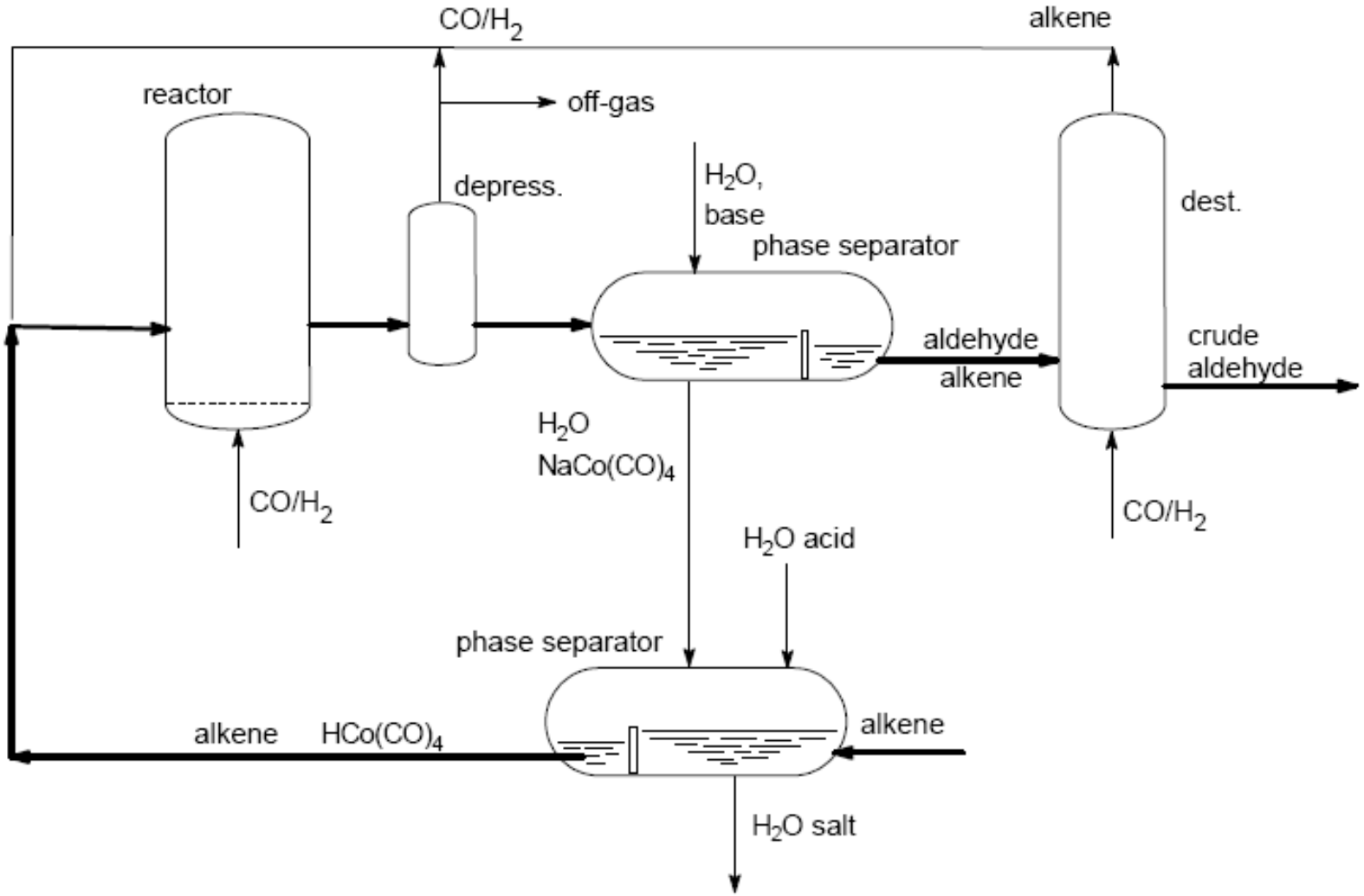
$[CoH(CO)_4]$ is the catalyst industrially applied.



Rate constants for the hydroformylation of selected alkenes

Alkene	$k / \times 10^{-5}\ s^{-1}$
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 ricycling



The Shell process

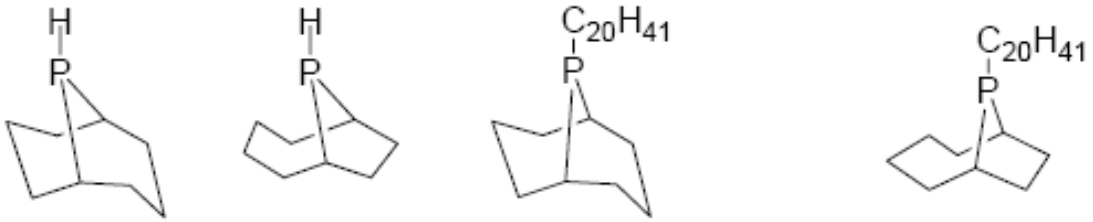
Introduction of catalysts based on phosphines: $[CoH(CO)_3(PR_3)]$.

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, $[CoH(CO)_3(PR_3)]$, is much more stable than $[CoH(CO)_4]$;
4. The catalyst results to be active also in the hydrogenation reaction.

Cat. Prec.	P (bar)	T (°C)	Pr.	lin. (%)	Cat. act.	alkanes (%)
$[CoH(CO)_4]$	200 – 300	100 – 180	ald.	70	5 (145°C)	1
$[CoH(CO)_3(PR_3)]$	25 – 100	100 – 200	alc.	90	1 (185°C)	15

Examples of tested monophosphines



phobane mixture

Examples of applied cobalt complexes

$Co_2(CO)_8$ $HCo(CO)_4$ $Co_2(CO)_6L_2$ $HCo(CO)_3L$

Effect of the phosphine on activity

$Ph_2EtP > PhBu_2P > Bu_3P > Et_3P > PhEt_2P > Cy_3P$

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

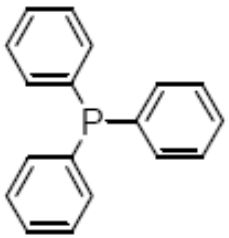
$Bu_3P > Et_3P = PhEt_2P = Cy_3P = PhBu_2P > Ph_2EtP$

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

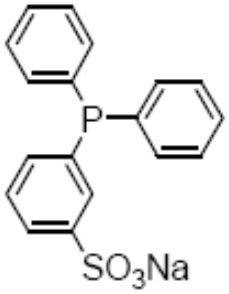
General features:

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.

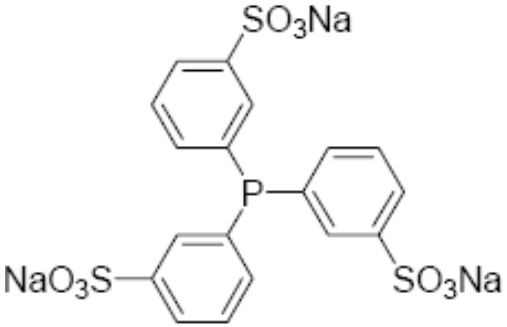
Examples of tested monophosphines and phosphites



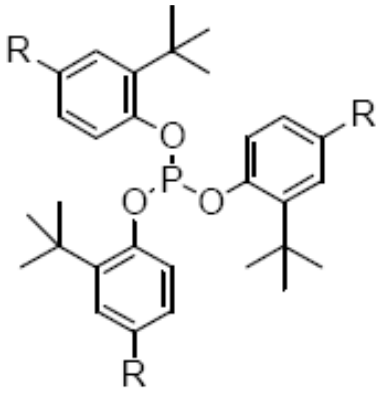
tpp



tppms



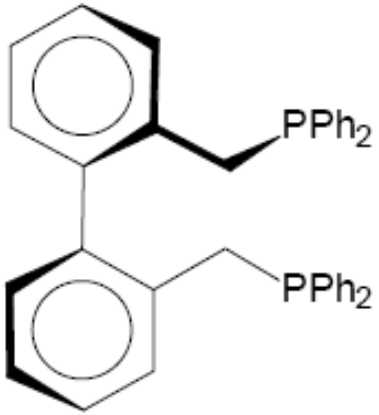
tppts



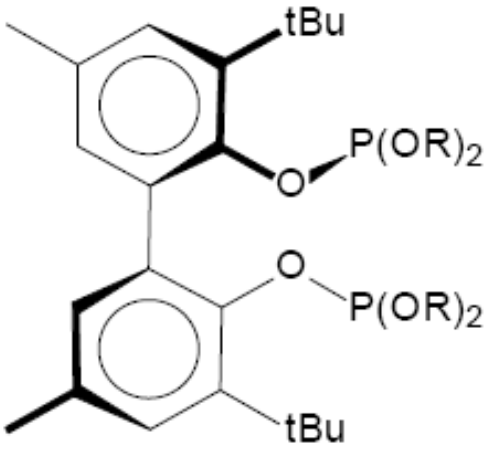
"bulky" phosphite

Cone angle = 195°

Examples of diphosphines and diphosphites

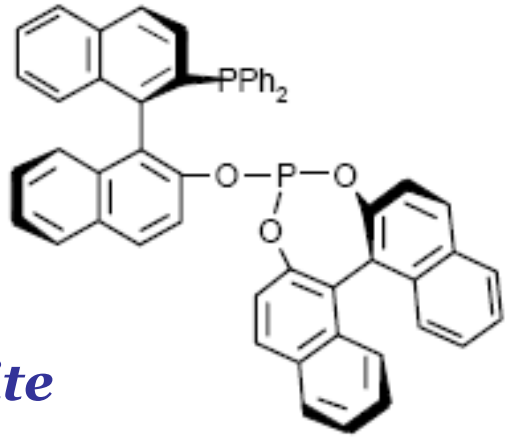


"BISBI"



general formula of diphosphite

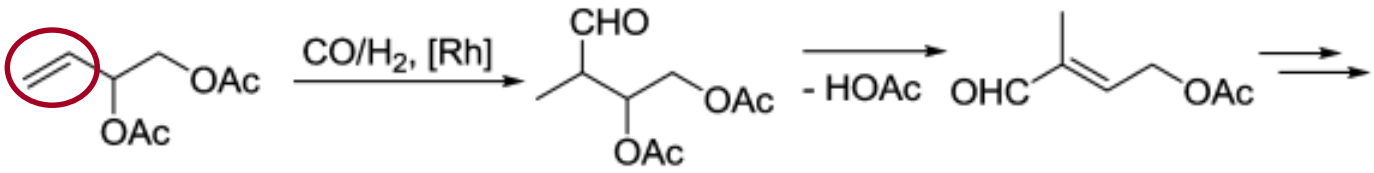
Union Carbide 1997



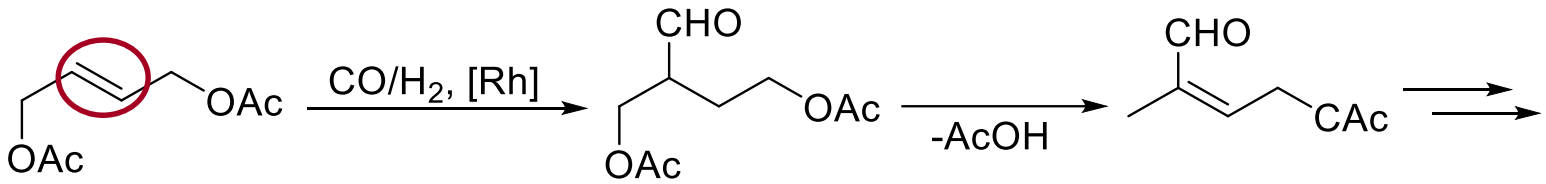
BINAPHOS: a chiral phosphino-phosphite

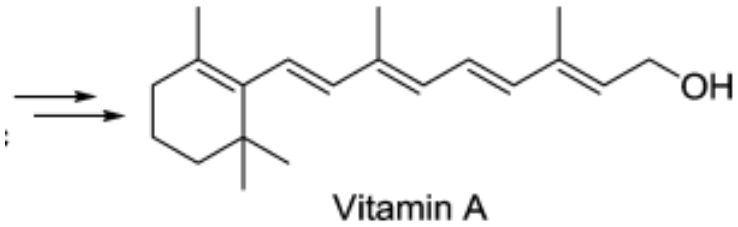
Synthetic technology for the production of Vitamin A

The BASF process



The Hoffmann-La Roche process

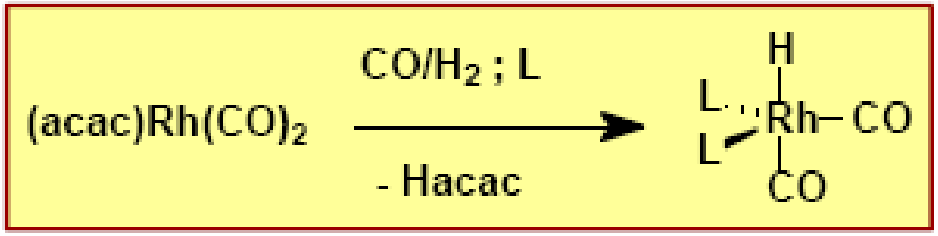




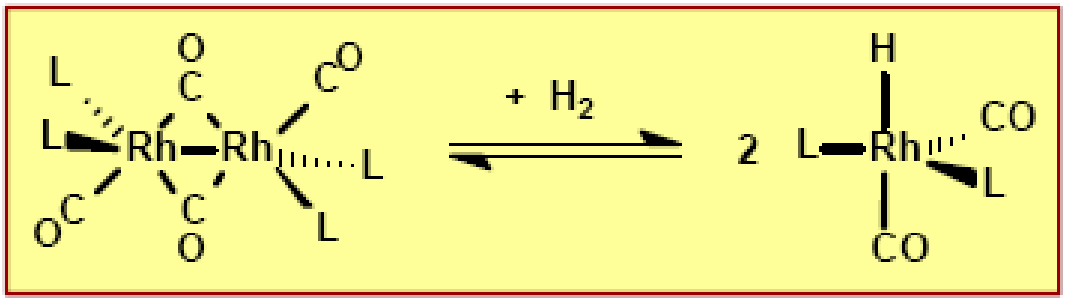
[Rh] = [$RhH(CO)_3$]

The Rh/tpp system

in situ catalytic system



Inactive species



The kinetic law

$$v = k\,[\text{alkene}]^{1}[Rh]^{1}[H_2]^{1}[PPh_3]^{-1}[CO]^{-1}$$

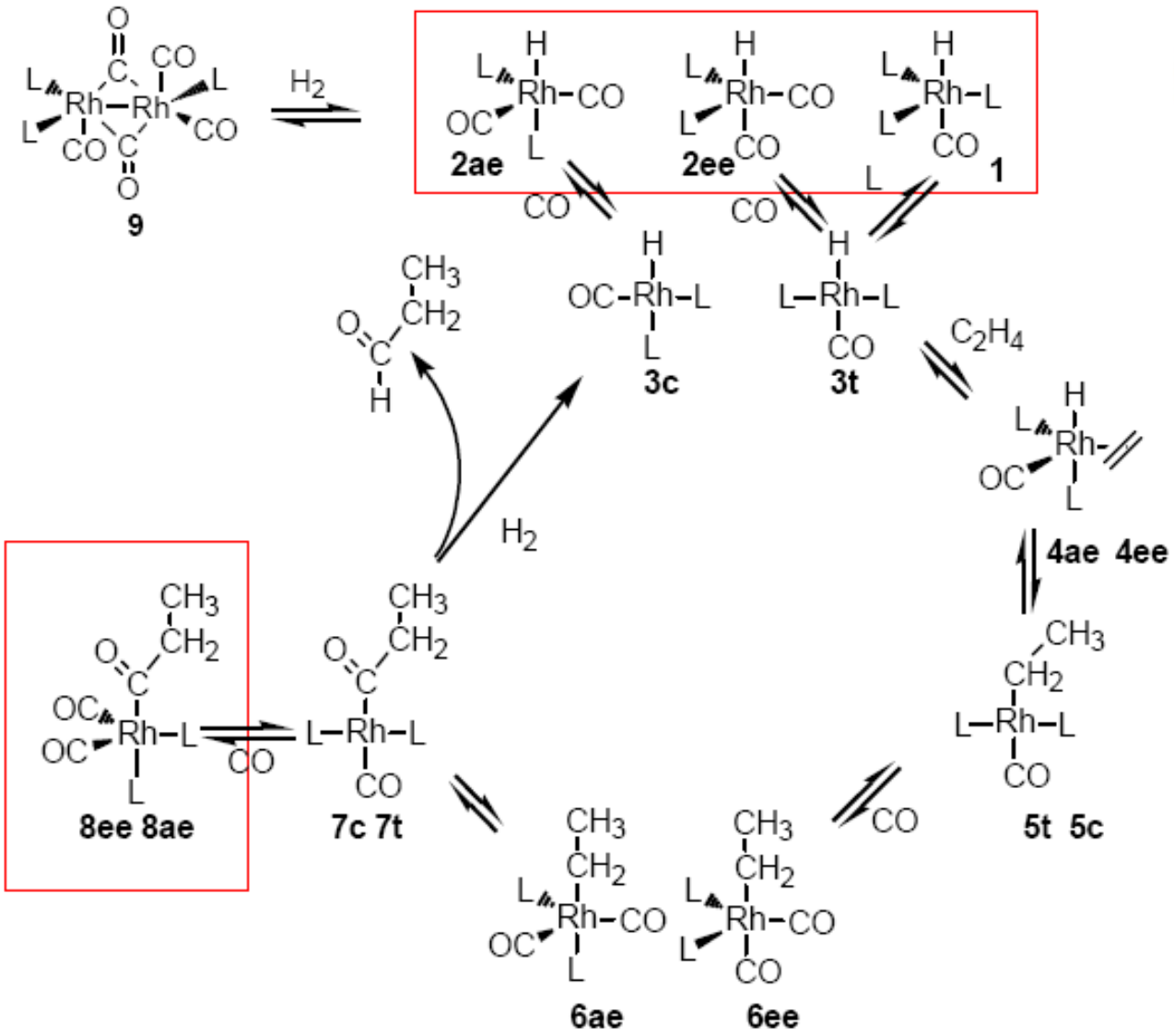
The kinetic law for the industrial synthesis of butanal

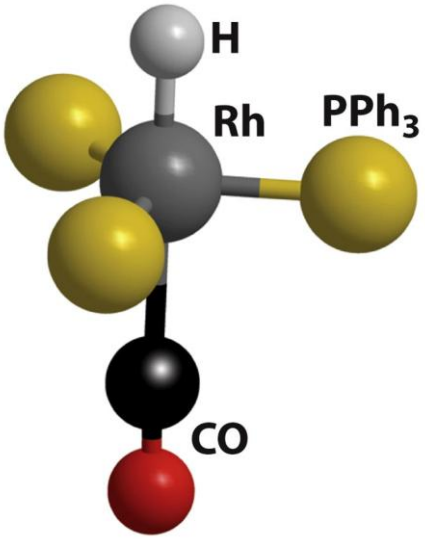
d'Oro's equation

$$V = k\,[C_3H_6]^{0.6}[Rh]^{1}[H_2]^{0}[PPh_3]^{-0.7}[CO]^{-0.1}$$

(conditions 90-110°C, 1-25 bar CO, 1-45 bar H_2, PPh_3/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 $[RhH(PPh_3)_3CO]$;
2. At low concentration of phosphine: the catalyst resting state is $[RhH(PPh_3)_2(CO)_2]$.

The rate determining step:

a. At high concentration of phosphine: the catalyst resting state is $[RhH(PPh_3)_3CO]$ 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.

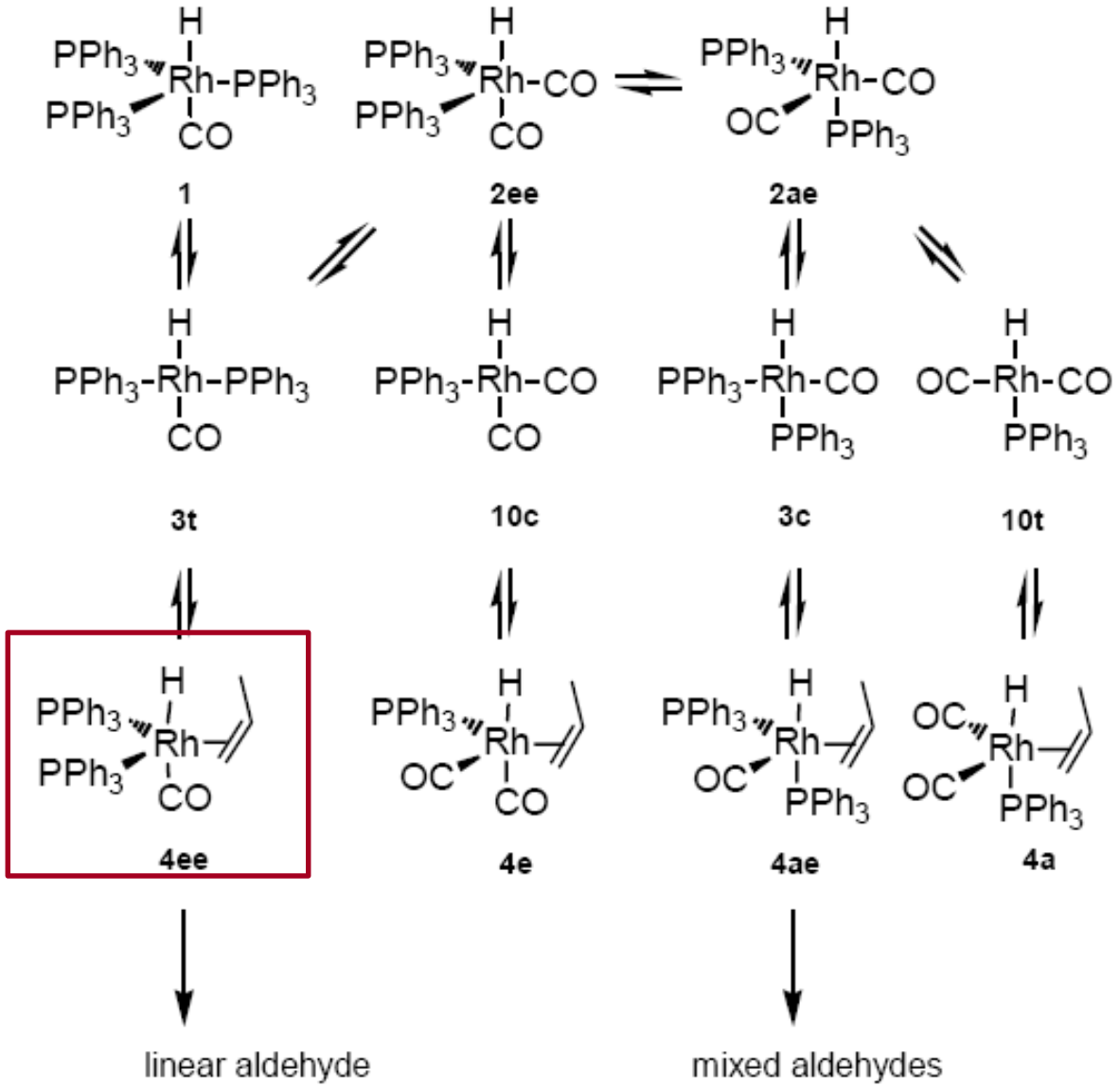
Activity: electronic effects

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;

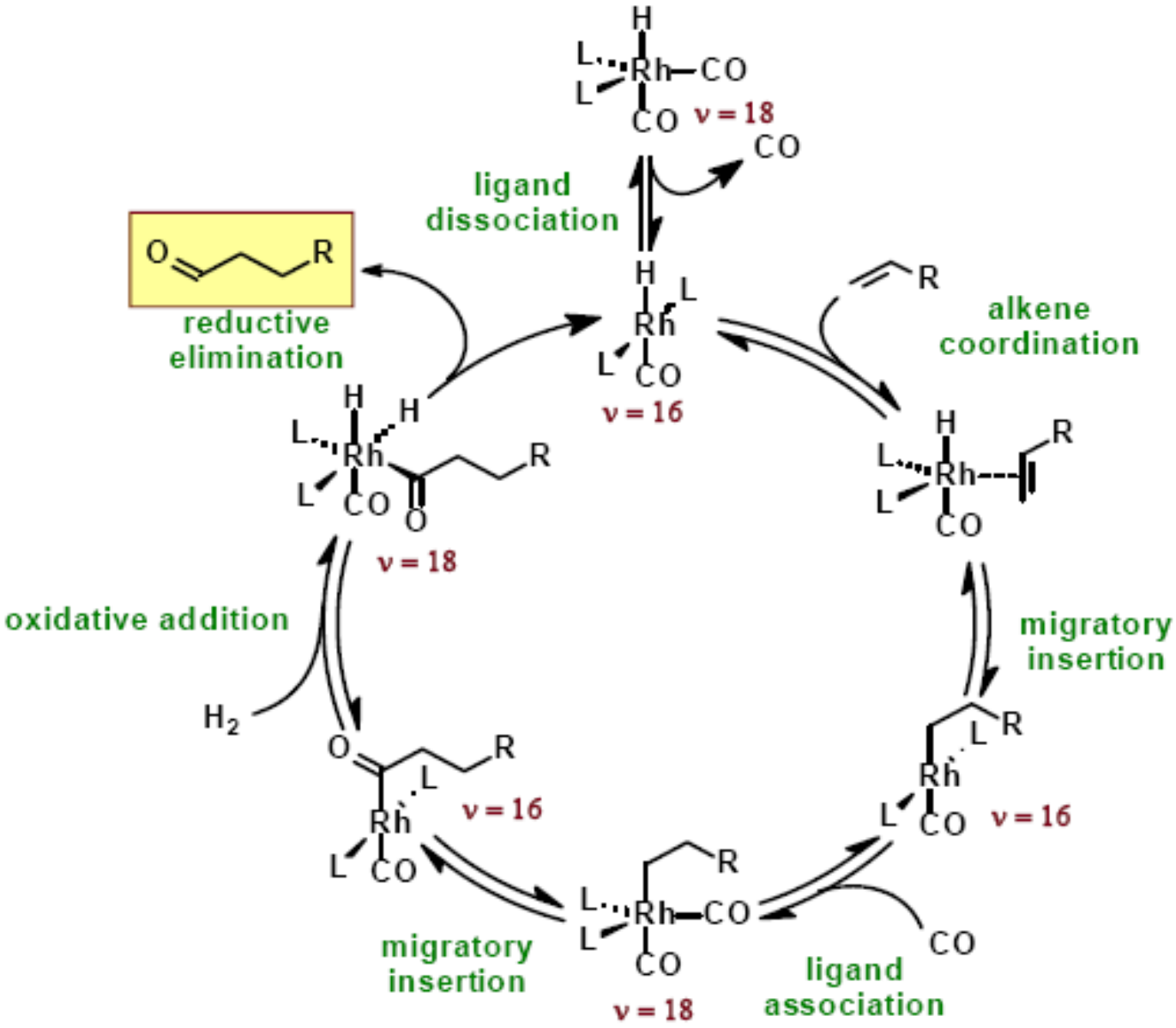
Phosphines **with a Lewis basicity higher** than tpp lead to slower catalysts;

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

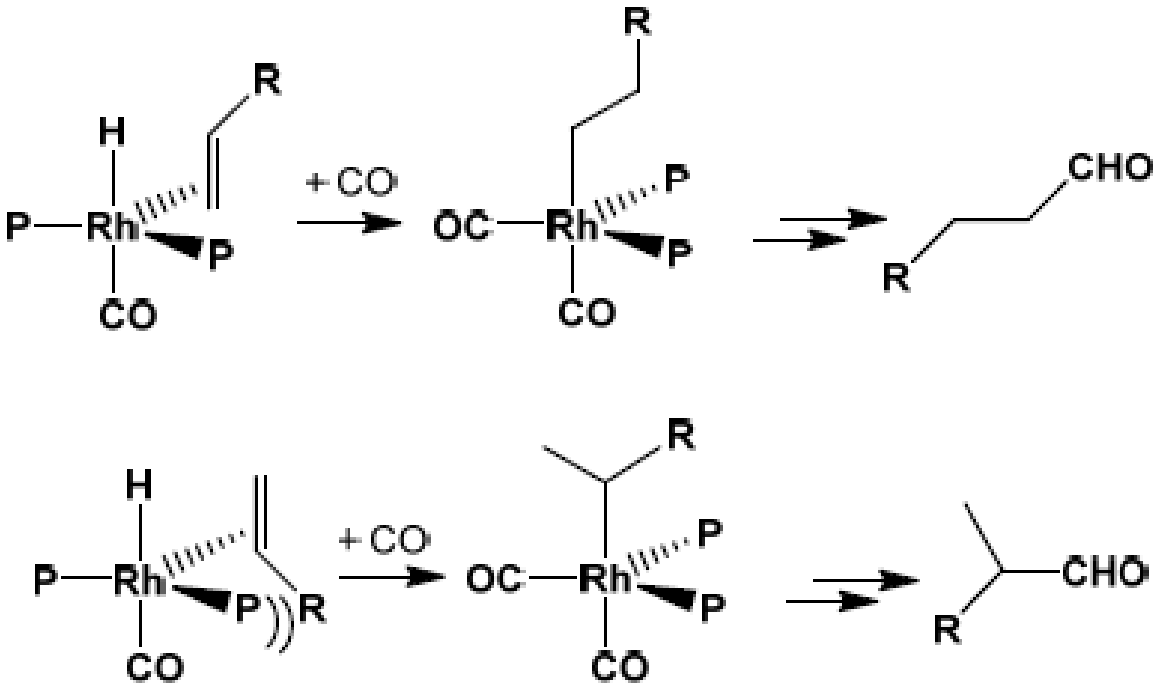
Regioselectivity



Simplified mechanism for hydroformylation with Rh/tpp



Regioselectivity: steric effects



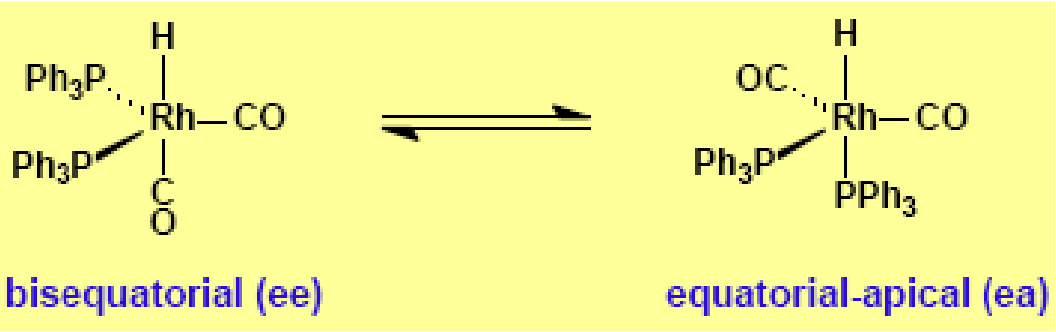
Selectivity in linear aldehyde increases:

- **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

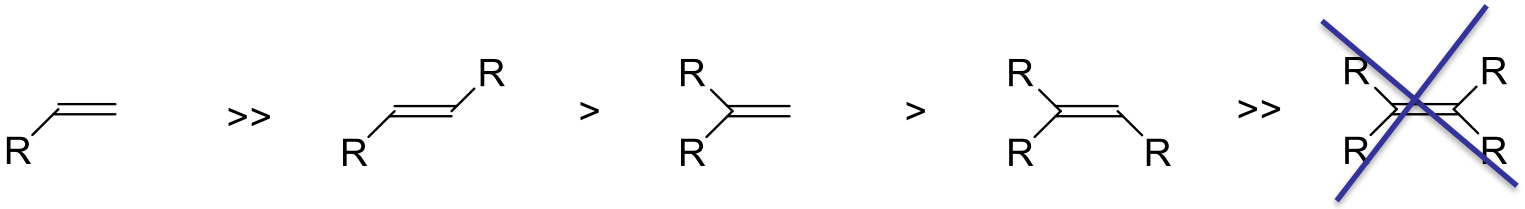
Alkylphosphines: stronger donors, stabilize Rh-CO bond, very SLOW reactions.



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

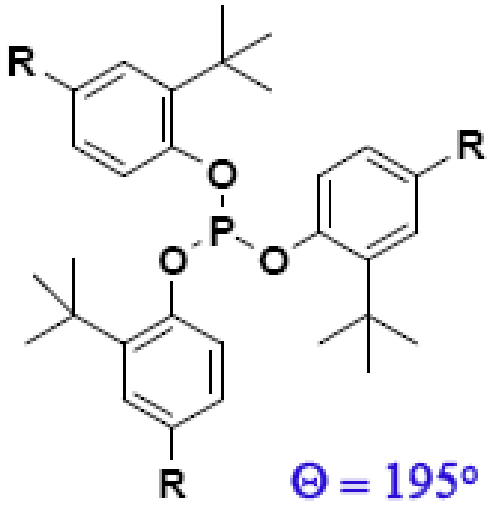
Larger arylphosphines give more linear product (equil. left hand side);

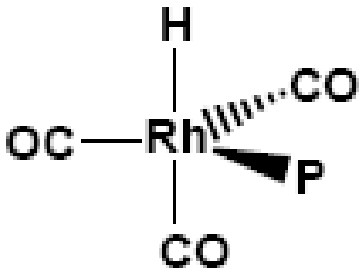
Effect of the alkene



Rhodium-phosphite

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



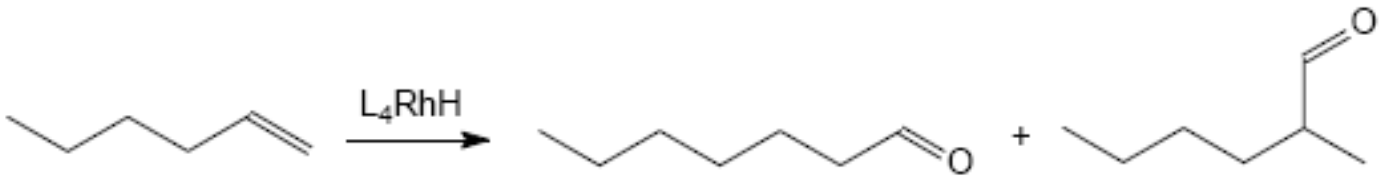


This complex may easy loose CO.

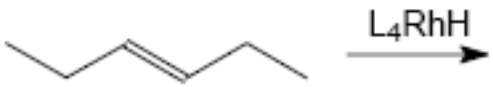
Effect of the alkene

Extremely fast hydroformylation for **1-alkenes** with high selectivty in the linear product;
Fast hydroformylation of **2-alkenes** and **other internal alkenes**.

Other examples of hydroformylations catalysed from Rh: effect of phosphine

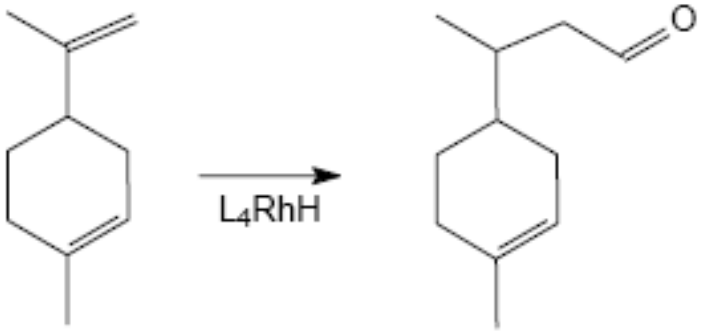


Linearity 40-96% depending on L



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

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



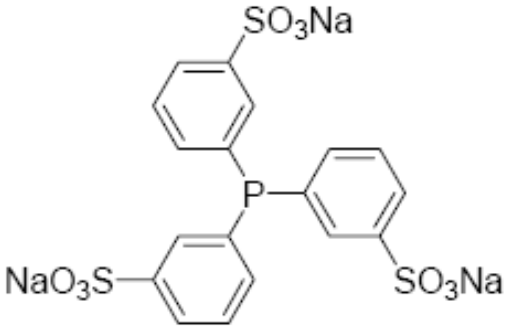
BASF, L=PPh_3

700 bar, 120 °C

L= bulky phosphite,

10 bar, 80 °C

The Ruhrchemie/Rhone-Poulenc process



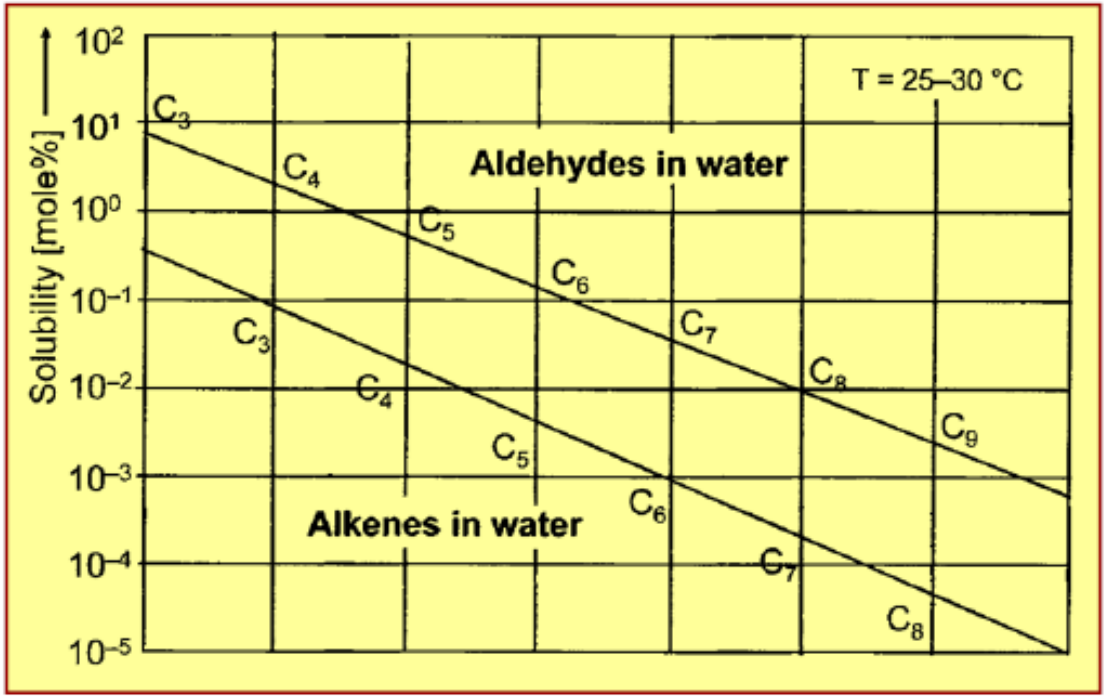
Ruhrchemie-Rhone Poulenc 1986

Propene and 1-butene

Same chemistry as tpp

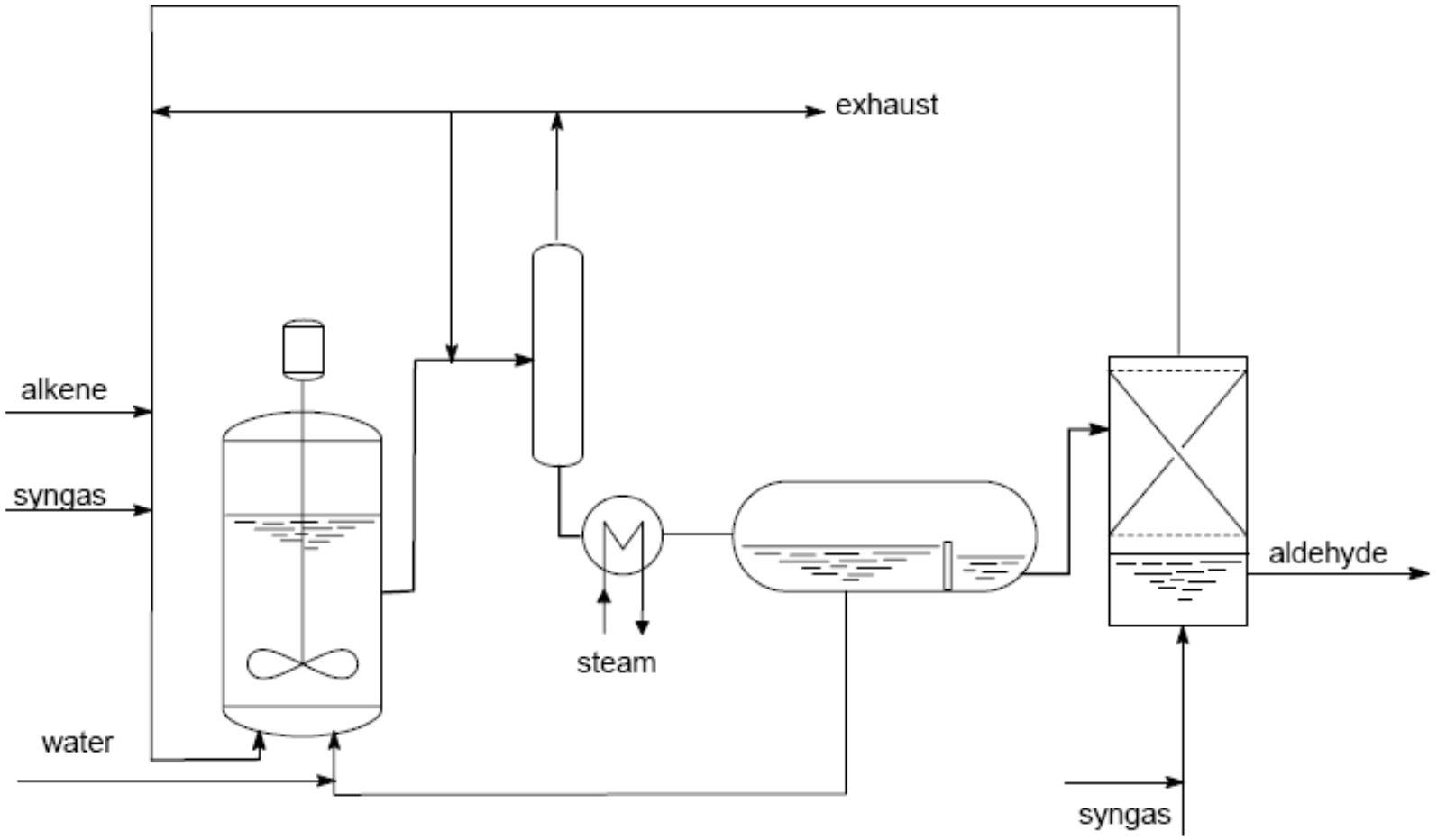
Solubility: 1 kg of ligand in 1 kg of water!

Solubility of alkenes and aldehydes in water



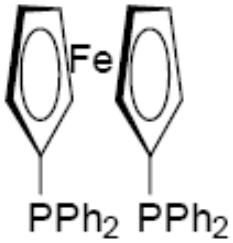
Solubility of higher alkenes is too low for efficient conversion in water .

Flow-scheme for Ruhrchemie/Rhone-Poulenc process

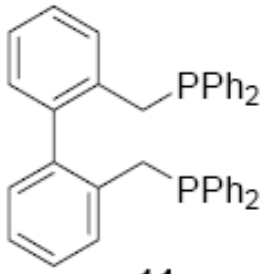


Hydroformylation with diphosphines

Ligand	Bite angle	Rate $m.m^{-1}.h^{-1}$	Ratio l: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



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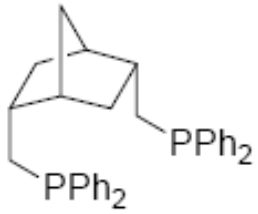

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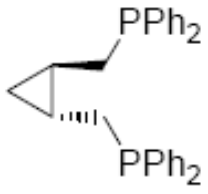
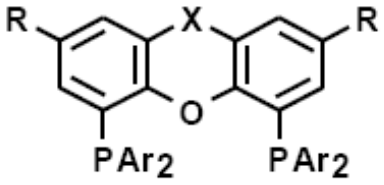


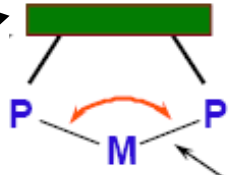
13

Hydroformylation with diphosphines

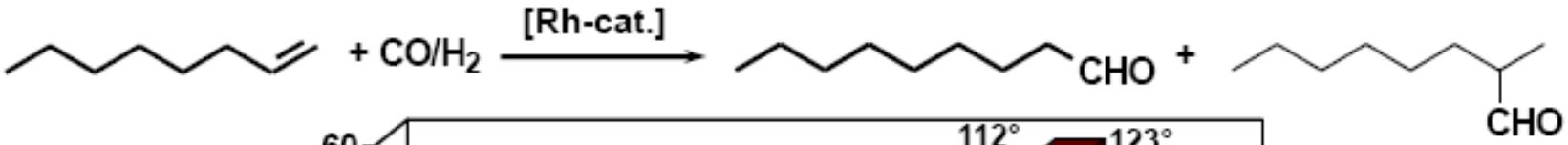


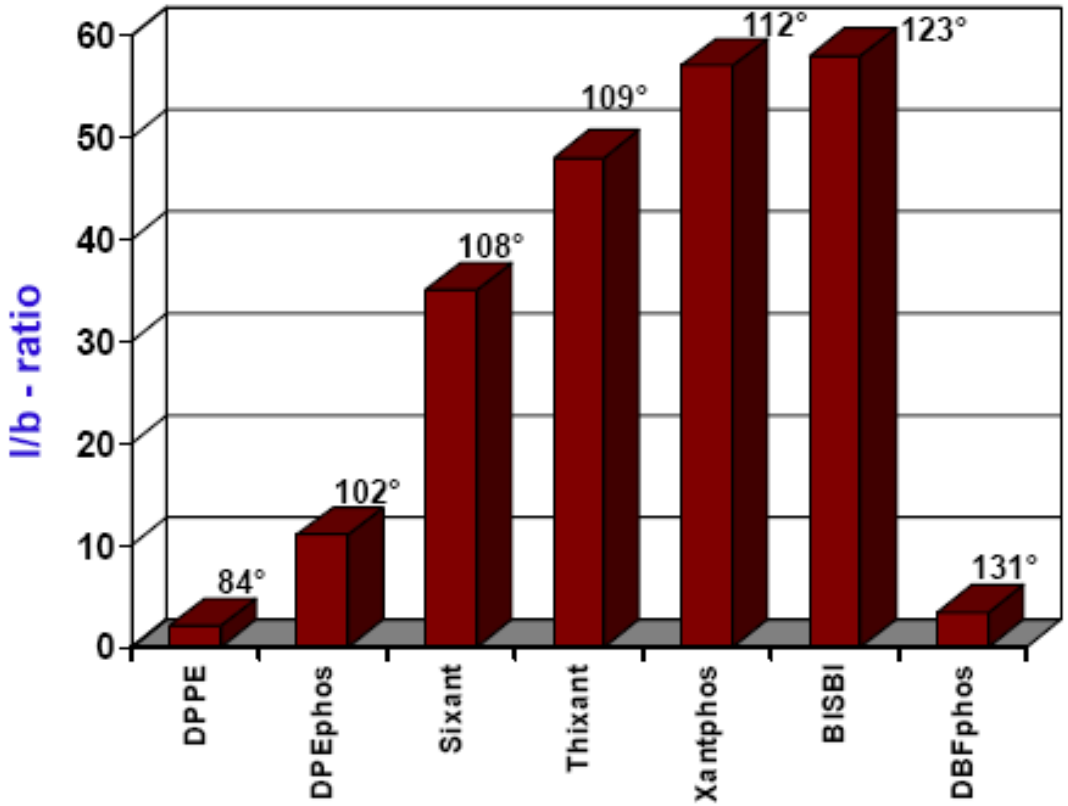
Xantphos ligands

Rigid backbone



large bite angle

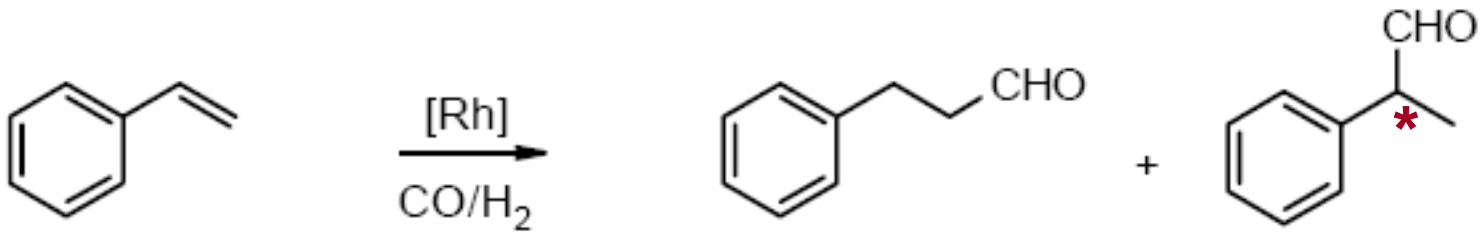




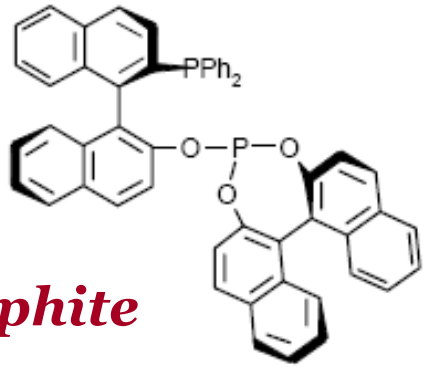
Piet van Leeuwen

T = 40°C, p = 10 bar CO/H_2 (1:1), substrate/Rh = 674, L/Rh = 2.2, [Rh] = 1.78 mM

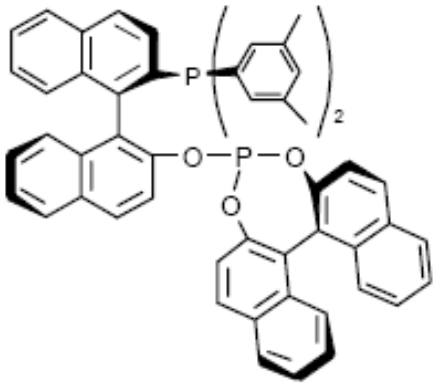
Asymmetric hydroformylation



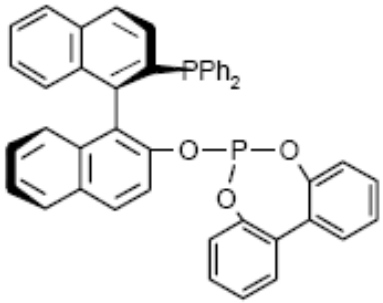
Phosphine-phosphite ligands



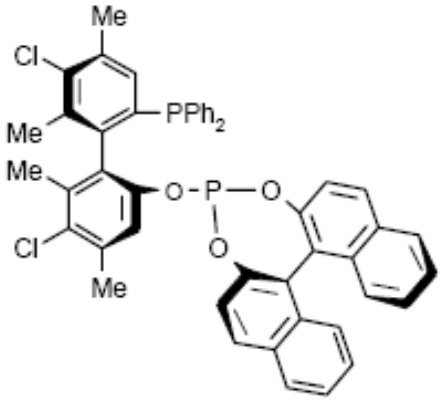
46 (R,S)-BINAPHOS



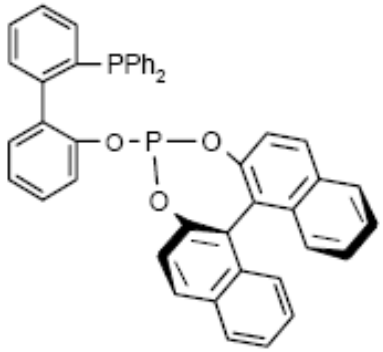
47 (R,S)



48(R)



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

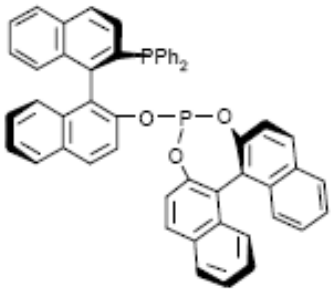


50 (R)

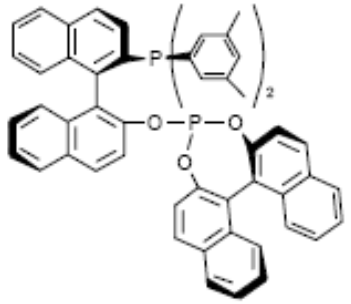
Phosphine-phosphite ligands

Reaction conditions: T = 60 – 80 °C, P_{TOT} = 100 bar.
Conversion > 99 %; b/l : 86 – 92 %.

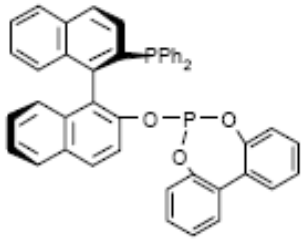
Ligand	% e.e.
46 (S,R)	94 (S)
46 (R,R)	25 (R)
47 (R,S)	85 (R)
48 (R,--)	83 (R)
49 (S,R)	94 (S)
49 (R,R)	16 (R)
50 (--,R)	69 (S)



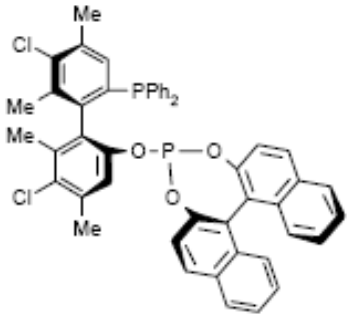
46 (R,S)-BINAPHOS



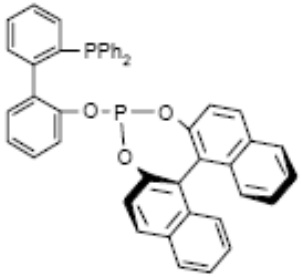
47 (R,S)



48(R)

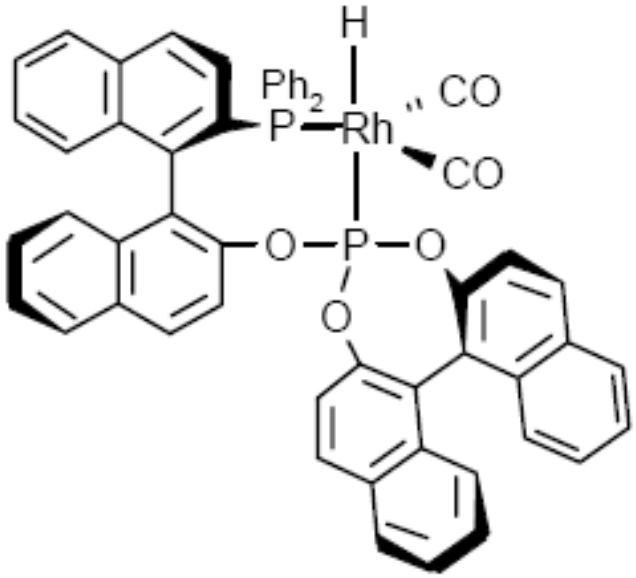


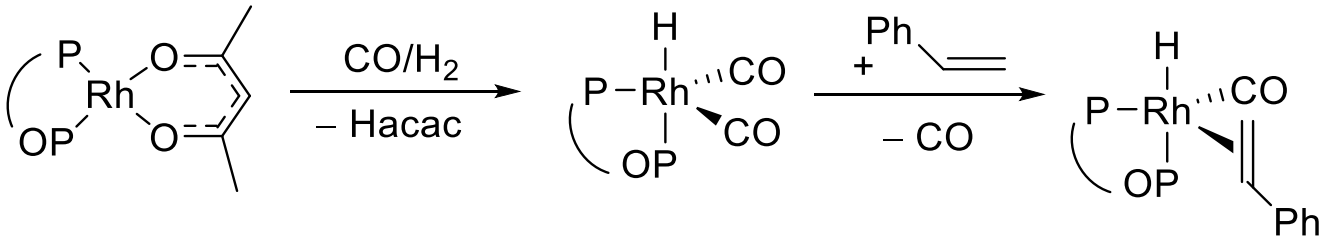
49a (S,R)
49b (R,R)



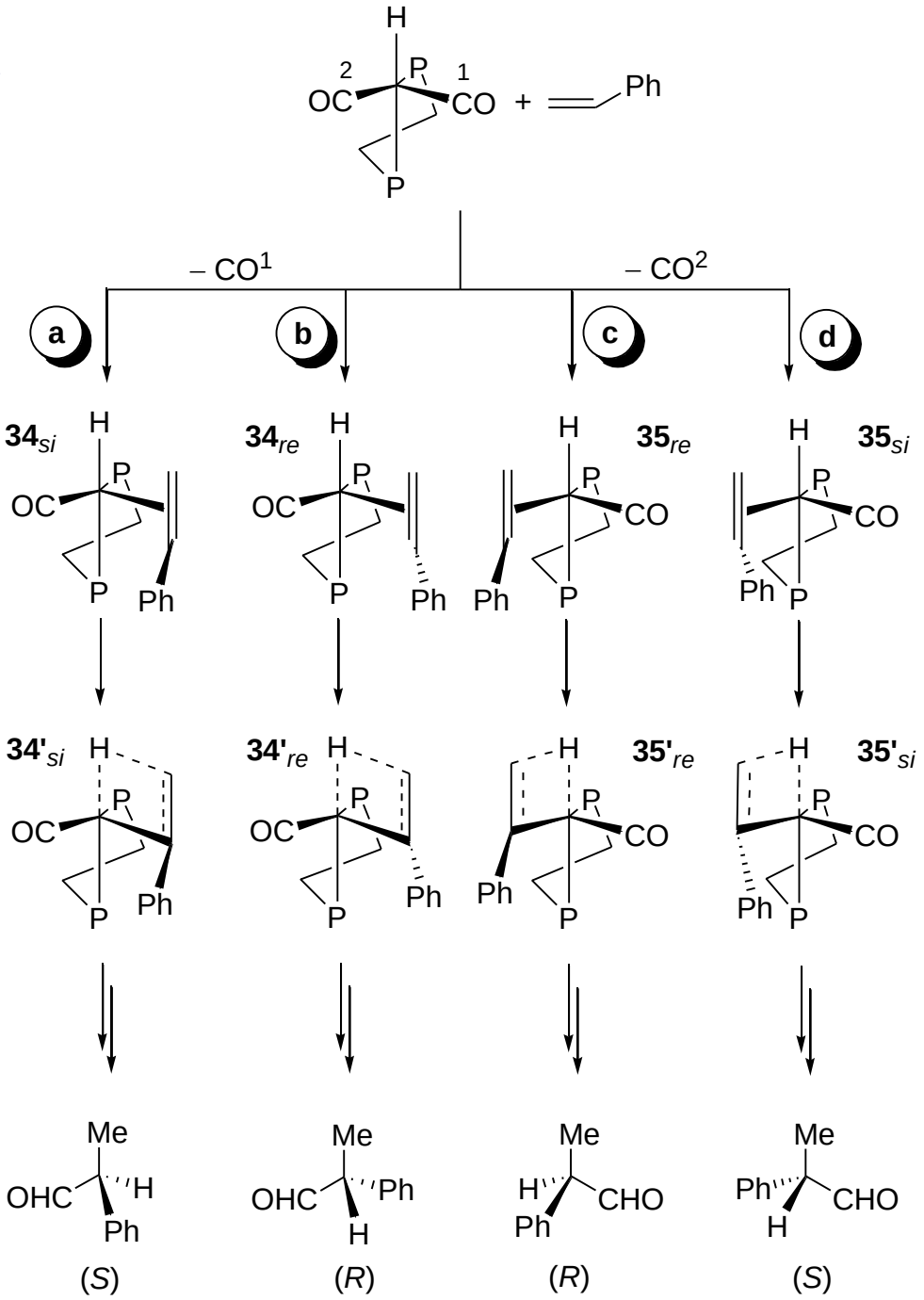
50 (R)

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

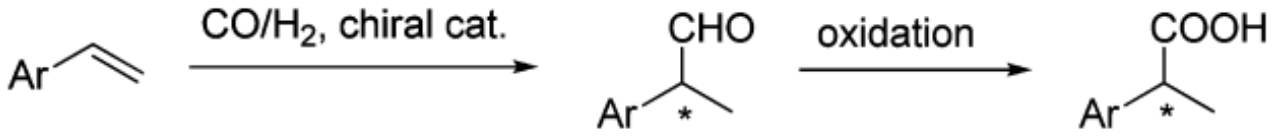


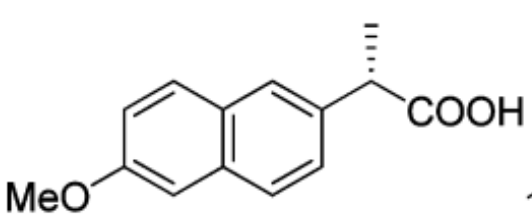


Stereodifferentiation in trigonal-bipyramidal rhodium complexes

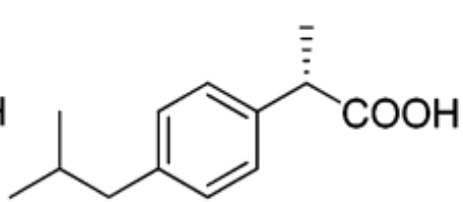


One of the possible applications of asymmetric hydroformylation

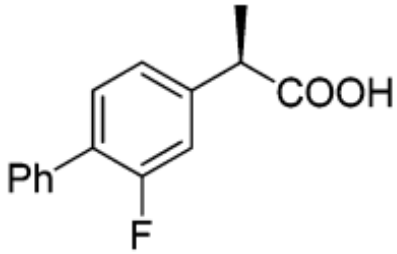




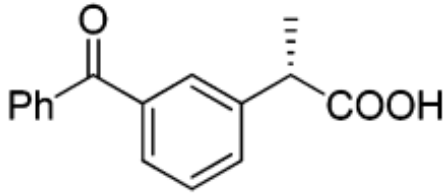
(*S*)-Naproxen



(*S*)-Ibuprofen



(*R*)-Flurbiprofen



(*S*)-Ketoprofen

Hydroformylation: Application in the synthesis of fragrances

Börner A. et al. *ChemCatChem* 2014, *6*, 382.