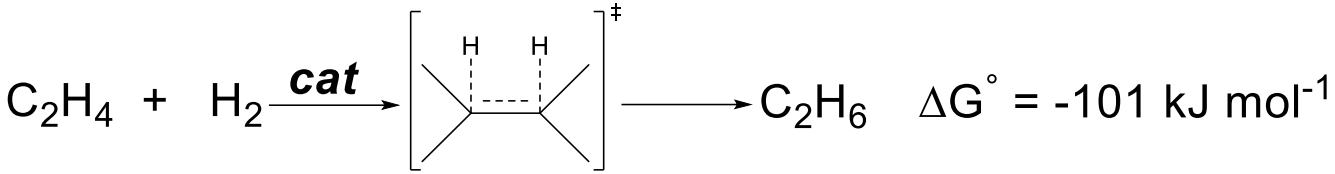
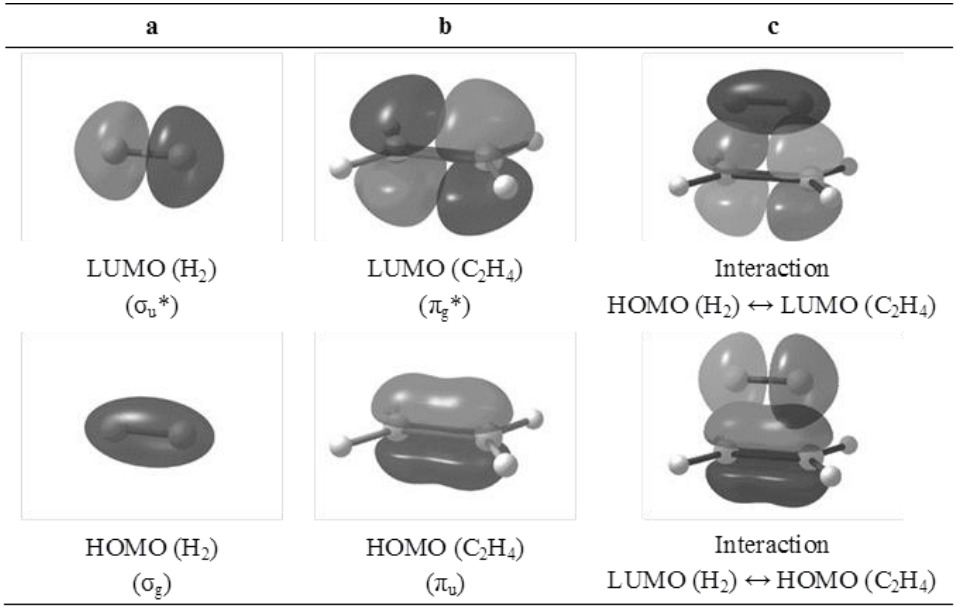
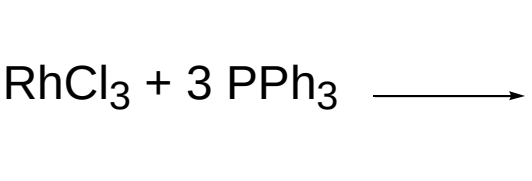
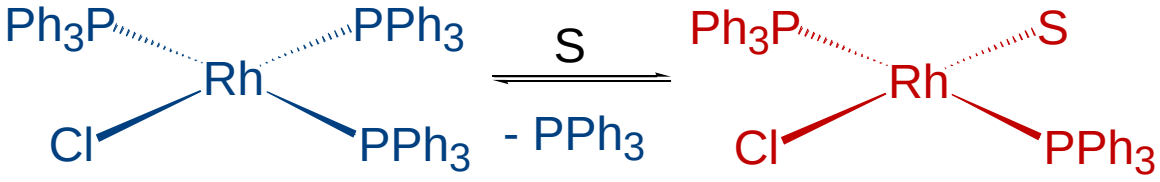
Hydrogenation reactions





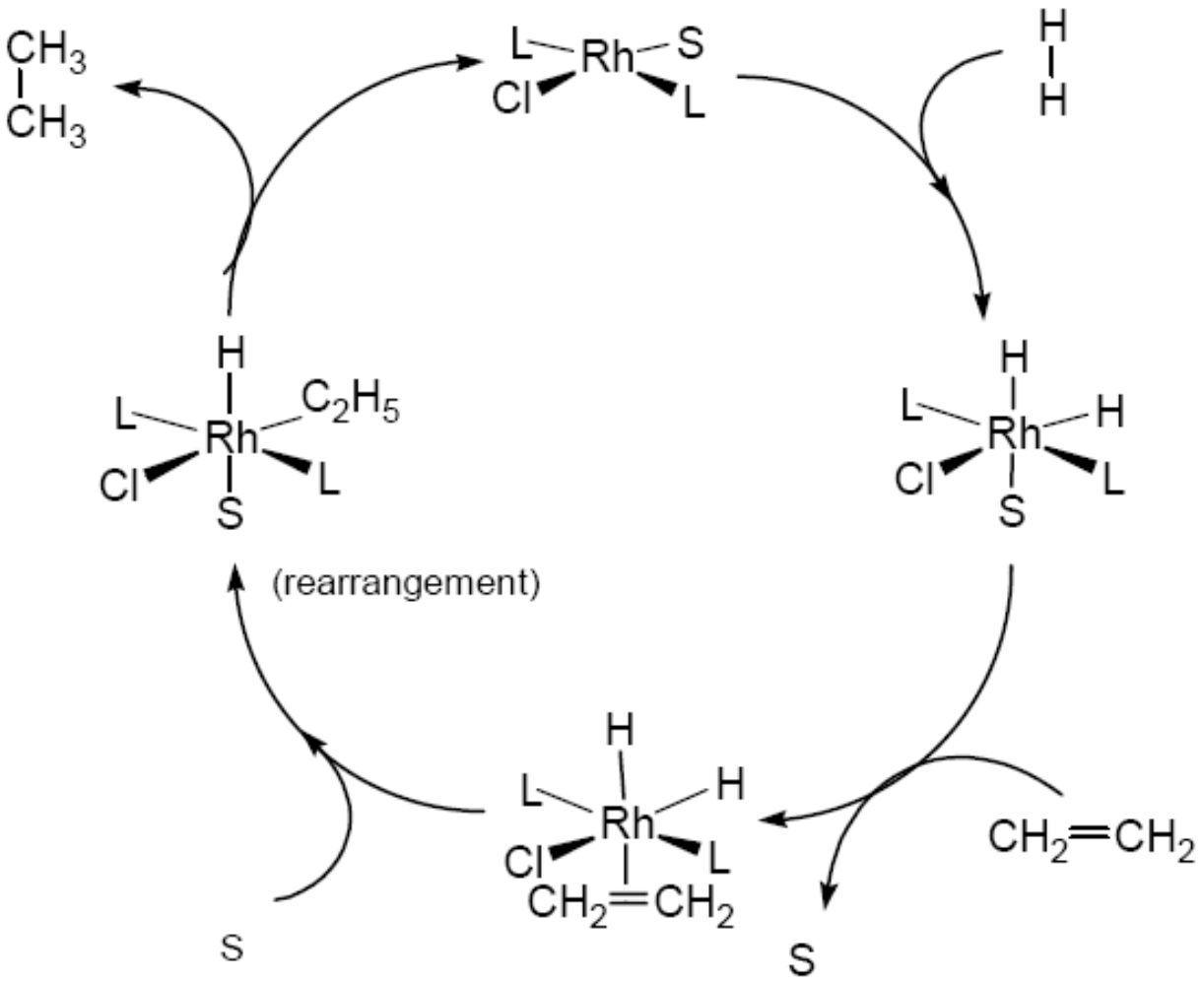


Wilkinson's catalyst



The active species

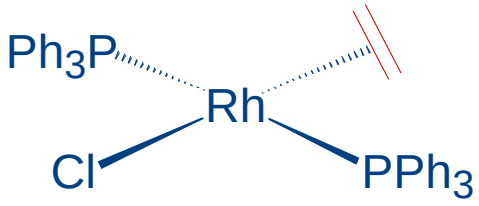
The catalytic cycle



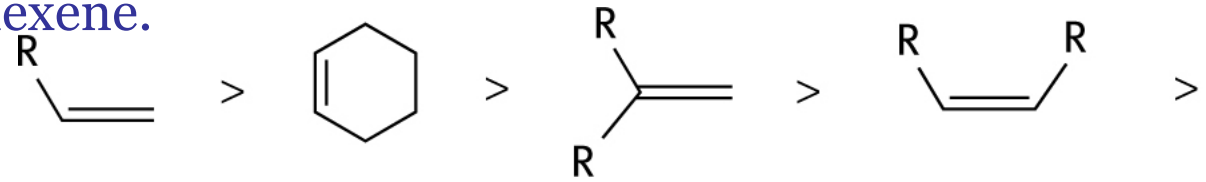
The effect of ancillary ligands

Ligand:	*Relative reactivity:*
$(4\text{-}ClC_6H_4)_3P$	1.7
Ph_3P	41
$(4\text{-}CH_3C_6H_4)_3P$	86
$(4\text{-}CH_3OC_6H_4)_3P$	100

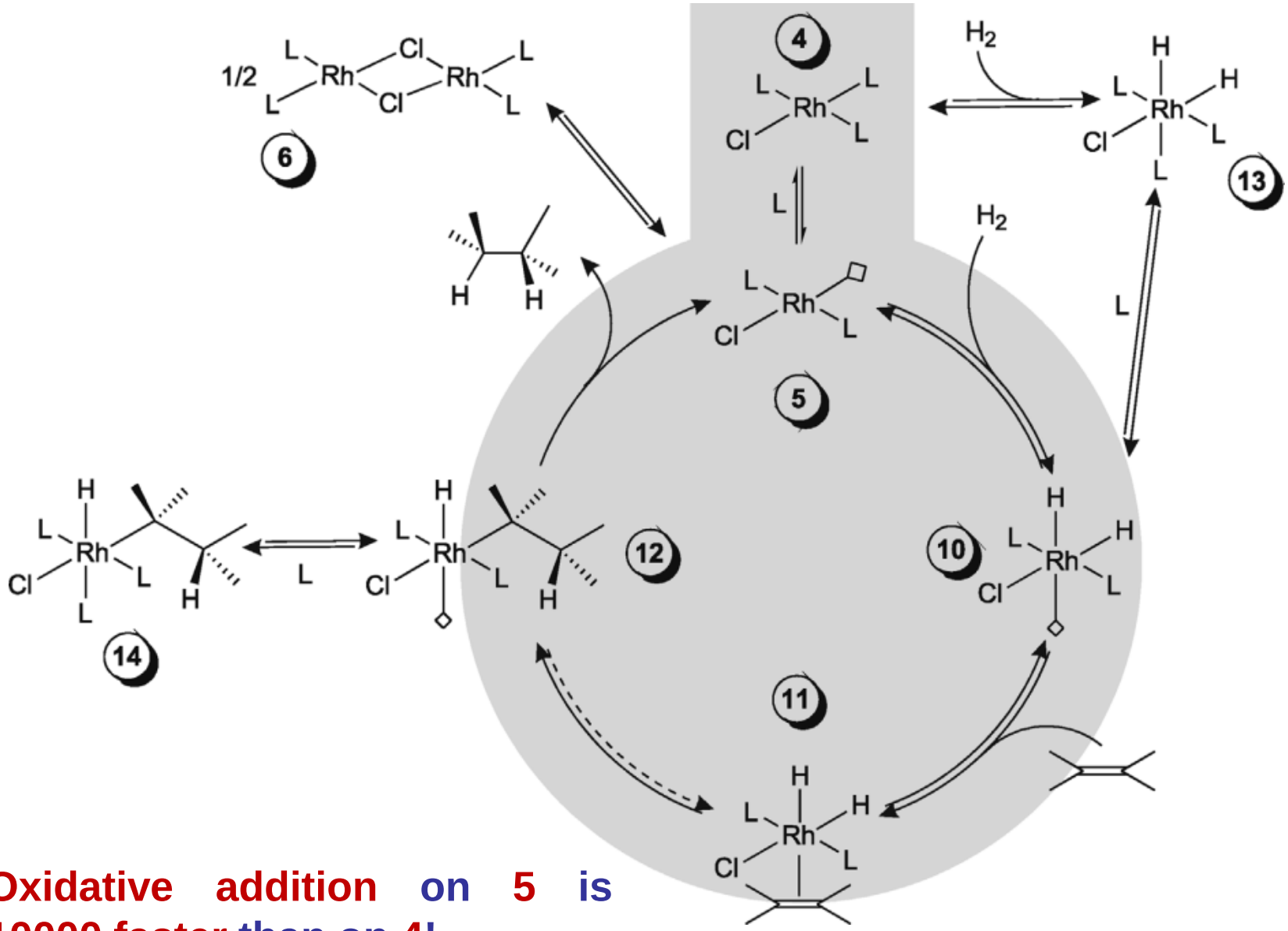
Effect of alkene: the Wilkinson catalyst is not able to hydrogenate ethene.



Cyclohexene > methyl cyclohexene; 1-hexene > cis 2-hexene > trans 2-hexene.



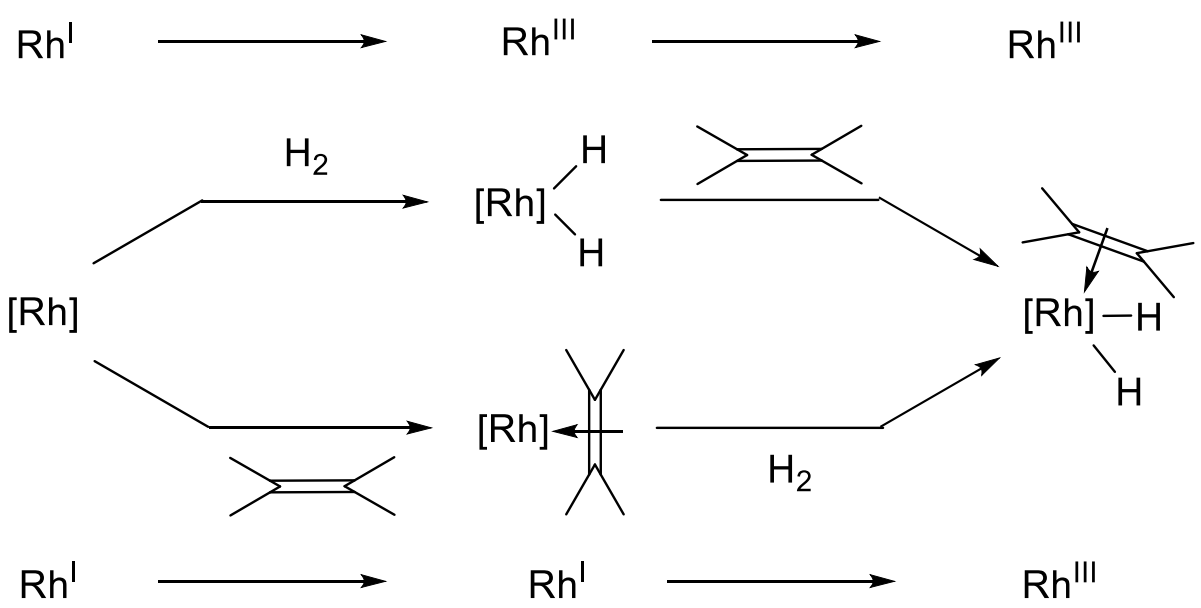
The catalytic cycle



Oxidative addition on 5 is 10000 faster than on 4!

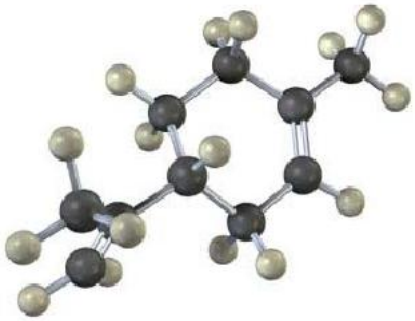
Two mechanisms

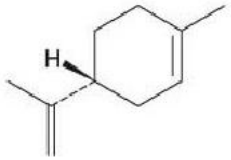
hydride mechanism



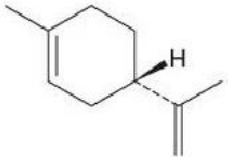
olefin mechanism

Chirality in nature

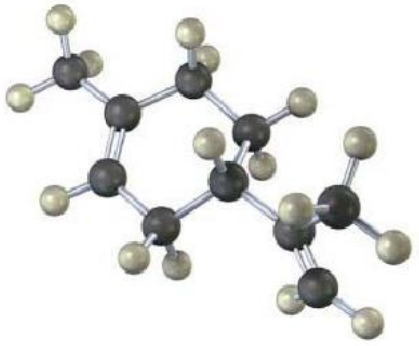




(+)-Limonene
(in oranges)



(−)-Limonene
(in lemons)



Top Drugs

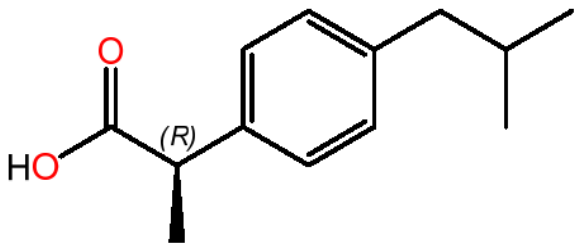
- ***About 1/3 of medicinal drugs are chiral***
- ***In 9 out of 10 of the top selling drugs, the active ingredient is chiral***

NAME	GLOBAL SALES 2008 (BILLION $)	ACTIVE INGREDIENT	FORM OF ACTIVE INGREDIENTS	THERAPEUTIC EFFECT
LIPITOR	**10.3**	***ATROVASTATIN***	Single Enantiomer	**Lipid-Lowering agent**
ZOCOR	**6.1**	***SIMVASTATIN***	Single Enantiomer	**Lipid-Lowering agent**
ZYPREXA	**4.8**	***OLANZAPINE***	Achiral	**Psychotropic agent**
NORVASC	**4.5**	***AMLODIPINE***	Racemate	**Calcium channel blocker**
PROCRIT	**4.0**	***EPOETIN A***	Protein	**Stimulant of blood cells production**
PREVACID	**4.0**	***LANSOPRAZOLE***	Racemate	**Inhibitor of gastric acid secretion**
NEXIUM	**3.8**	***ESOMEPRAZOLE***	Single Enantiomer	**Inhibitor of gastric acid secretion**
PLAVIX	**3.7**	***CLOPIDOGREL***	Single Enantiomer	**Inhibitor of platelet aggregation**
ADVAIR	**3.7**	***SALMETEROL***	Racemate	**β_2-Adrenergic bronchodilator**
		FLUTICASONE	Single Enantiomer	**Anti-inflammatory agent**
ZOLOFT	**3.4**	***SERTALINE***	Single Enantiomer	**Inhibitor of serotonin re-uptake**
TOTAL	*48.3*			

Rouhi, A. M.: *Chem. Eng. News.* **2009**, June 14, p. 47
Rouhi, A. M.: *Chem. Eng. News.* **2009**, Sept. 6, p.41.

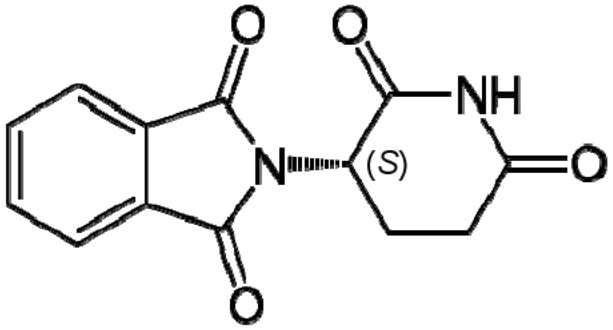
Chirality in drugs

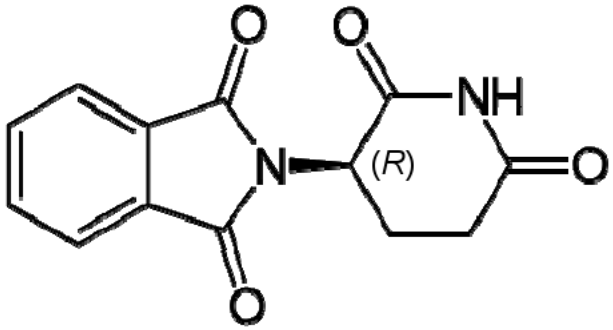
Ibuprofen (Moment)



R enantiomer: analgesic, anti-inflammatory;
S enantiomer : inactive, slightly hinhibit the *R* enantiomer.

Thalidomide

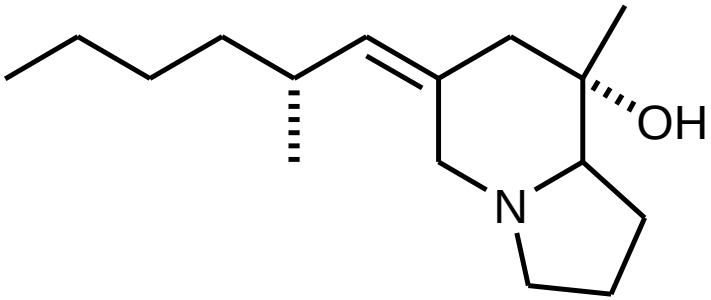




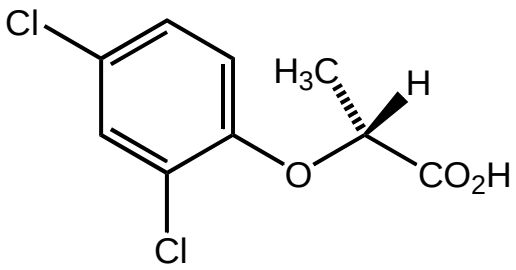
R enantiomer: sedative;
S enantiomer: teratogen.

Chirality in compounds

PTX (+)-251D

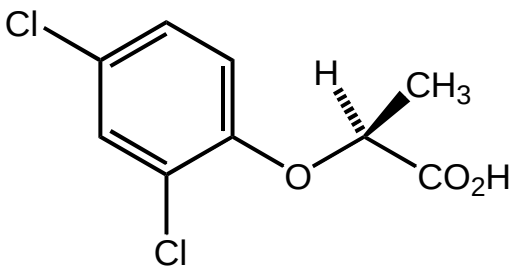


Enantiomer (+): mosquito repellent of high effectiveness;
Enantiomer (-): effectiveness 10 times lower.



(*R*)-(+)-Dichloroprop (Active)

R enantiomer: herbicide;
S enantiomer: inactive.



(*S*)-(–)-Dichloroprop (Inactive)

Asymmetric catalysis

Life depends on molecular chirality. R. Noyori

It represents the most convenient method for the production of enantiomerically pure organic compounds.
Other methods are:

- The reaction between a prochiral substrate and an achiral reagent leading to a racemic mixture, which requires a resolution in the two enatiomers;
- The reaction between a prochiral substrate and a chiral reagent in stoichiometric amount;
- Enzymatic Catalysis.

At the beginning of '90: 88 % of chiral drugs were sold as racemates;
Drug distribution in 2008: 63 % as pure enantiomers,
32 % as achiral compounds; 5 % as a racemate.

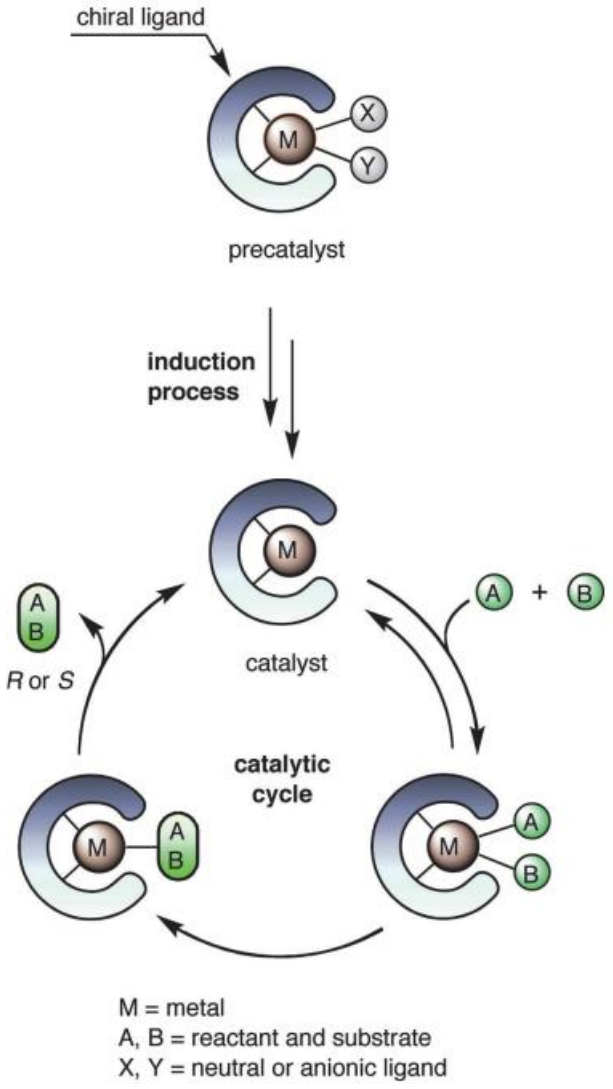
R. Noyori, *Angew. Chem. Int. Ed.* **2013**, *52*, 79.

Asymmetric catalysis

Asymmetric catalysis is based on the ability of a chiral organometallic compounds to discriminate with high precision (energetic differences exceeding 10 kJ mol^{-1}) between enantiotopic faces of a prochiral substrate.

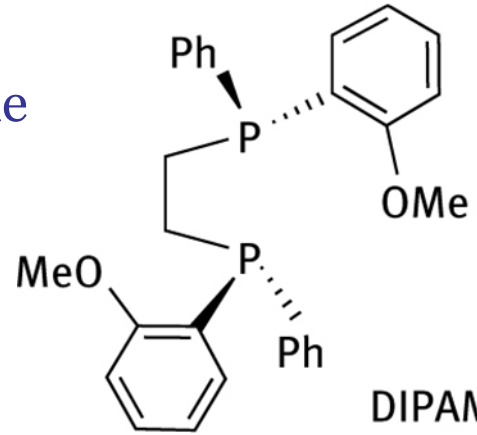
The chiral organometallic compounds consist of a chiral organic ligand bound to the metal ion.

Measurement of the enantiomeric excess: HPLC with a polysaccharide-based chiral stationary phase. It allows for the direct analysis of the obtained chiral products, without the need of derivatization.



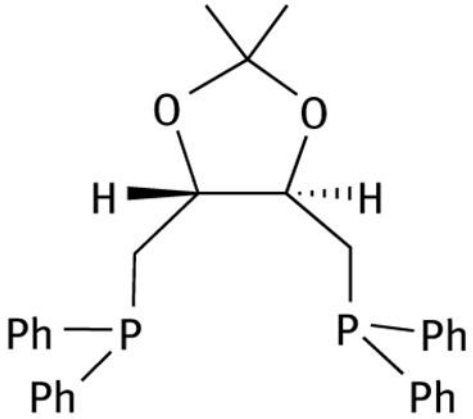
Chiral bidentate phosphines

1. Chirality at the phosphorus atom

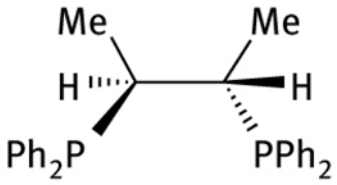


DIPAMP

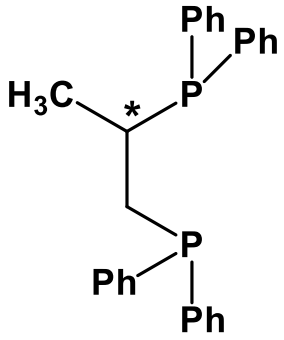
2. Chirality on the backbone



(*R*, *R*)-DIOP



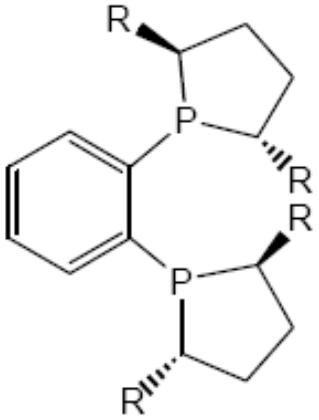
CHIRAPHOS



PROPHOS

Chiral bidentate phosphines

3. Chiral substituents on phosphorus



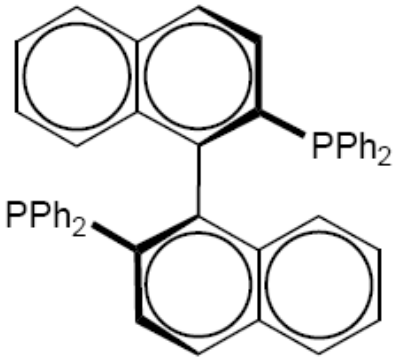
DuPHOS

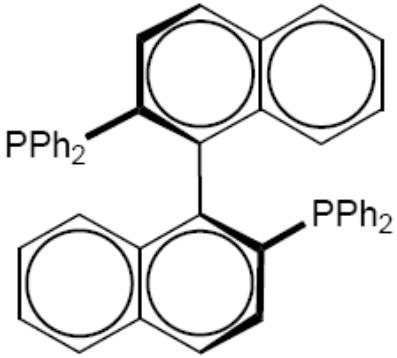
R = CH_3, C_2H_5, iC_3H_7

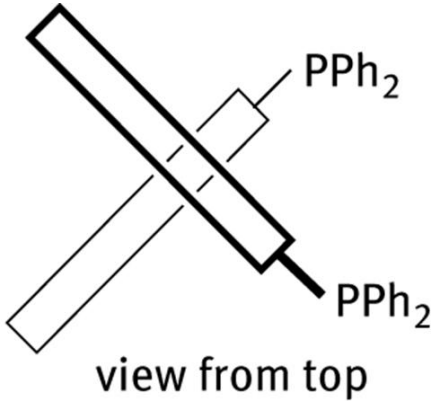
4. Axial (or helical) chirality

BINAP

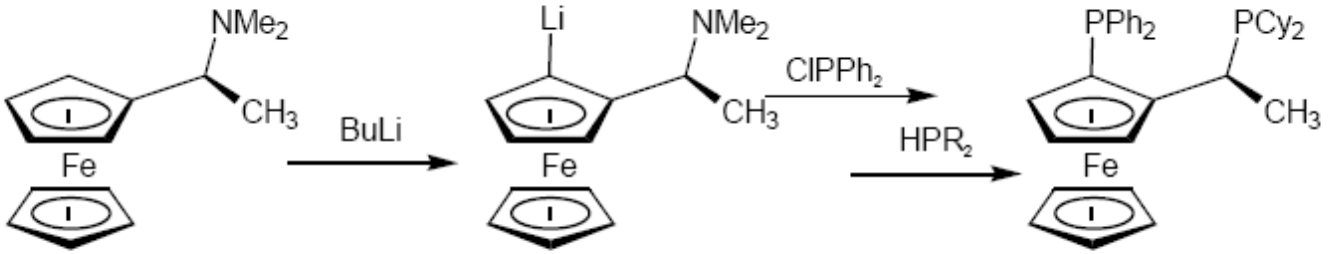
The two enantiomers







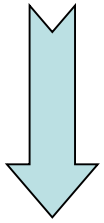
5. Planar chirality



JosiPhos

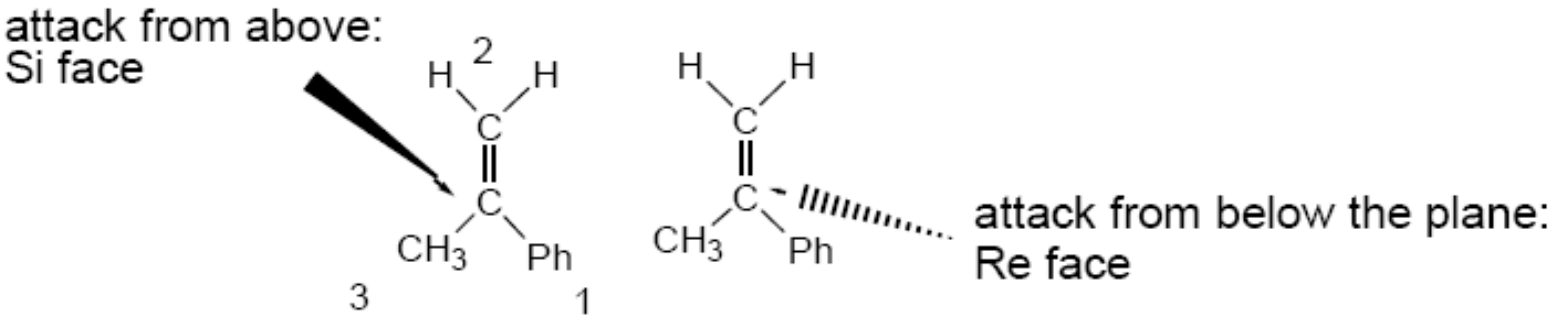
Prochiral Substrates

When planar molecules possessing a double bond that does not have C_{2v} simmetry coordinates to a bare metal ion a chiral complex is formed. This planar molecule is a prochiral molecule.
Depending on the enantiotopic face involved in the coordination, one of the two enantiomers is obtained.

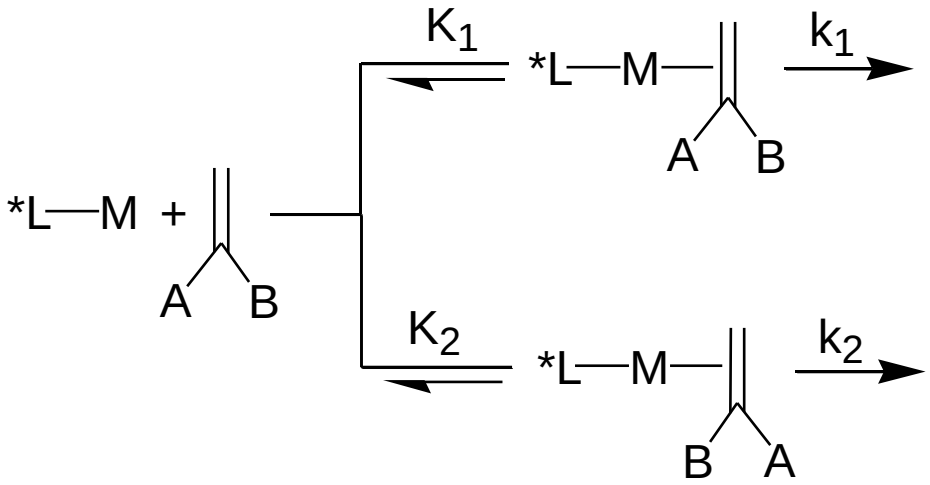


When a prochiral molecule coordinates to a chiral metal complex, the resulting complex is a diastereomer.
When the chiral metal complex coordinates to both faces of the alkene, a mixture of diastereomers can form.
Diastereomers have different energies and thus they have different properties and different reactivities.

Enantiotopic faces



For complexes of planar molecules to metals the rules to denote the faces of the planar molecules are called ***re*** face and ***si*** face.
If all four substituents of the alkene are different, it is necessary to determine the re/si faces of both carbon atoms, leading to ***re,re*** and ***si,si*** or ***re,si*** and ***si,re***.
There is no correlation between the enantiotopic face of the alkene and the absolute configuration of the formed stereogenic centre: ***re*** face can lead to both ***R*** and ***S*** and ***si*** face can lead to both ***R*** and ***S***. It depends on the catalytic reaction.



Basic principle of asymmetric catalysis:

A high optical yield is achieved, if:

a. The equilibrium between the two diastereomers is COMPLETELY shifted to one side;

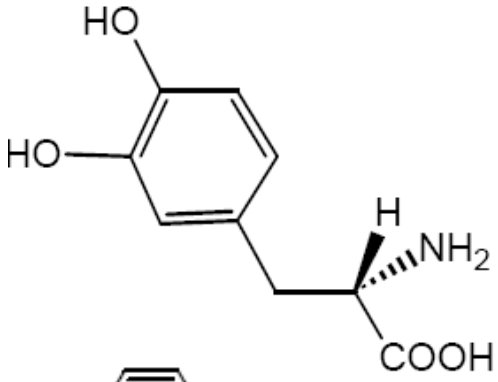
or

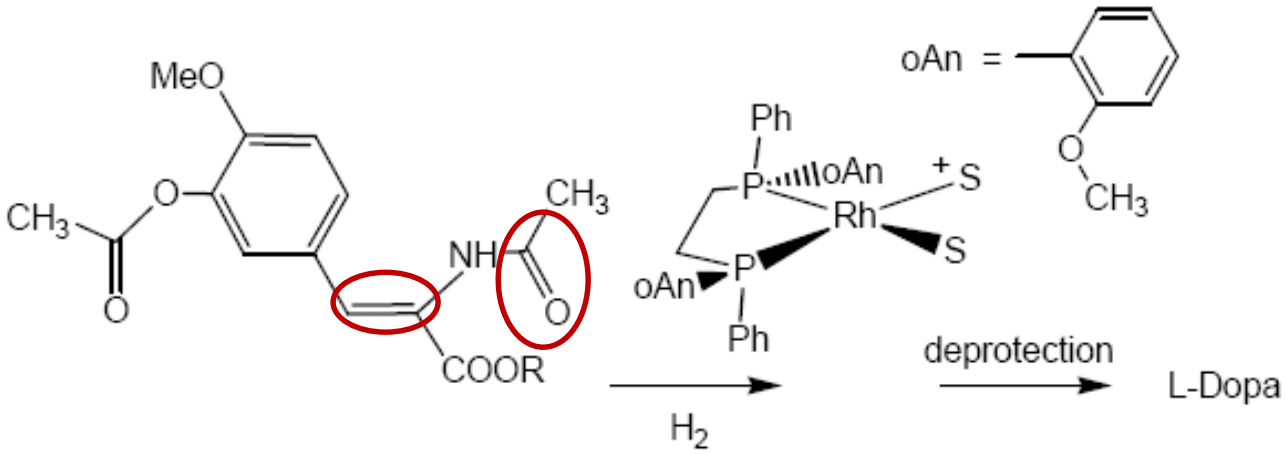
b. The equilibrium between the two diastereomers is NOT completely shifted to one side :

b1. the thermodynamically more stable species is also the most reactive;

b2. the thermodynamically less stable species is by far the most reactive: kinetically controlled enantioselectivity.

Synthesis of L-Dopa

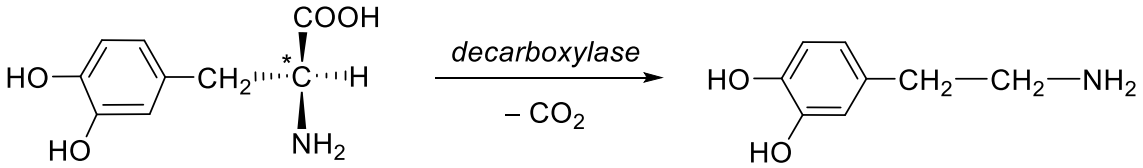




TON = 20000

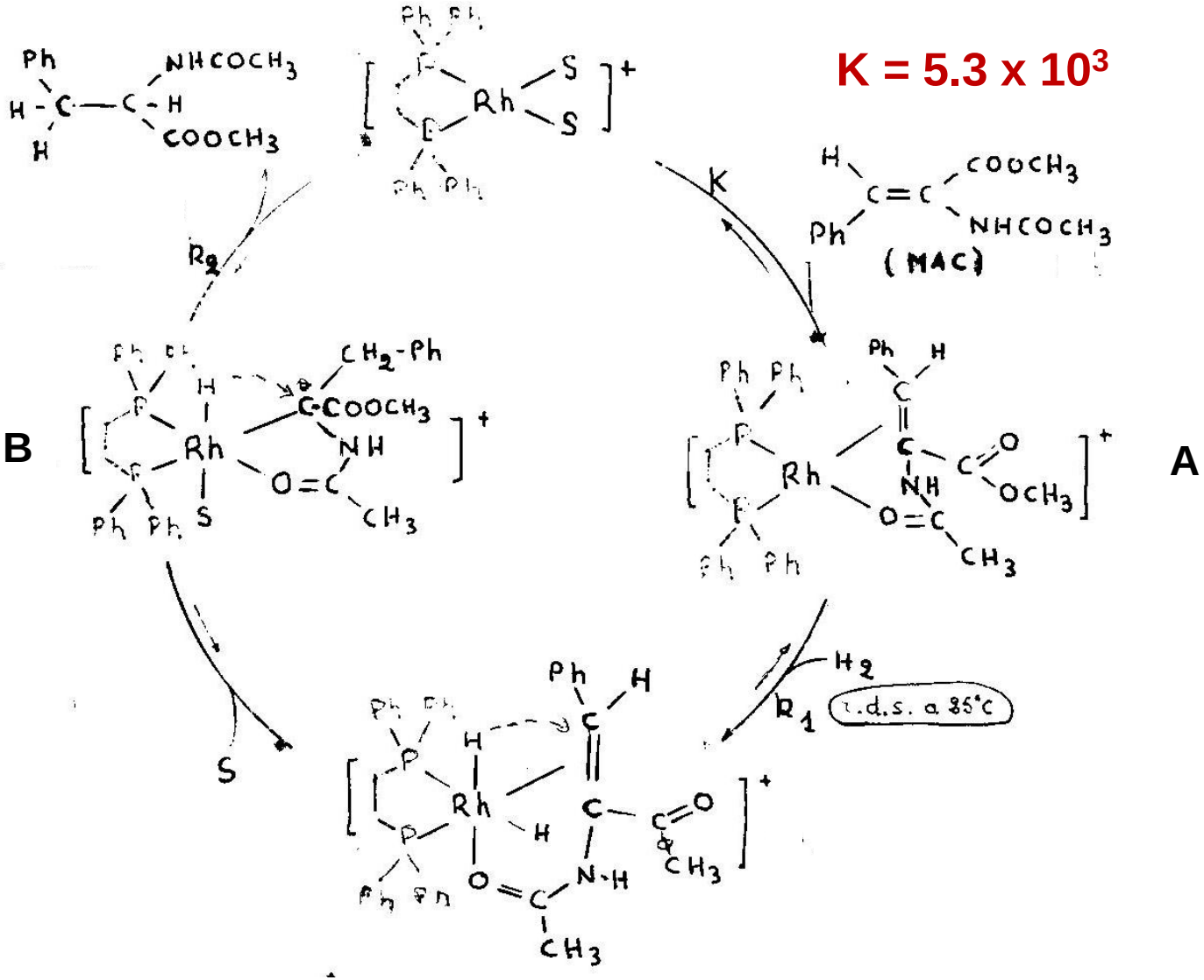
TOF = 1000 h^{-1}

ee = 95 %

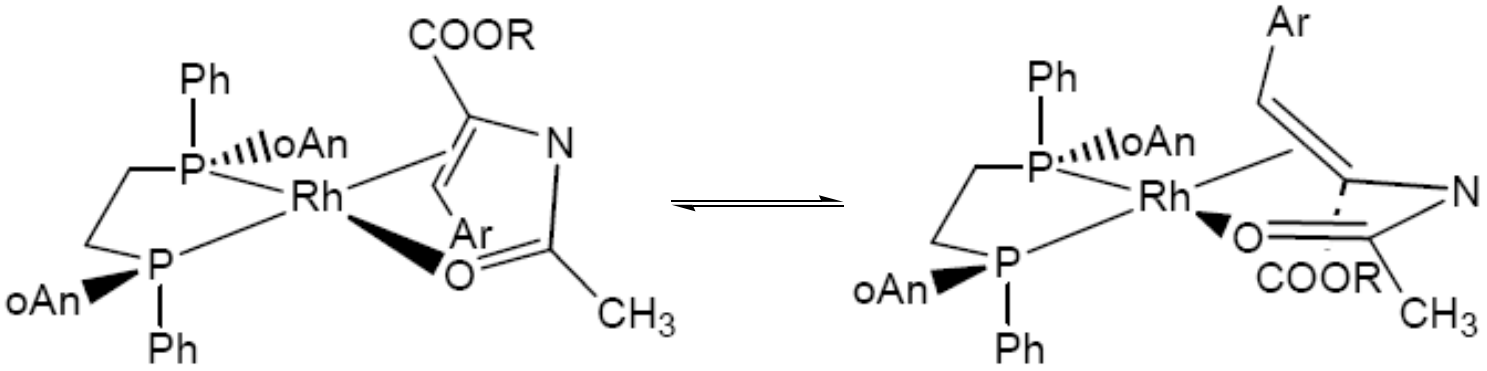


(L-DOPA) (dopamine)

The "achiral" catalytic cycle



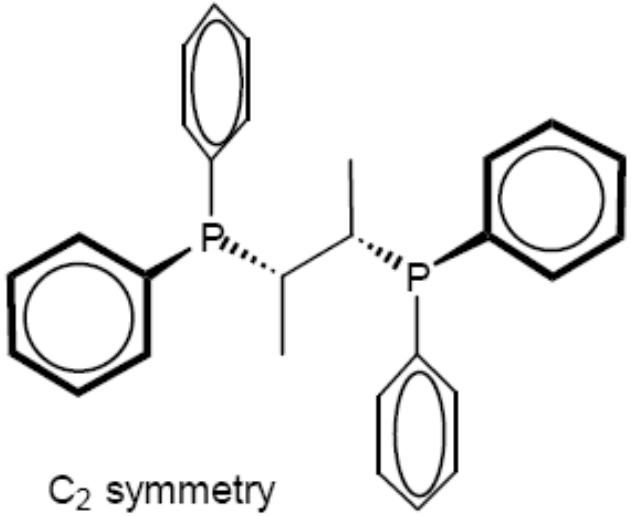
The steps of the enantioselective catalytic cycle



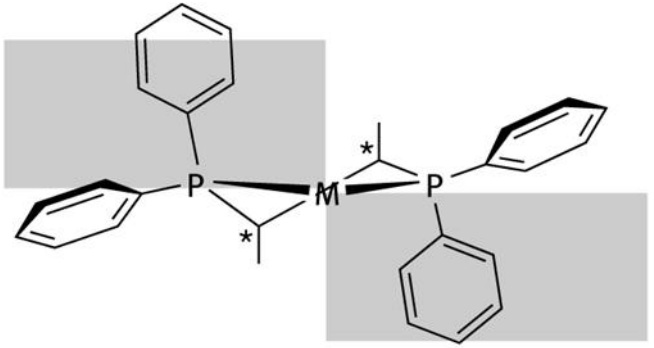
si,si-face complex, major

re,re-face complex, minor

The steps of the enantioselective catalytic cycle

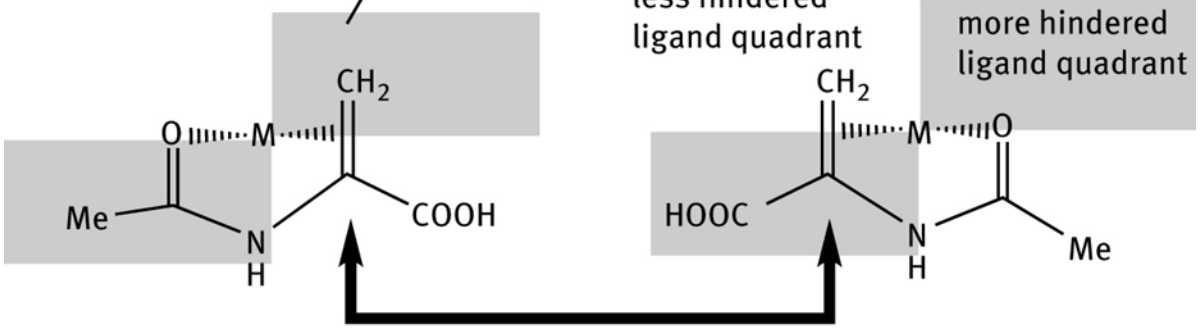


C_2 symmetry

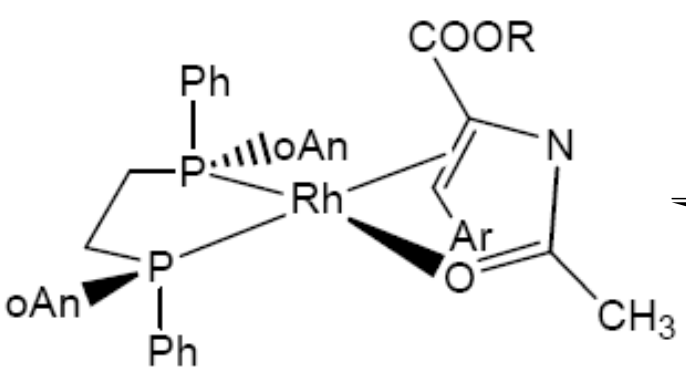


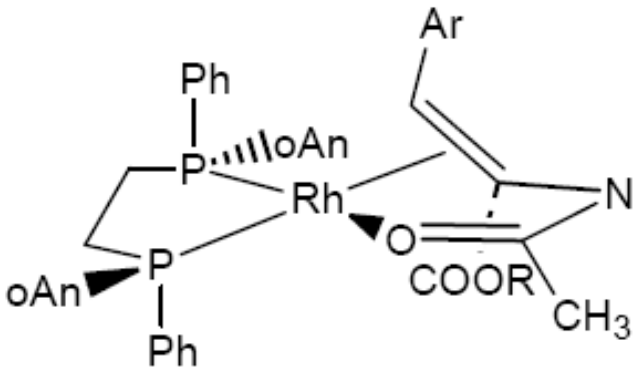
Chiral bridge:
Locked in one conformation
Translates into C_2-symmetric geometry around M
Shaded areas indicate crowded ligand quadrant

C_2-symmetric ligand system:
One enantiomer only



C=C in different environments:
different energies
One diastereomer will react faster





si,si-face complex, major

re,re-face complex, minor

si gives R Dopa

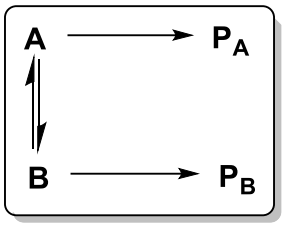
RR-DIPAMP produces S-Dopa

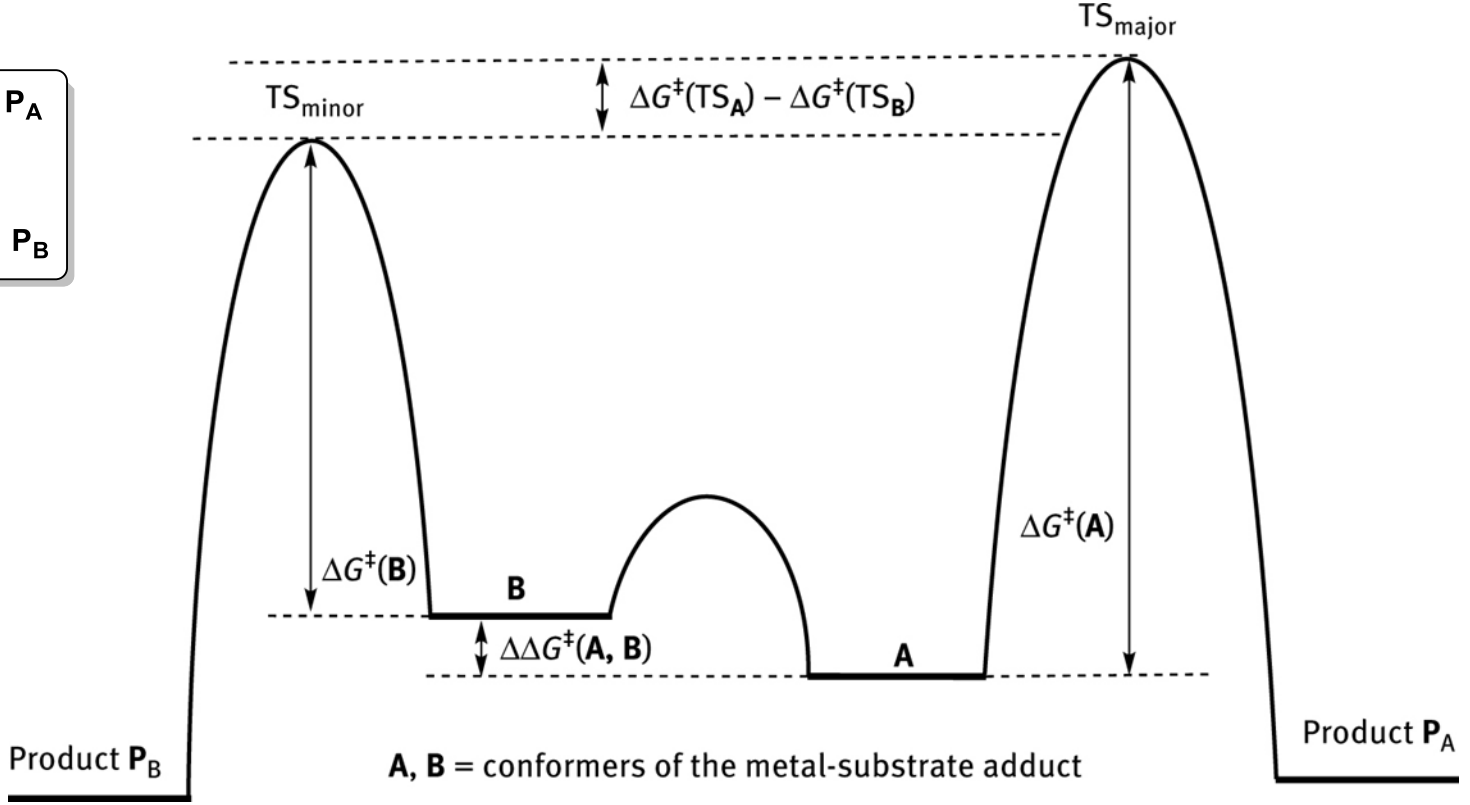
re gives S-Dopa

RR-DIPAMP produces S-Dopa

Enantioselectivity is under kinetic control and it does not depend on the position of the equilibrium between the two diastereomers.

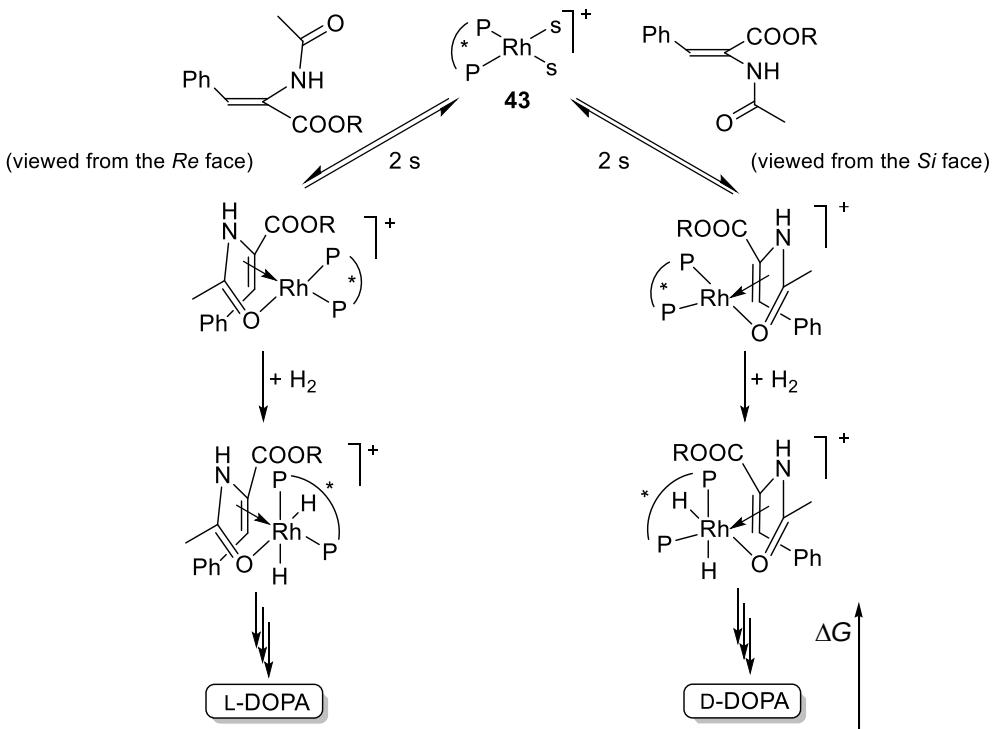
The Curtin-Hammett principle

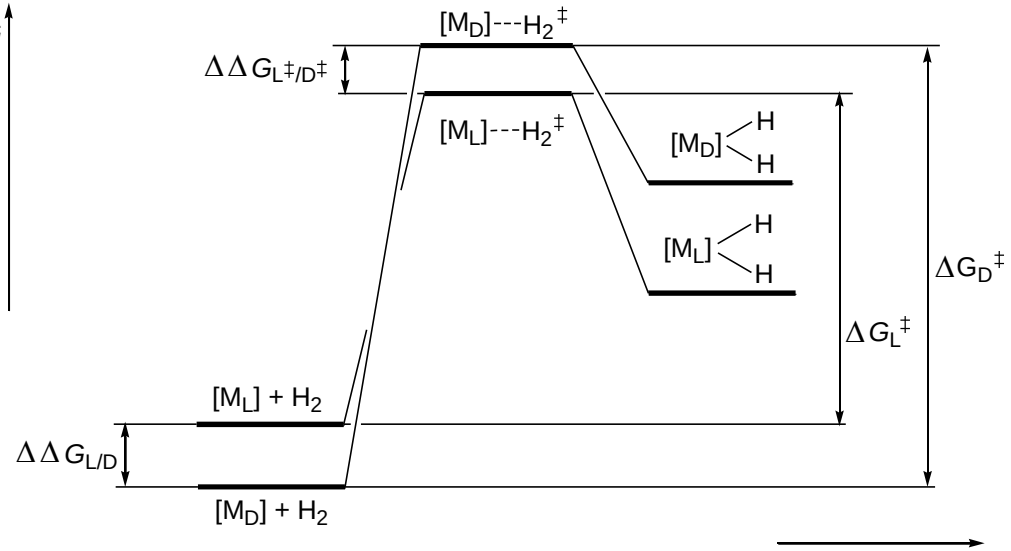




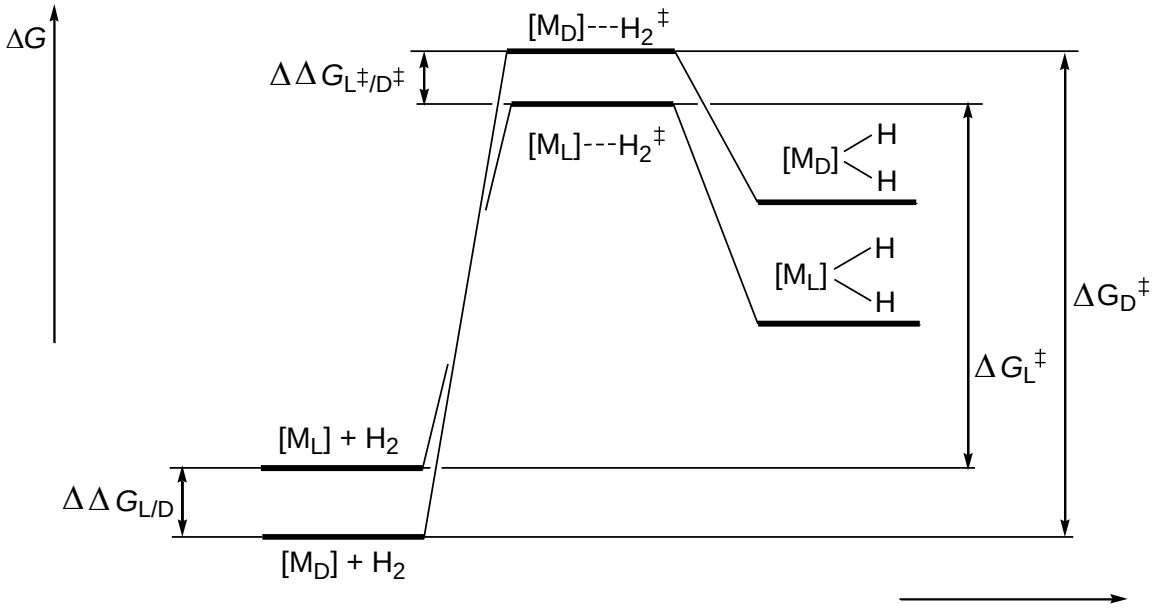
In cases where the cat-sub adduct exists as 2 conformers, A and B, which exchange more rapidly than the subsequent formation of the products P_A and P_B, then the product composition P_A/P_B is determined by energy difference of the two transition states and NOT by the difference in activation energy, neither by the position of the equilibrium between the two conformers of the reactants, c_A/c_B.

The steps of the enantioselective catalytic cycle





The steps of the enantioselective catalytic cycle



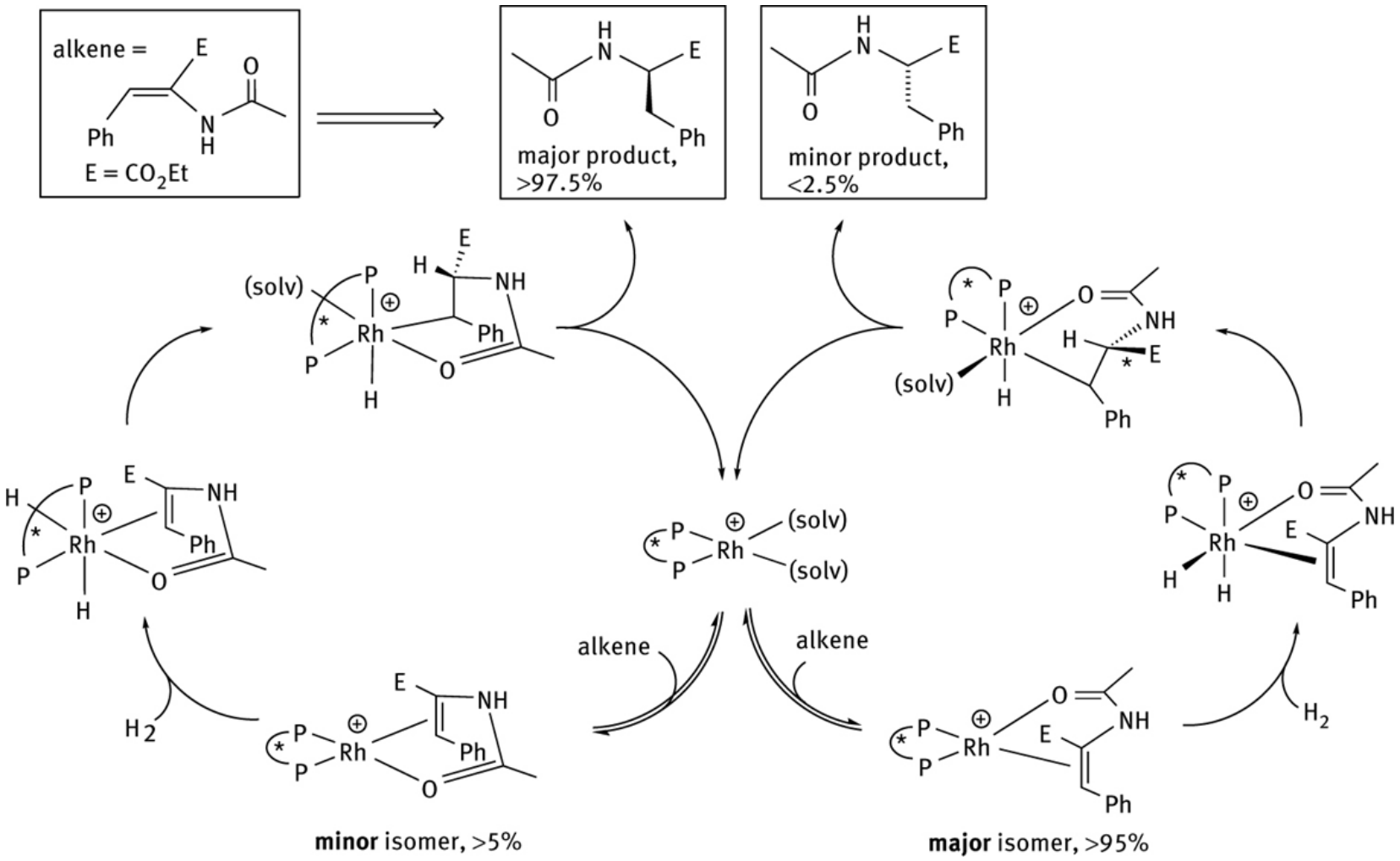
$\Delta\Delta G_{L/D}$ = difference in thermodynamic stability between the two diastereomers

$$\Delta\Delta G_{L/D} = - RT \ln K_{L/D}$$

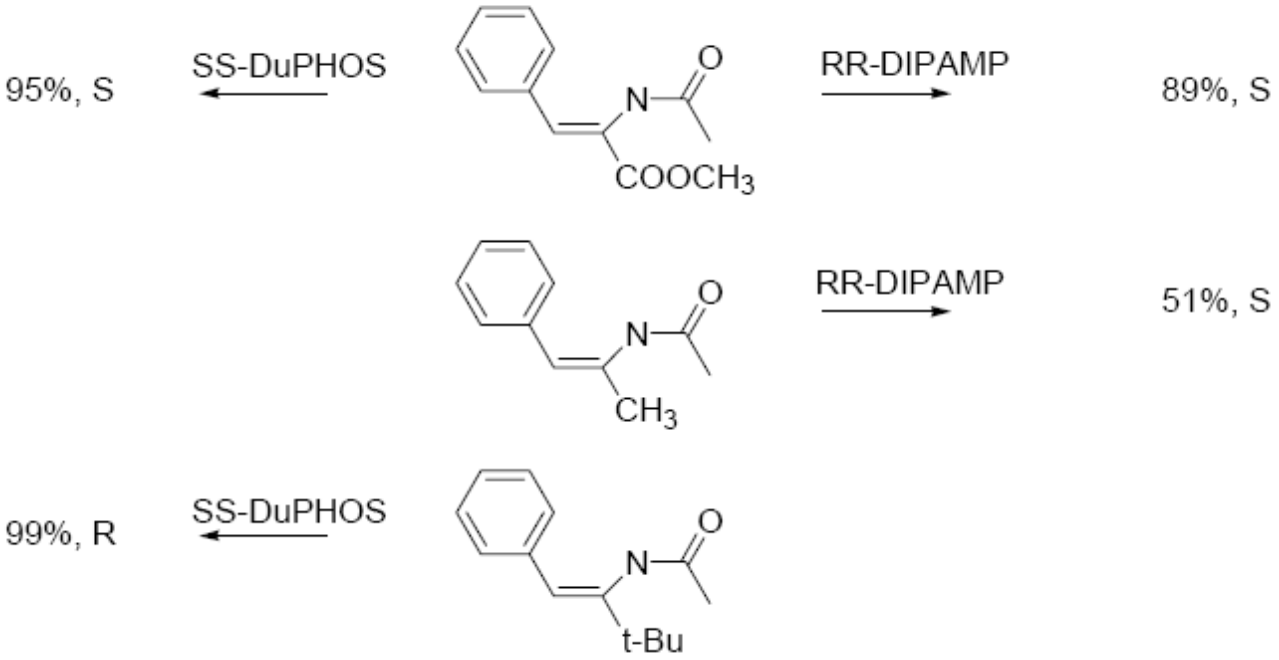
$\Delta\Delta G_{L}^{\ddagger}{}_{/D}^{\ddagger}$ = difference between the Gibbs free energies of the transition states; determines the reaction rates of the two diastereomers; determines the enantiomeric excess;

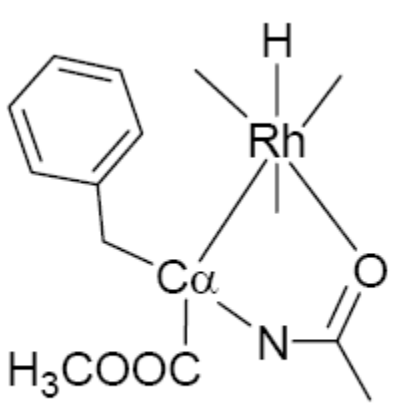
$\Delta G_{L}^{\ddagger} - \Delta G_{D}^{\ddagger}$ = difference between the Gibbs free energies of activation for the two reactions on the two diastereomers; does NOT determine ee!

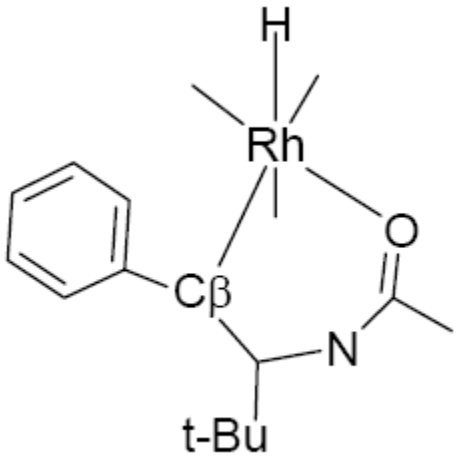
The enantioselective catalytic cycle



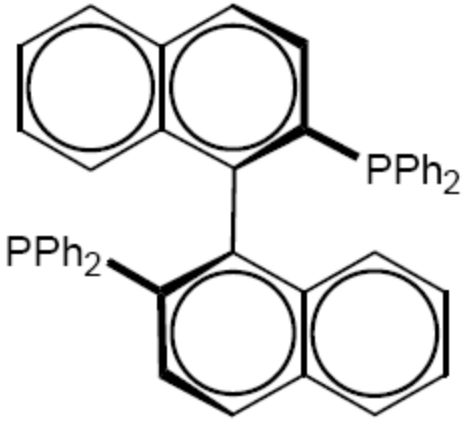
The effect of the substrate



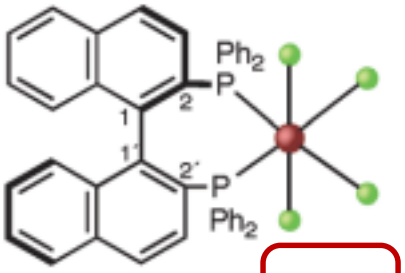




Examples of other ligands for asymmetric hydrogenation



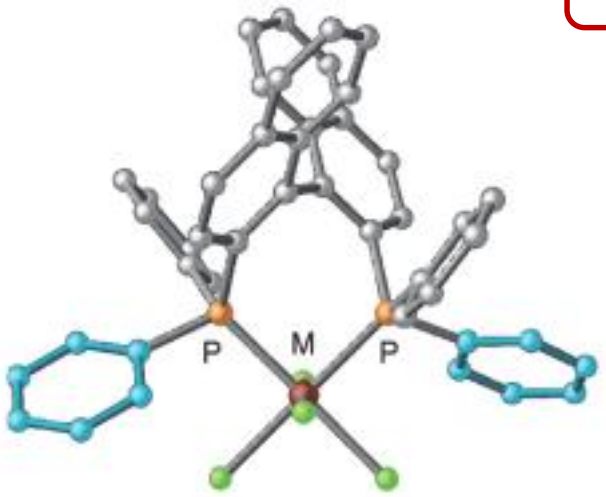
S-BINAP



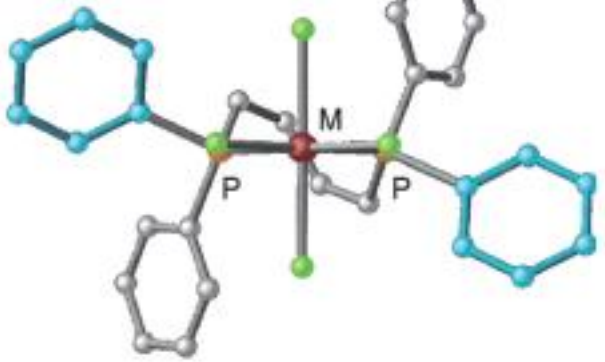
(*R*)-BINAP

Rh

Dihedral angle between naphthyl planes: 74.4°;
Bite angle P-Rh-P: 91.8°.

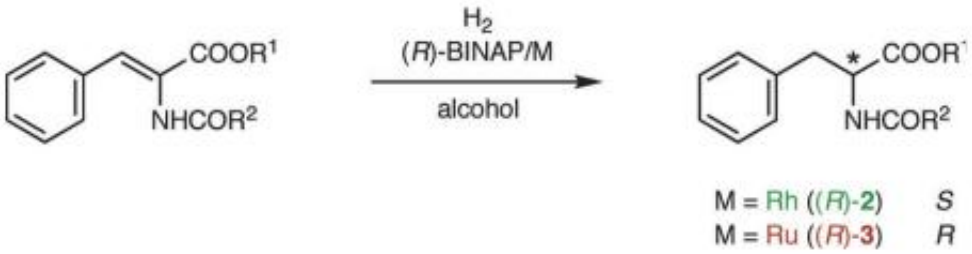


top view

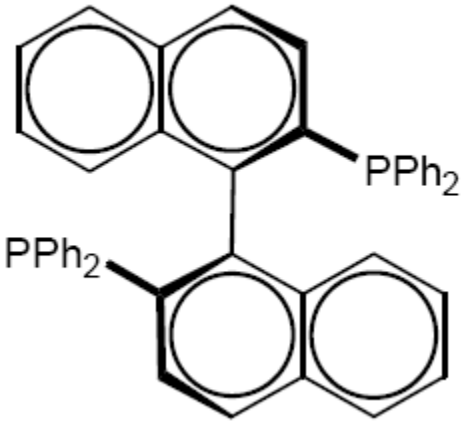


side view

Asymmetric hydrogenation of dehydroamino acids: H_2 4 atm, r.t., yield: 97%, high e.e. in *S* enantiomer.



Examples of other ligands for asymmetric hydrogenation

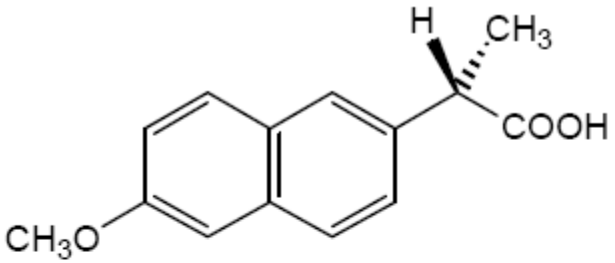


S-BINAP

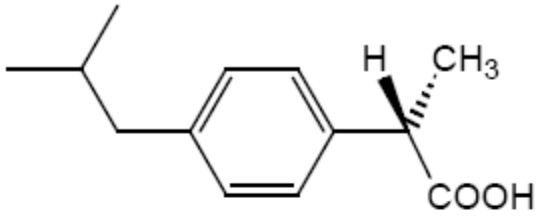
BINAP/Ru complexes are efficient catalysts for asymmetric hydrogenation reactions of prochiral alkenes, which **do not** have additional polar groups.

Ru

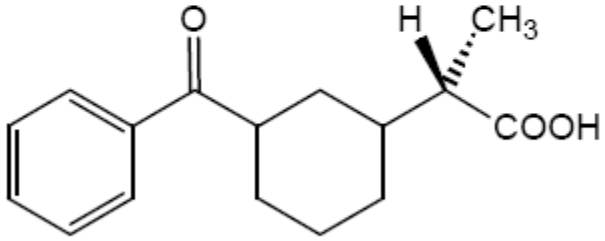
Dihedral angle between naphthyl planes: 65.6°;
Bite angle P-Ru-P: 90.6°.



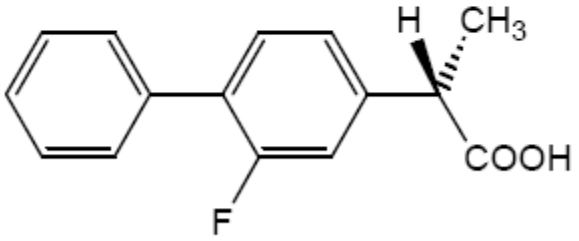
Naproxen



Ibuprofen

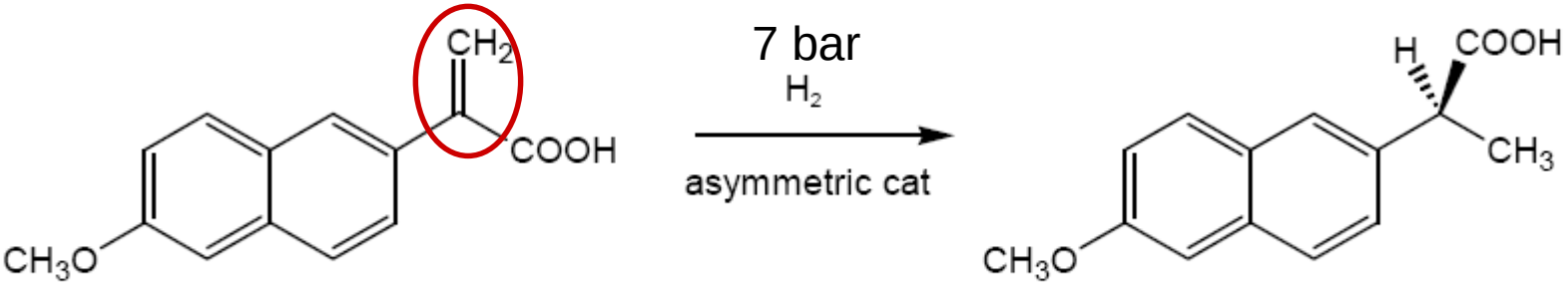


Ketoprofen

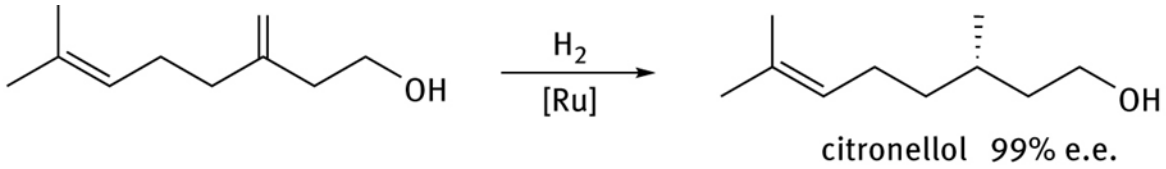


Flurbiprofen

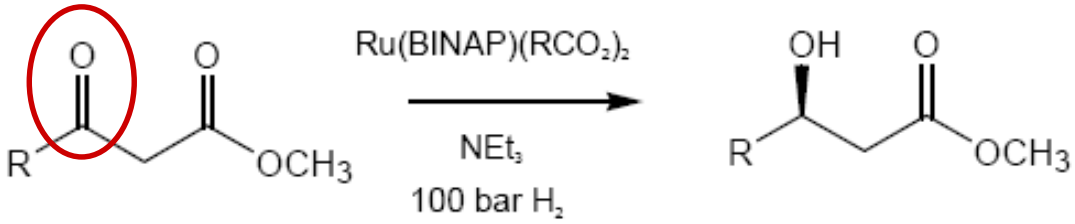
Monsanto route to S-Naproxan; hydrogenation step



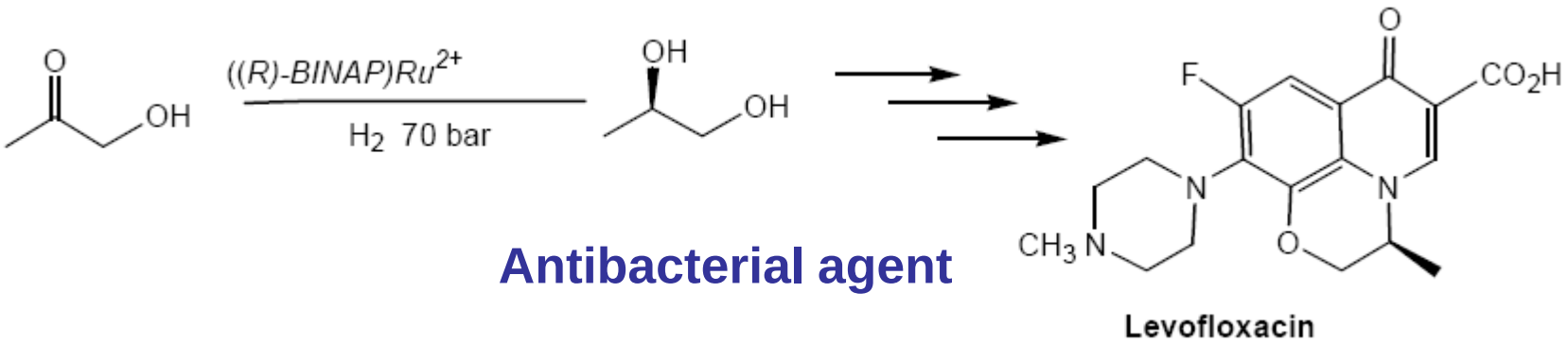
TON = 3000
ee = 98.5 %



citronellol 99% e.e.



99 % e.e.

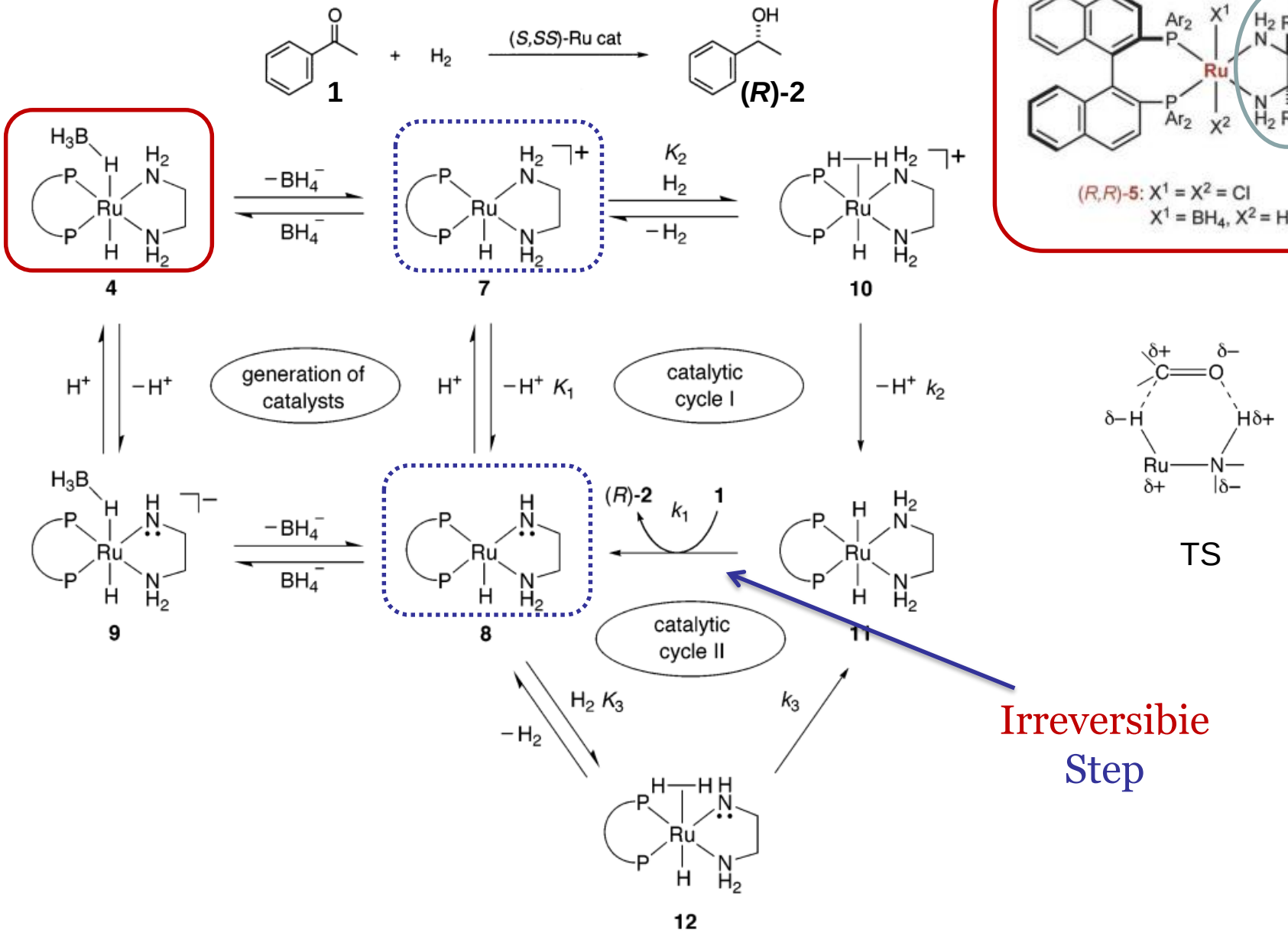


Antibacterial agent

Levofloxacin

The catalytic system Ru/BINAP

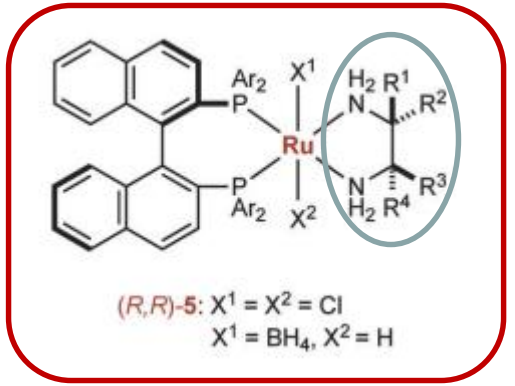
Outer-sphere Mechanism

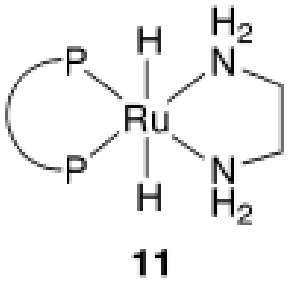


The catalytic system Ru/BINAP

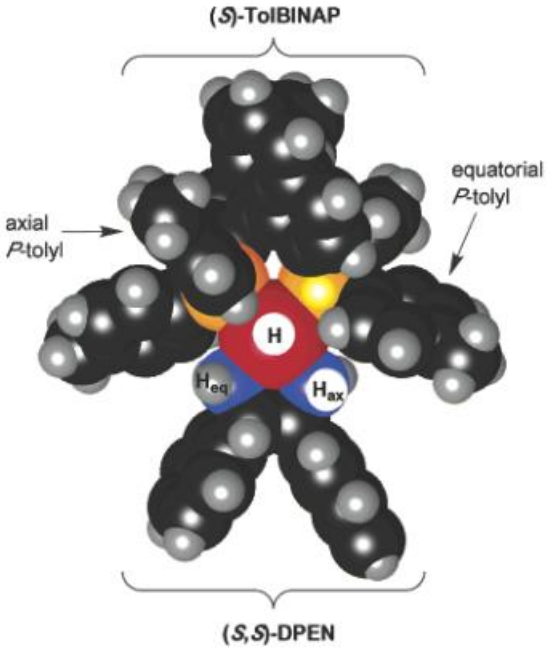
Outer-sphere Mechanism: enantioselection

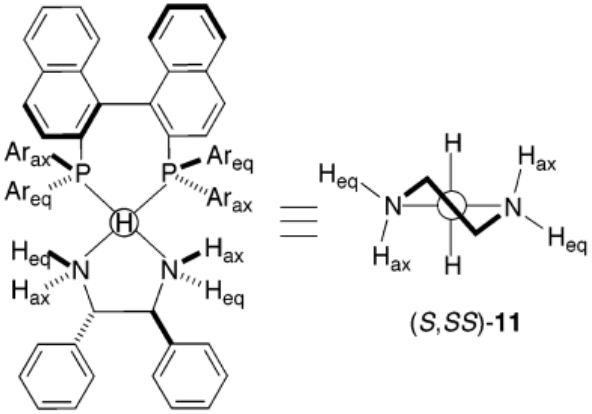
Key intermediates and their molecular modelling

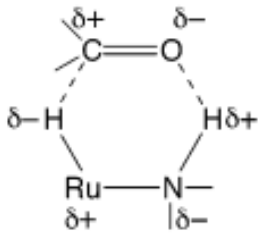




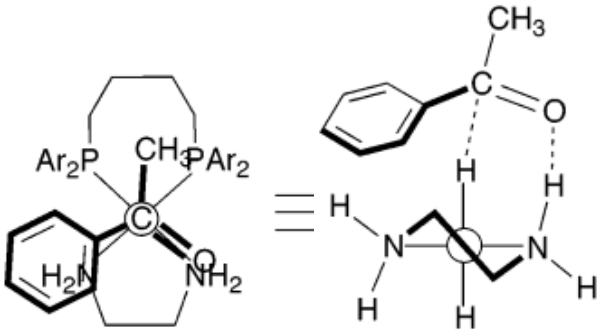
11



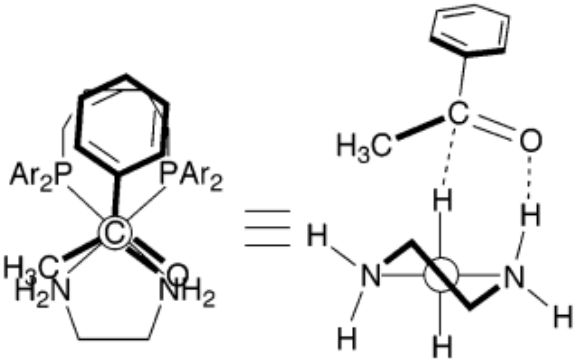




13 (TS)



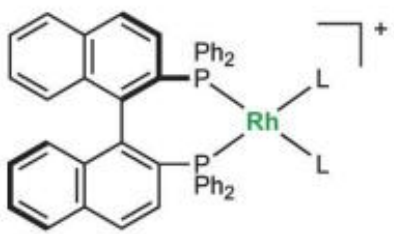
17_{Si} (favored)



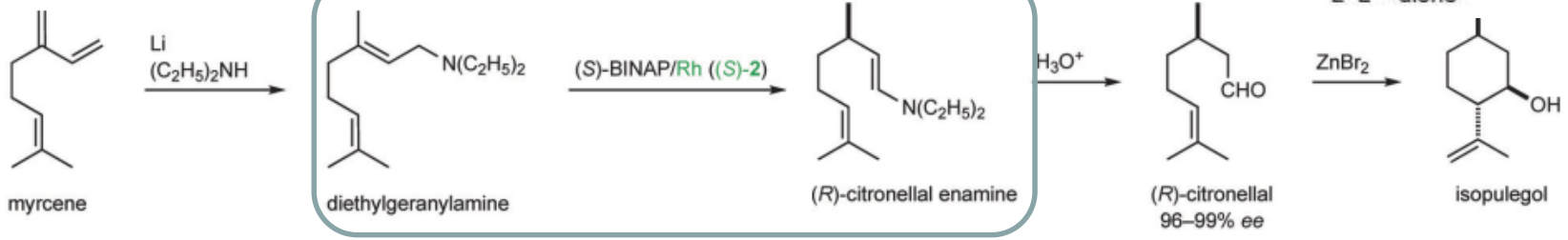
17_{Re} (unfavored)

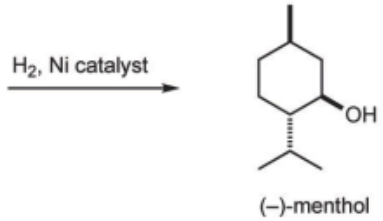
The catalytic system Rh/BINAP

Asymmetric 1,3-hydrogen shift reaction



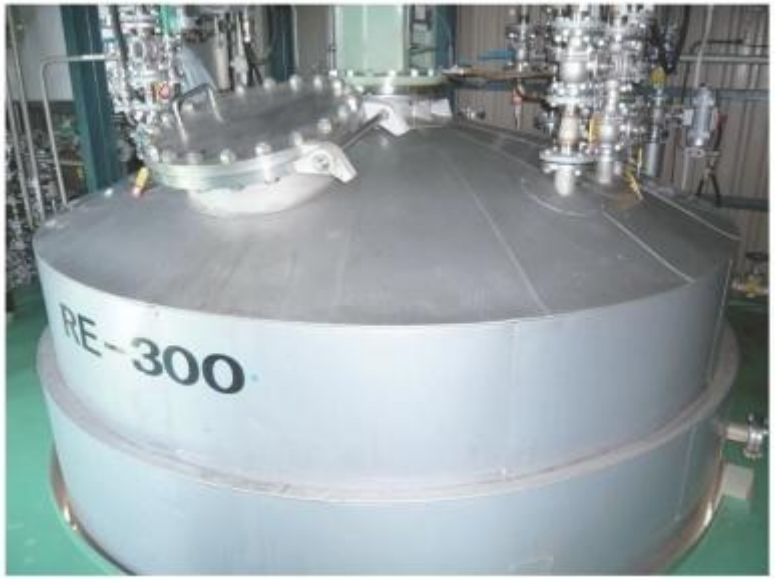
(*R*)-**2**: L = CH_3OH, THF, etc.
L–L = diene





9 ton di geranylamine
9.8 kg of Rh/BINAP **TON: 200 000**
2.7 m^3 di THF

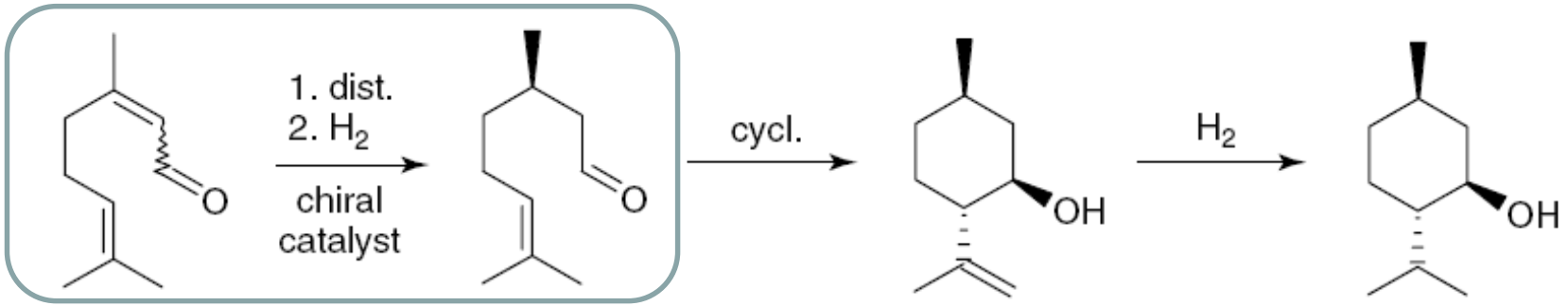
Product:
2800 ton/year of (-)-menthol;
(*R*)-citronellal ee 98% *vs* 80% ee of the natural product collected from rose oil.

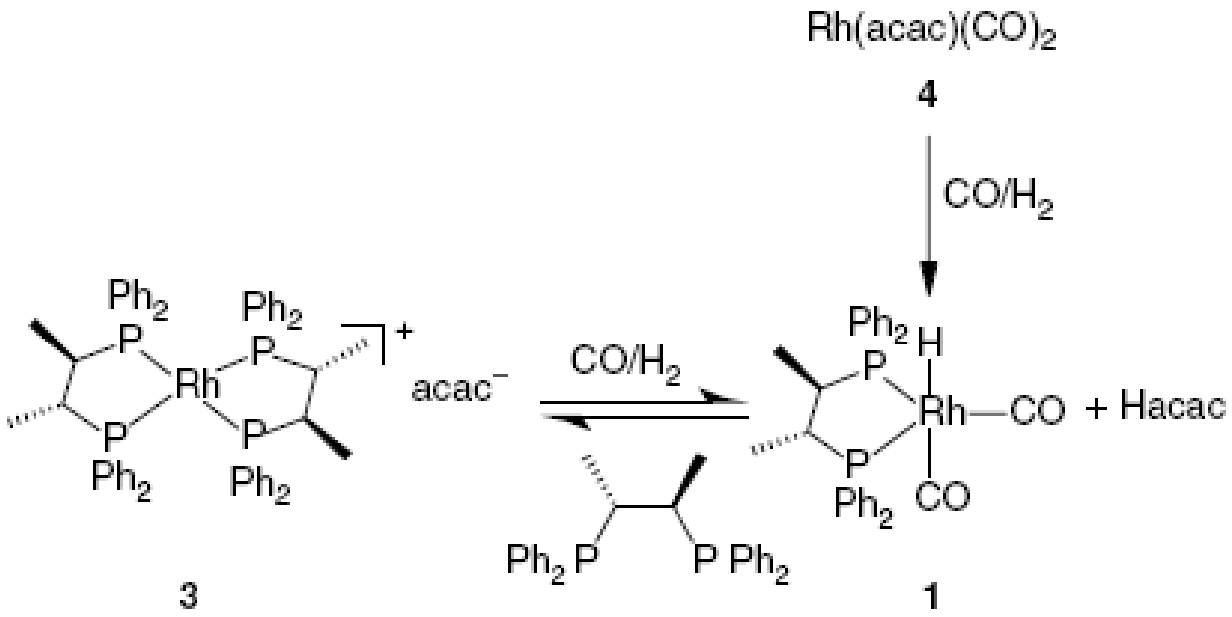


Takasago Reactor (in 2012)

The catalytic system Rh/Chiraphos (BASF)

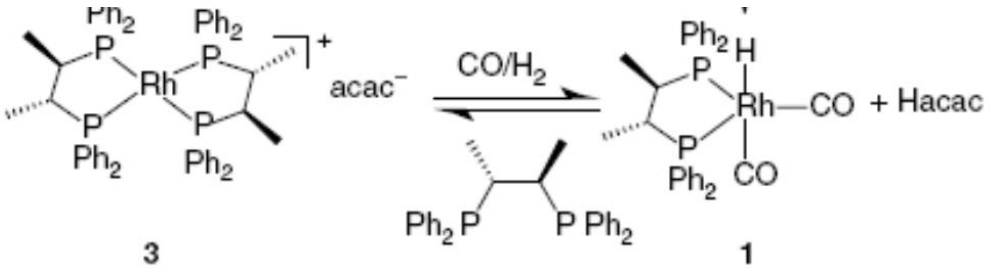
Asymmetric hydrogenation for synthesis of L-menthol

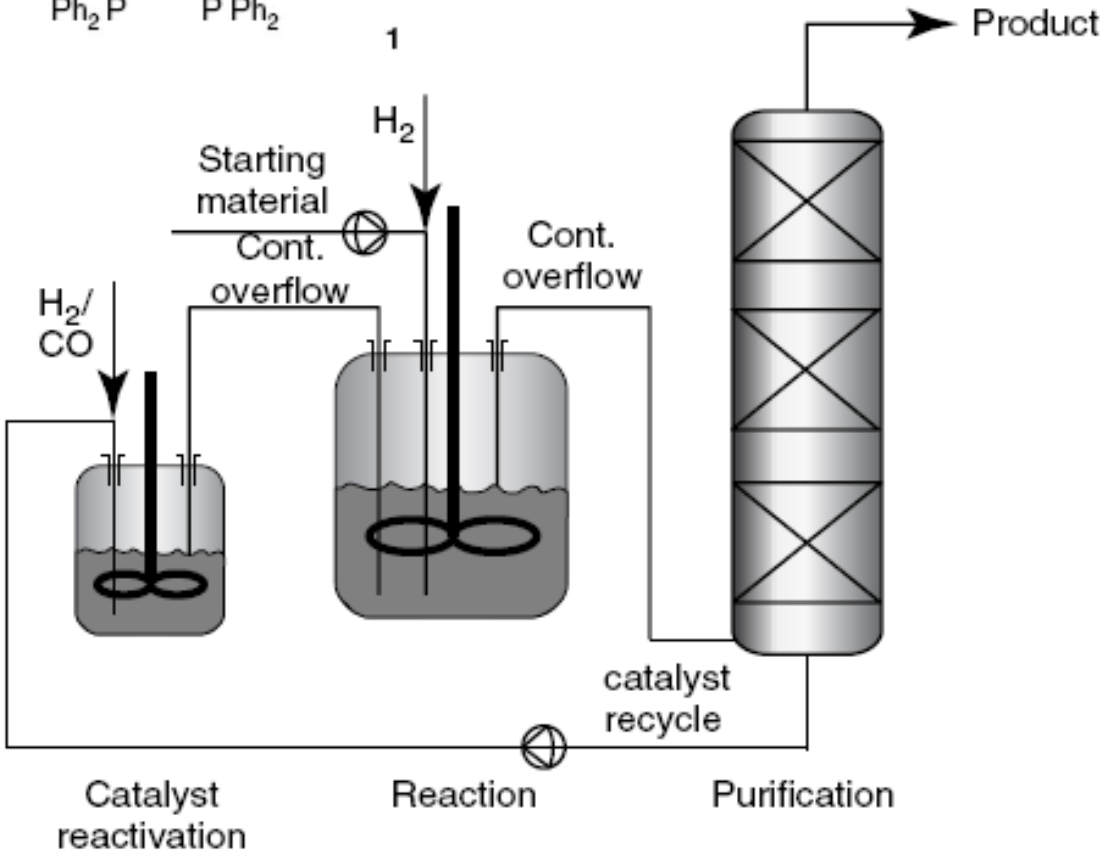




The catalytic system Rh/Chiraphos (BASF)

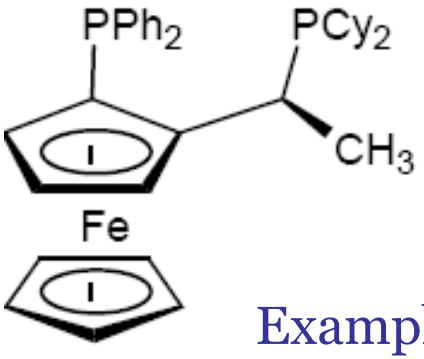
Flow scheme of the continuous process





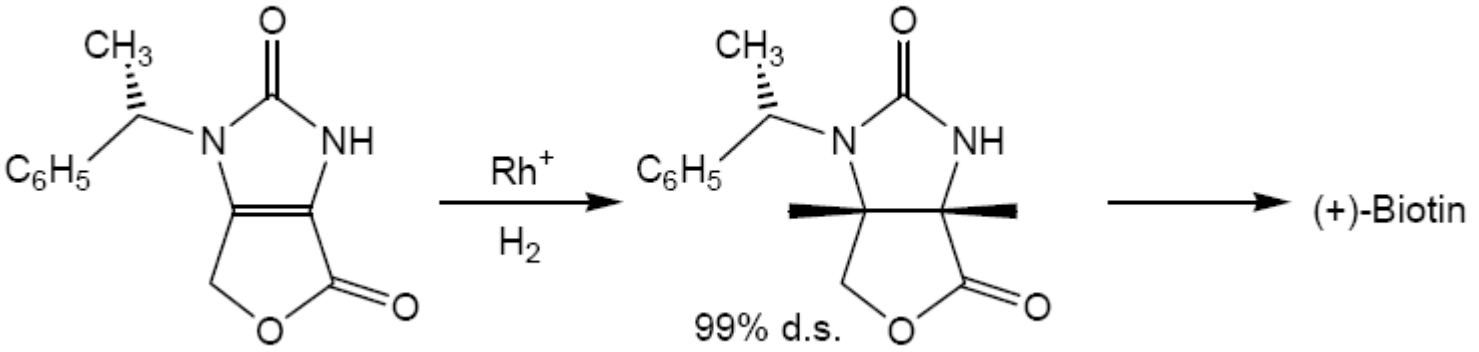
TON = 100 000

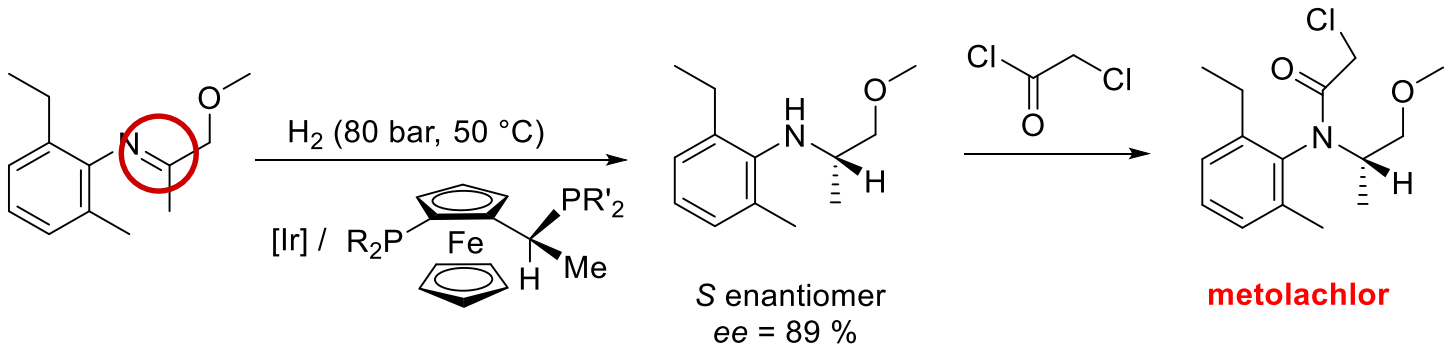
Examples of other ligands for asymmetric hydrogenation



JosiPhos

Examples of JosiPhos industrial applications





S enantiomer
ee = 89 %

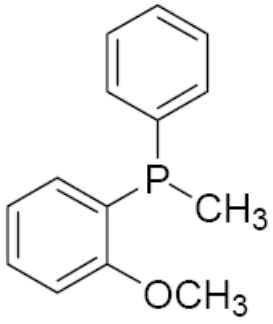
metolachlor

20 000 ton/year; TON = 10^6; TOF = 200 000 h^{-1}

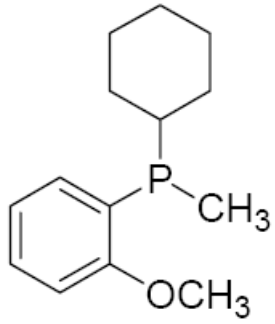
Chiral bidentate phosphines

1. They ensure the cis geometry at the catalyst;
2. The effectiveness of the chirality transfer can be tuned by varying both the hydrocarbon bridge between the two phosphorus atoms and/or the substituents on the phosphorus atoms.

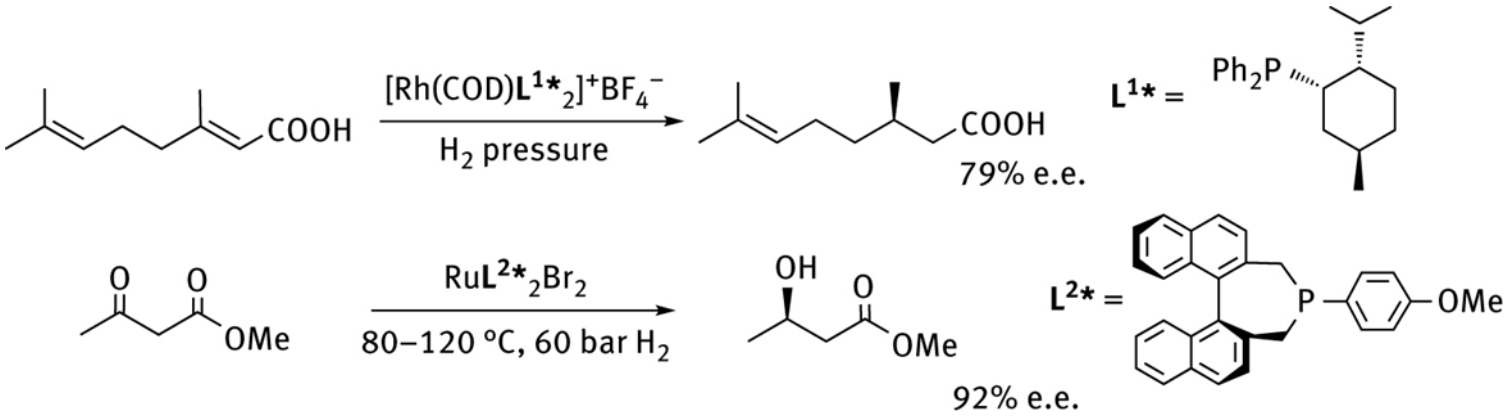
Chiral monodentate phosphines



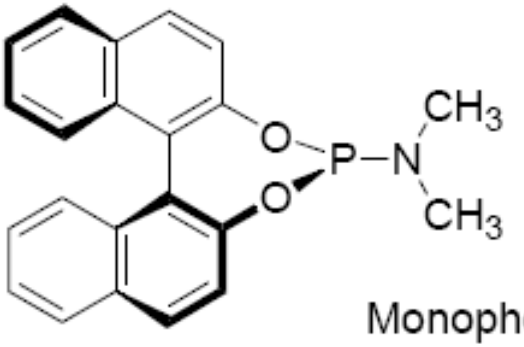
PAMP



CAMP

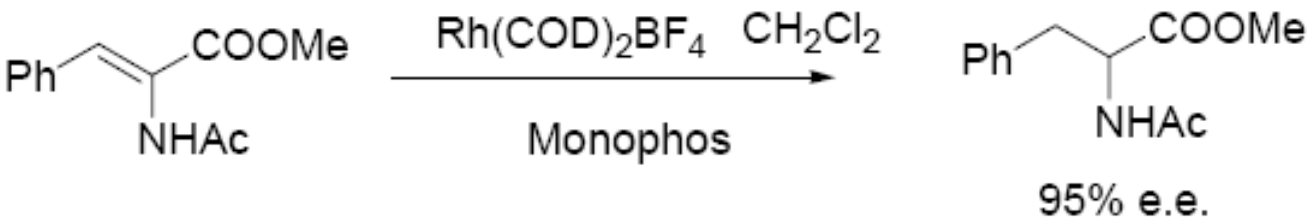


Chiral monodentate phosphines



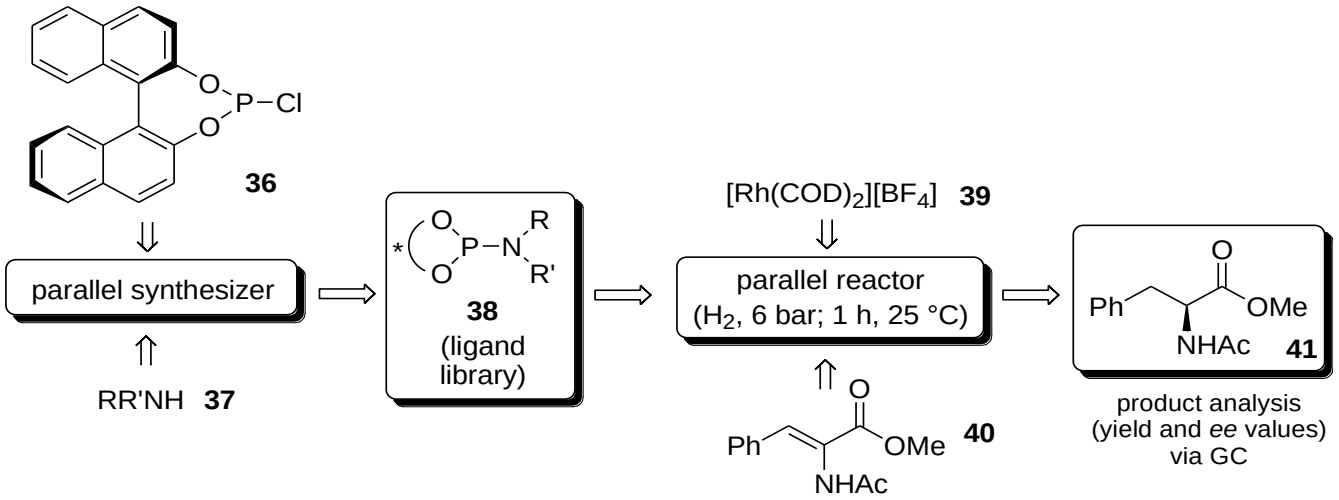
Monophos

The class of phosphoramidites;
Axial chirality;
Binaphthol backbone (BINOL);
Versatility of substituents on nitrogen atom.



95% e.e.

An example of application of combinatorial chemistry to catalysis.



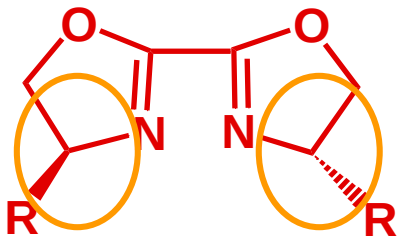
An example of a parallel reactor for high-throughput screening

Achiral and chiral nitrogen-donor ligands

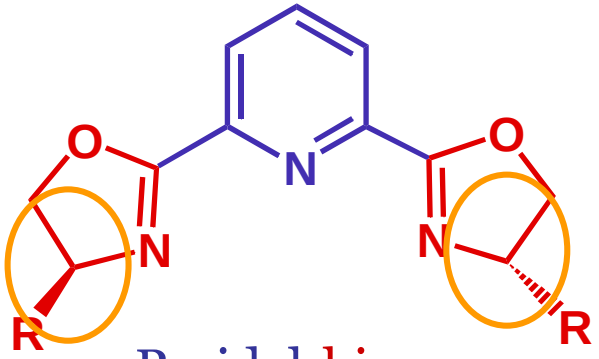
Amines:
sp^3 hybridised nitrogen-donor atom;
Hard ligands;
Strong σ-donor;
Stabilise high-valent metal complexes.

Pyridines and other N-heterocycles:
sp^2 hybridised nitrogen-donor atom;
Soft ligands;
Good σ-donor and poor π-acceptor;
Stabilise medium-, high-valent metal complexes.

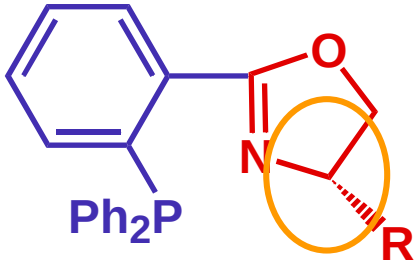
Examples of classes of nitrogen-donor ligands



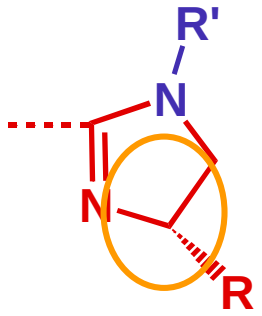
bi-oxazolines



Pyridyl-bis-oxazolines



phosphine-oxazolines



imidazolines

Examples of enantioselective catalytic reactions using phosphine-oxazolines