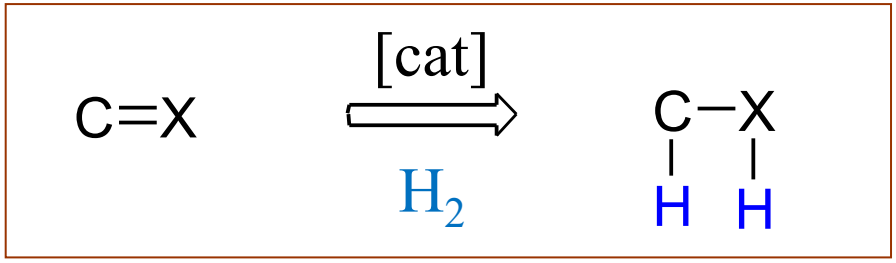
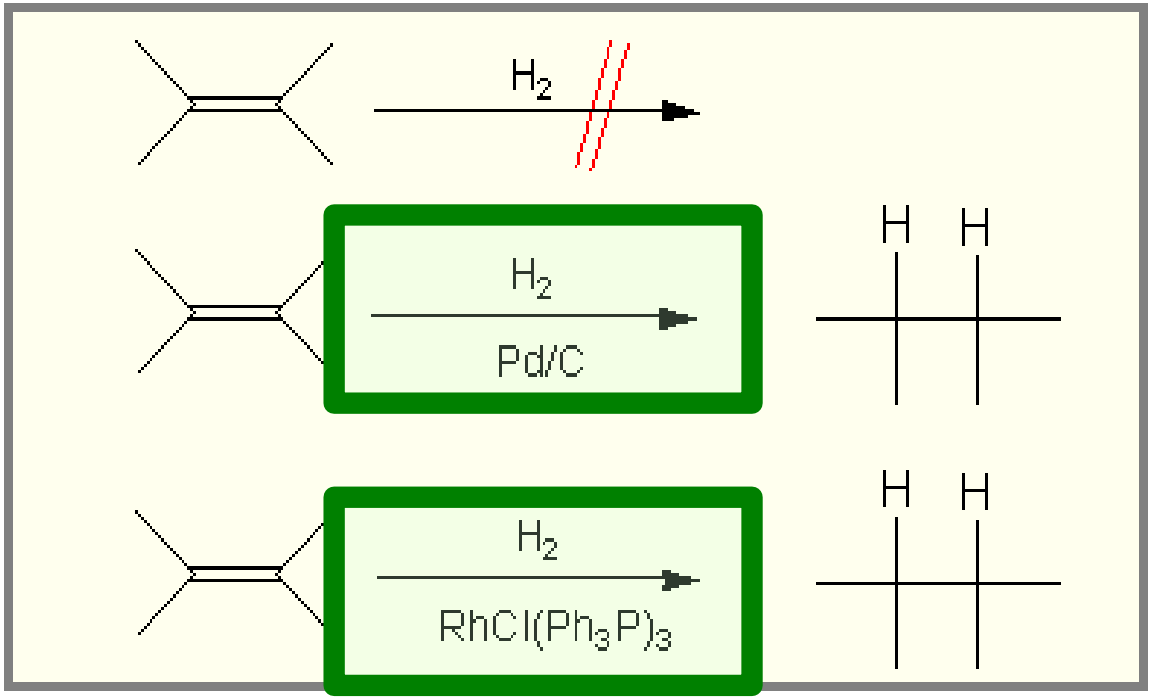
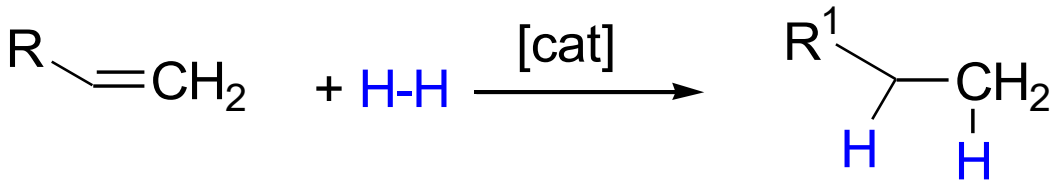
Hydrogenation

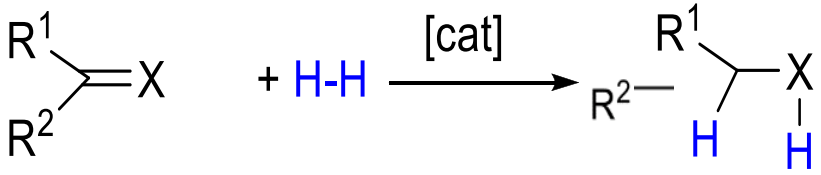
Hydrogenation of organic substrates





Hydrogenation of organic substrates

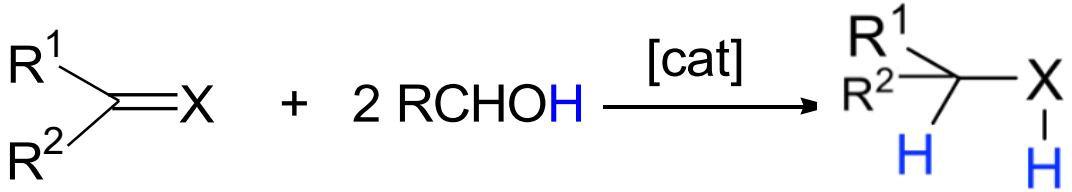




X = O ⟶ alcohols

X = NH ⟶ amines

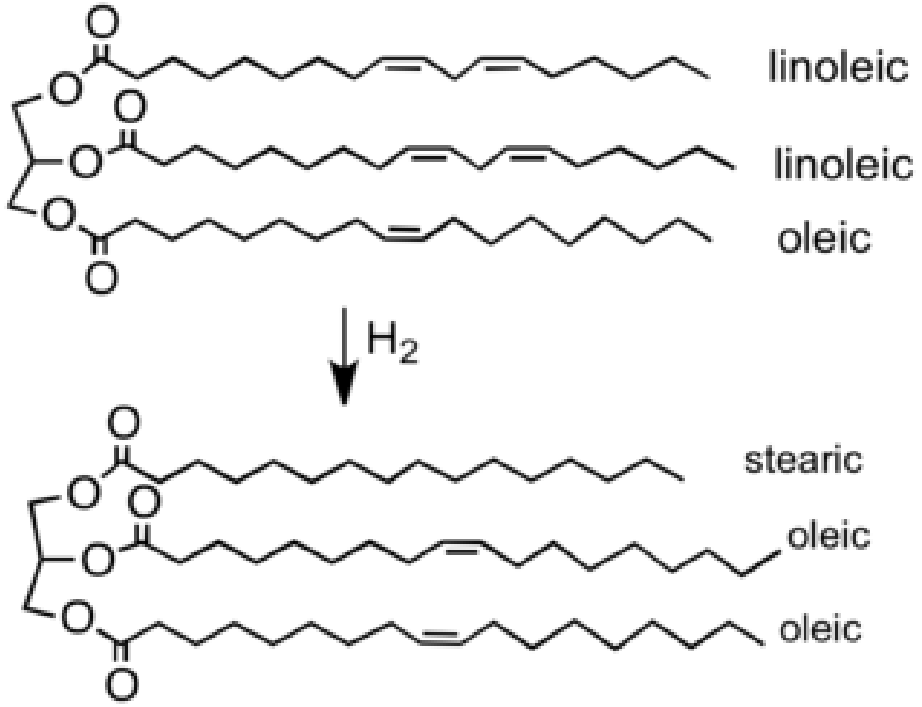
Reduction by hydrogen transfer (transfer hydrogenation)



Catalytic hydrogenation: an example of daily application that should be avoided

Food industry:

- Processing of vegetable oils and fats:
  Partial hydrogenation of a typical vegetable oil to a typical component of margarine. Most of the C=C double bonds are removed in this process, which elevates the melting point of the product. But bad for your health!!



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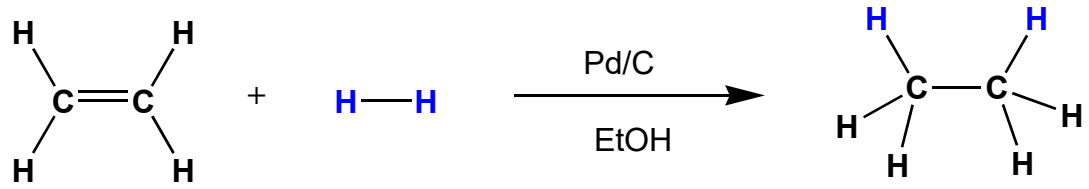
I. Heterogeneous hydrogenation

<u>Heterogenous Hydrogenation</u> of Alkenes – addition of H-H (H_2) to the π-bond of alkenes to afford an alkane. The reaction must be catalyzed by metals such as Pd, Pt, Rh, and Ni.



C-C π-bond = -243 kJ/mol

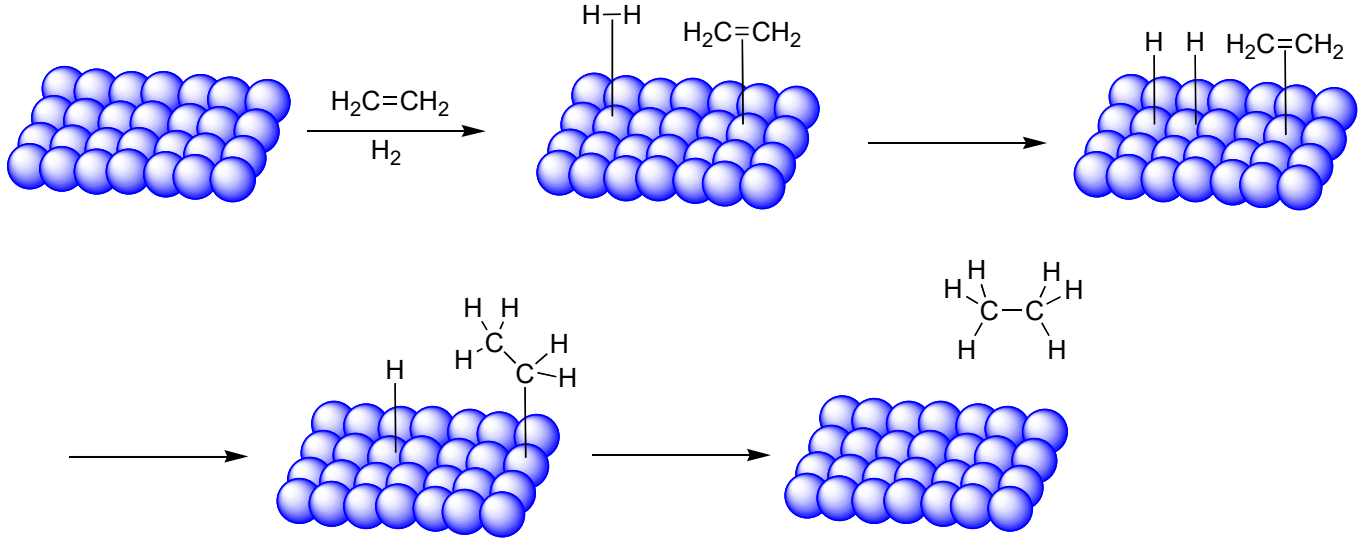
H-H = -435 kJ/mol

C-H = 2 x -410 kJ/mol

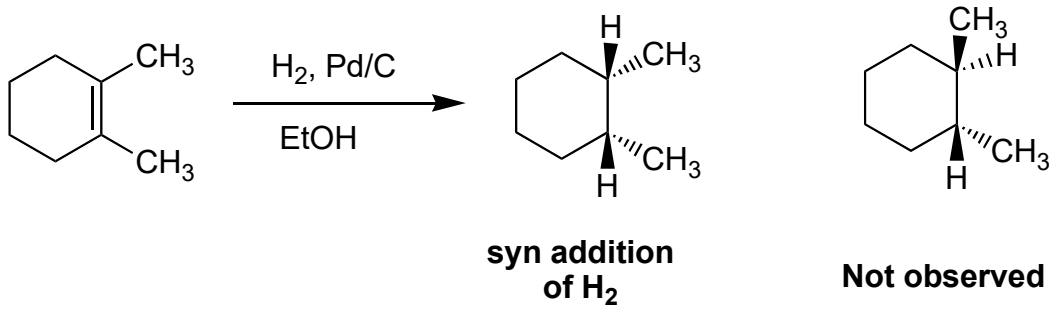
= **-142 kJ/mol**

- The catalysts is not soluble in the reaction media, thus this process is referred to as a *heterogenous* catalysis.
- The catalyst assists in breaking the π-bond of the alkene and the H-H σ-bond.
- The reaction takes places on the surface of the catalyst. Thus, the rate of the reaction is proportional to the surface area of the catalyst.

Heterogeneous catalysis: Stereochemistry of Alkene Hydrogenation Mechanism:



The addition of H_2 across the π-bond is *syn, i.e.,* from the same face of the double bond

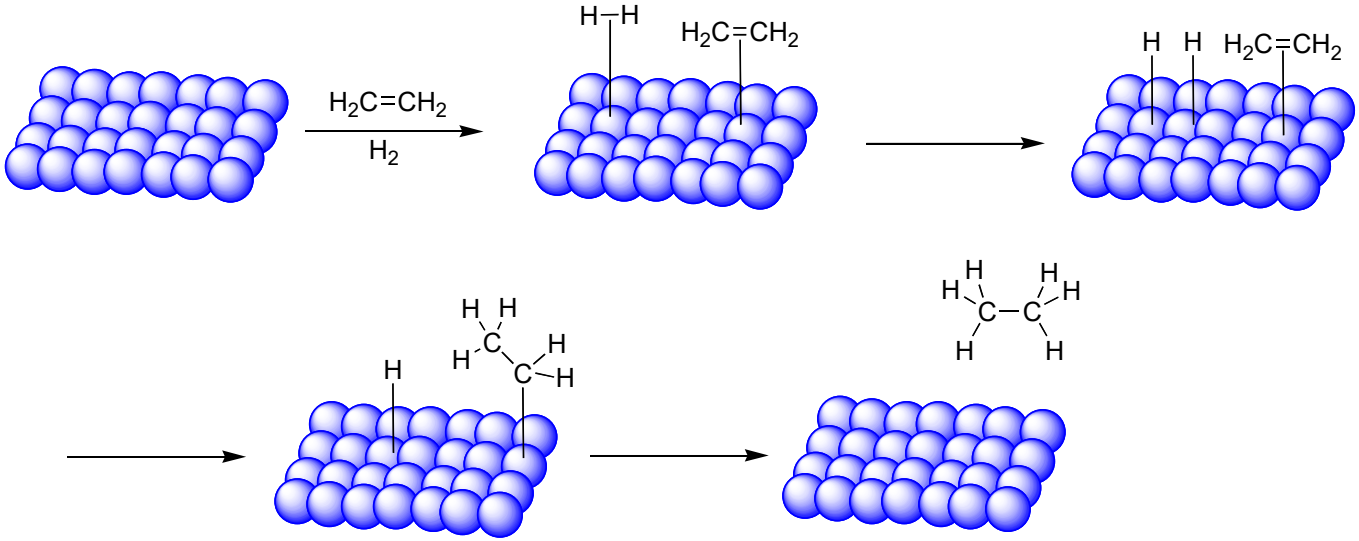


syn addition of H_2

Not observed

Heterogeneous catalysis: Stereochemistry of Alkene Hydrogenation

Mechanism:



What happens if you have more than one alkene moiety? Why?

CH_2=CH-CH=CH_2 + H_2 ==> CH_2=CH-CH_2-CH_3 Pd catalyst

CH_2=CH-CH=CH_2 + $2H_2$ ==> CH_3-CH_2-CH_2-CH_3 Pt catalyst

The selectivities of hydrogenation reactions depend primarily on the relative probability of adsorption of the unsaturated functional groups located either in different molecules or in the same molecule. Theoretical calculations of the chemisorption energies of unsaturated molecules on model metal surfaces can account for selectivity data. Thus, in butadiene hydrogenation, the higher selectivity to 1-butene on palladium than on platinum can be interpreted from calculated adsorption energies. On **Pd(111), the chemisorption energy** of the di- adsorbed form of **butadiene** was found **twice** as large as that of 1-butene, so that butadiene displace butene from the metal surface once it is formed. In contrast, on **Pt(111), butadiene and 1-butene have similar chemisorption energies**, so that 1-butene remains adsorbed and is further hydrogenated into butane.

II. Homogeneous hydrogenation

Hydrogen activation

Homolytic:

$$[RhCl(PPh_3)_3] + H_2 \rightarrow [Rh(H)_2Cl(PPh_3)_3]$$

$$2\,[Co(CN)_5]^{3-} + H_2 \rightarrow 2\,[CoH(CN)_5]^{3-}$$

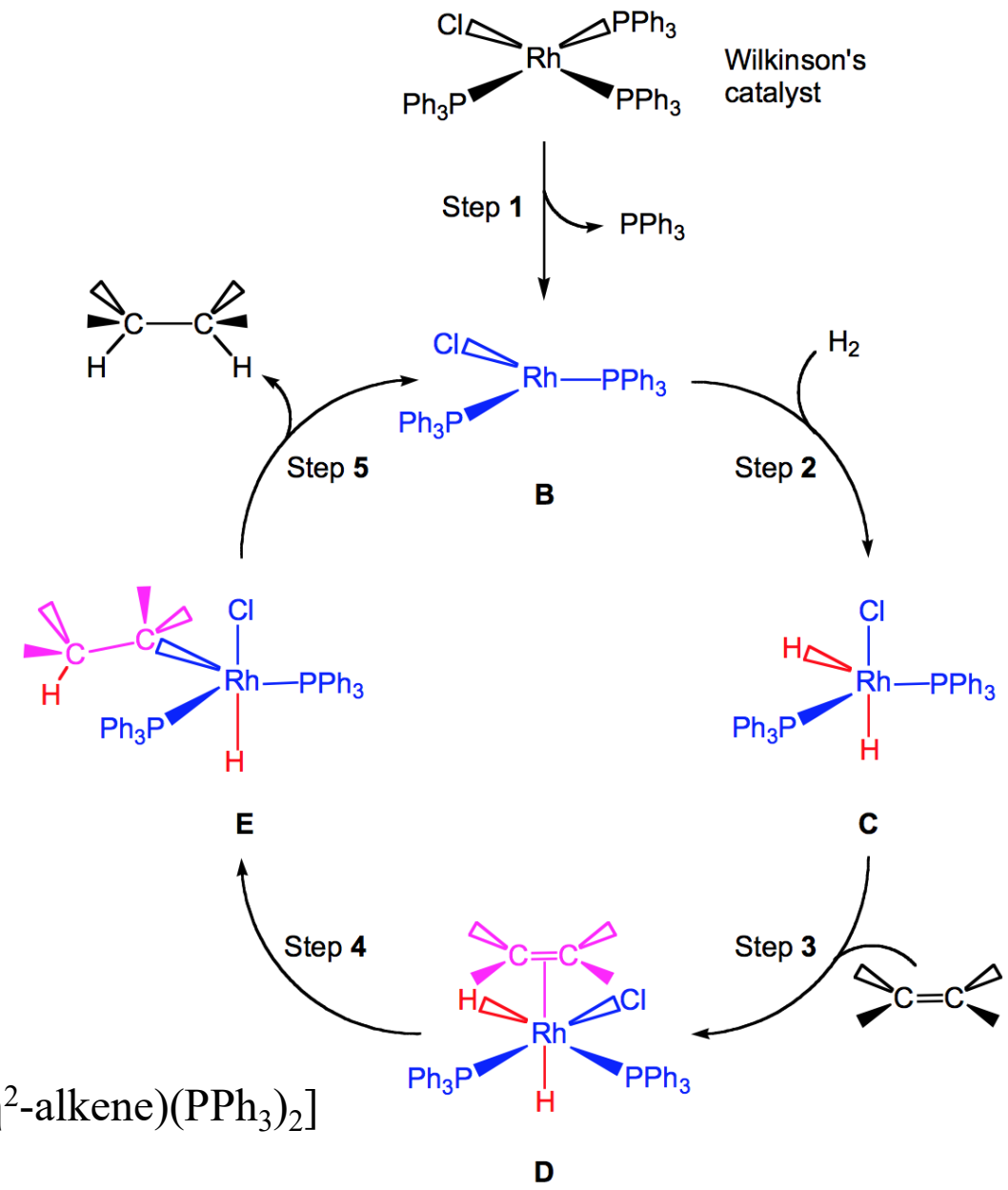
Heterolytic:

$$MY + H_2 \rightarrow MH + H^+ + Y^-$$

Examples: $[RuCl_2(PPh_3)_3] + H_2 + NEt_3 \rightarrow [RuHCl(PPh_3)_3] + Et_3NHCl$

$[PtCl(SnCl_3)(PPh_3)_2] + H_2 \rightarrow [PtH(SnCl_3)(PPh_3)_2] + HCl$

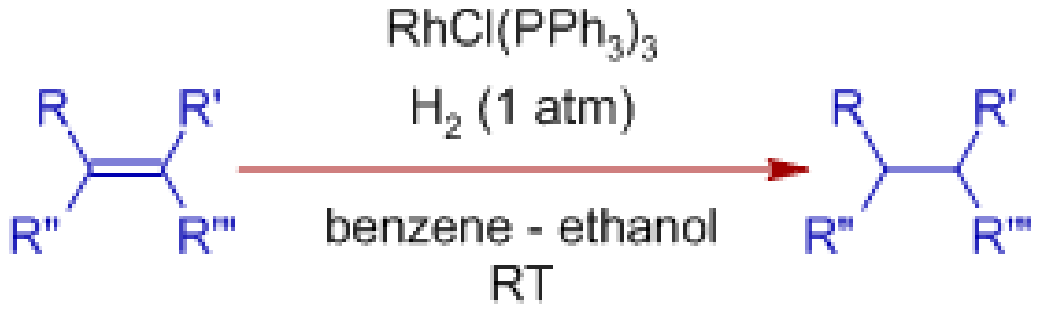
The classic catalyst for hydrogenation reactions was developed by Wilkinson, $Rh(PPh_3)_3Cl$. Catalytic cycle (simplest scheme):



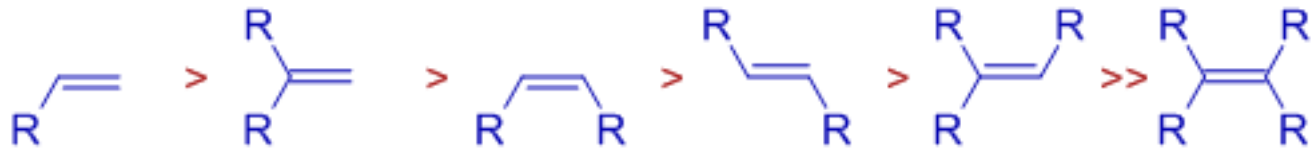
$[RhH_2Cl(\eta^2\text{-alkene})(PPh_3)_2]$

Synthesis of catalyst:

Homogeneous catalytic, selective hydrogenation:
alkenes and alkynes without affecting the functional groups
(C=O, CN, NO_2, Aryl, CO_2R)

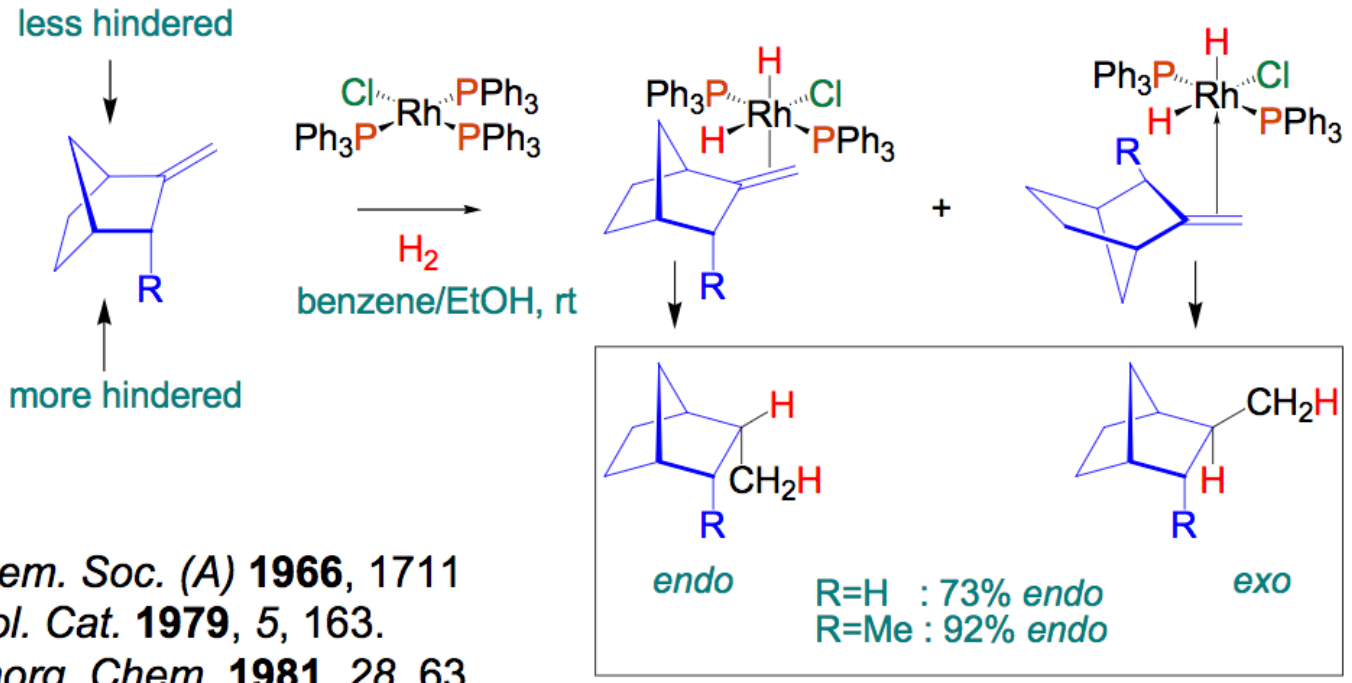


rates of hydrogenations decrease with increase in the alkyl group
substitution on double bond - steric factors



Selectivity of the hydrogenation (Wilkinson)

Rh preferentially binds to the least sterically hindered face of the olefin:



Wilkinson, *J. Chem. Soc. (A)* **1966**, 1711
Rousseau, *J. Mol. Cat.* **1979**, *5*, 163.
Jardine, *Prog. Inorg. Chem.* **1981**, *28*, 63.

III. Mechanism of Wilkinson’s catalyst

Detailed reaction mechanism of the hydrogenation (Wilkinson)

Mechanistic studies:

- the rate of reaction decreases when excess of PPh_3 is added; indicating the initial dissociation of one of the PPh_3 ligand before dihydrogen activation.

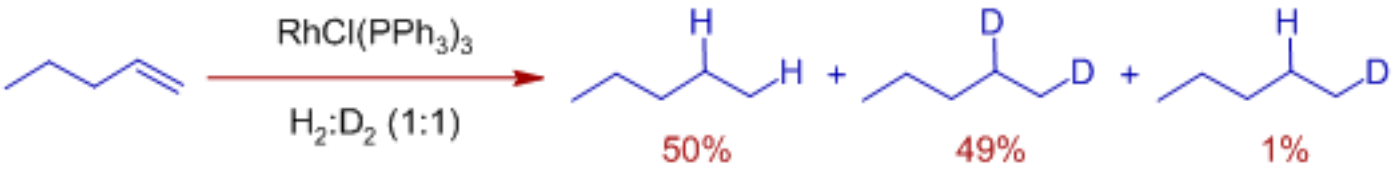
- H_2 activation at first before alkene coordination

- Rate determining step is the migratory insertion

Detailed reaction mechanism of the hydrogenation (Wilkinson)

Mechanistic studies:

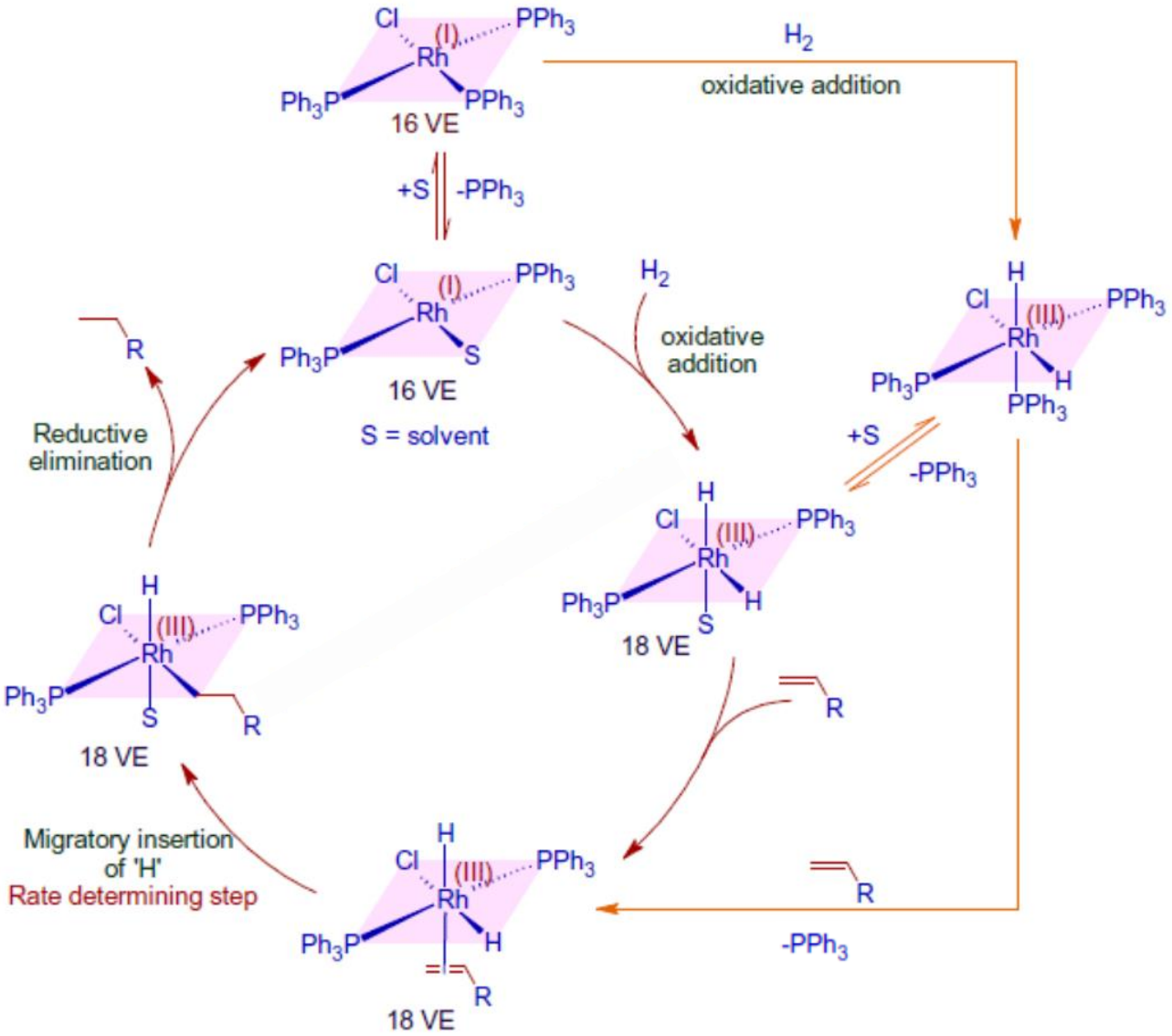
- no H/D exchange is observed:



- formation of dihydrido complex that transfers both of its hydrido ligands to the olefin

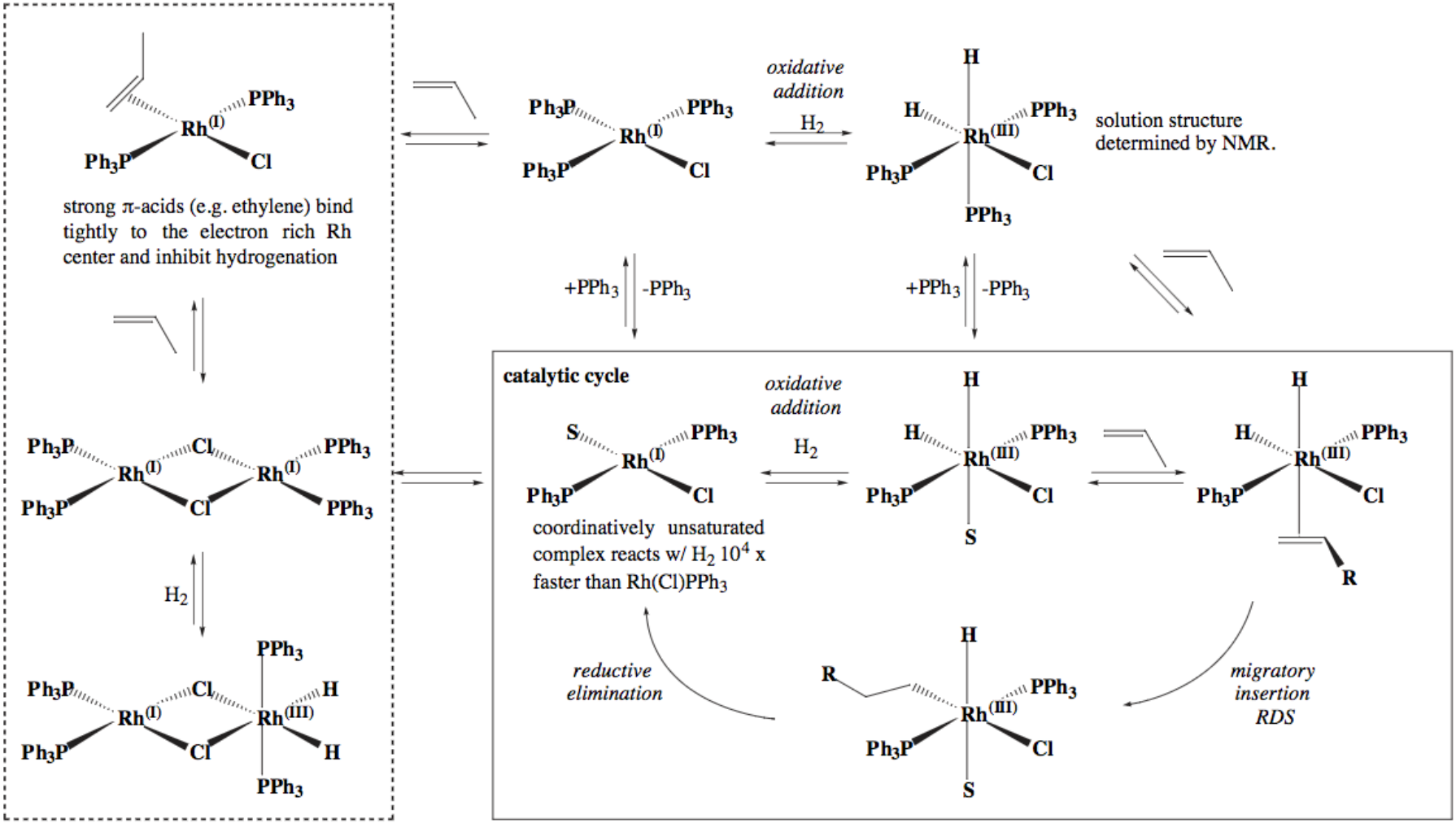
- The reverse of migratory insertion is not significant (why?)

Detailed reaction mechanism of the hydrogenation (Wilkinson)



Detailed reaction mechanism of the hydrogenation

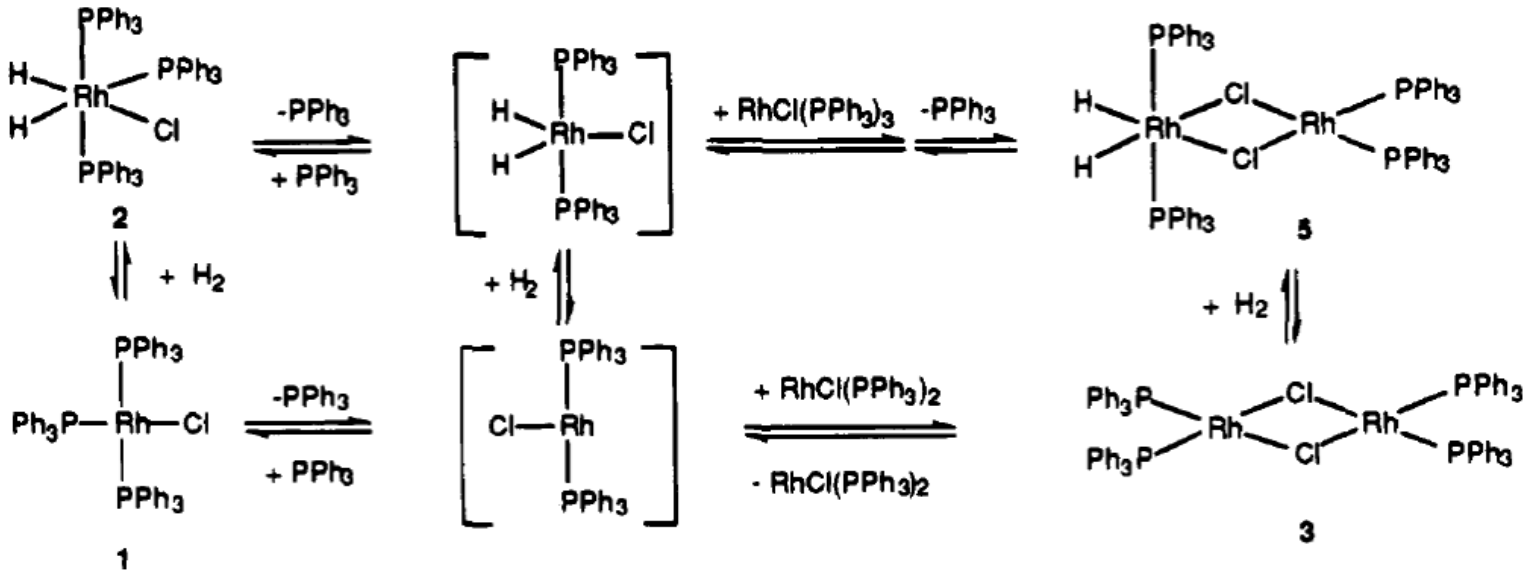
Wilkinson hydrogenation: classic dihydride mechanism



Intermediates observed by NMR or as isolated solids in the reaction system. Formation of these "side-products" results in a reduction in the rate of hydrogenation.

Halpern *Chem. Comm.* **1973** 629.
Halpern *J. Mol. Catal.* **1976** (2) 65.
Halpern *Inorg. Chim. Acta.* **1981** (50) 11.

Other intermediates have also been identified – notably dimers at higher temperatures:

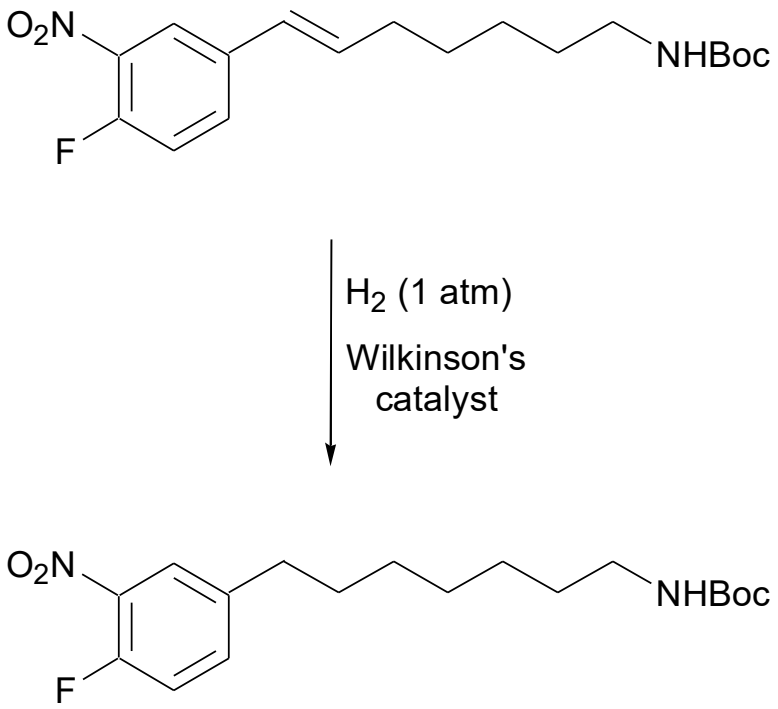


(Figure taken from *J. Am. Chem. Soc.*, **1994**, *116*, 10548)

The dimers are less active than the monomers and their presence leads to reduce activity.

Increasing the steric bulk of the phosphine in Wilkinson's catalyst should lead to increased activity, since the rate determining step (RDS) can be the first phosphine ligand dissociation, however, as the size of the phosphine increases the formation of dimers increase, hence activity decreases.

Solvent effects: solvent influences Wilkinson's catalyst.
For example, the hydrogenation of the functional alkene varies considerably with the solvent.



Solvent	Yield (% after 48 h)
Benzene	0
Toluene	20
Methanol	80
THF	91
Methanol-THF	93

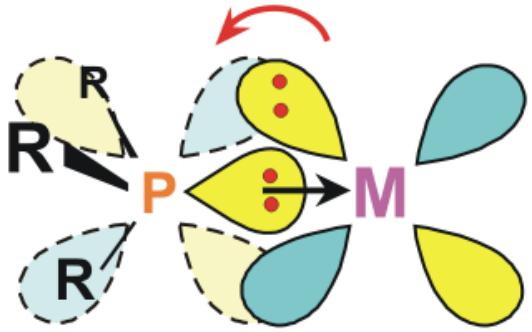
Polar solvents probably reduce the formation of dimers which are less active. Therefore, careful choice of solvent can be used to improve catalytic activity, but is limited by the solubility of the catalyst and substrates in the solvent.

IV. Improvement of Wilkinson’s catalyst

LIGAND DESIGN – how to improve a catalyst.

Phosphines PR_3, Phosphites $P(OR)_3$

empty d orbitals on phosphine can act as π-acceptor orbitals } not very important unless R-groups are electron-withdrawing



neutral $2e^-$ donor

Phosphine ligands

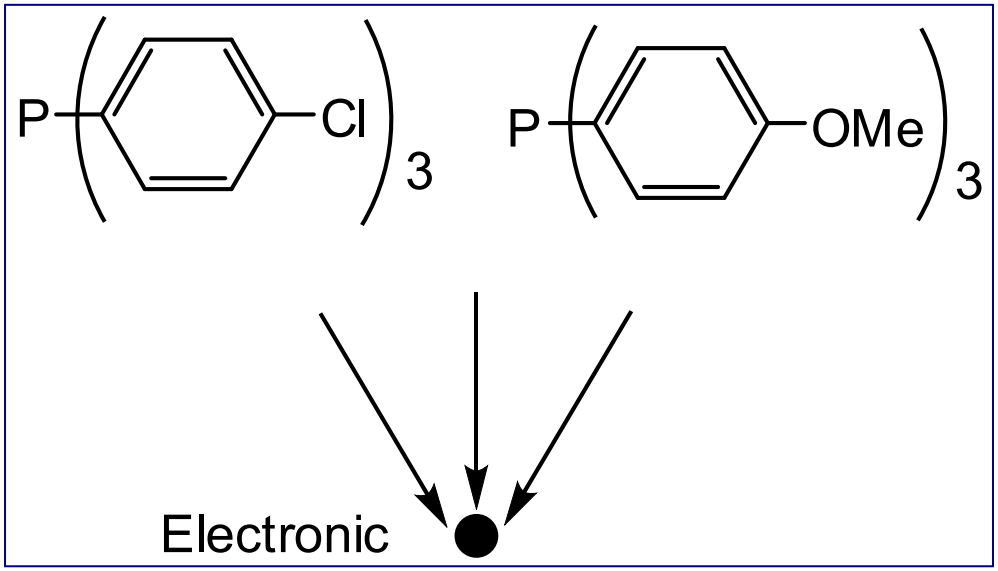
excellent soft-donor ligands with a wide variety of easily adjusted steric and electronic factors

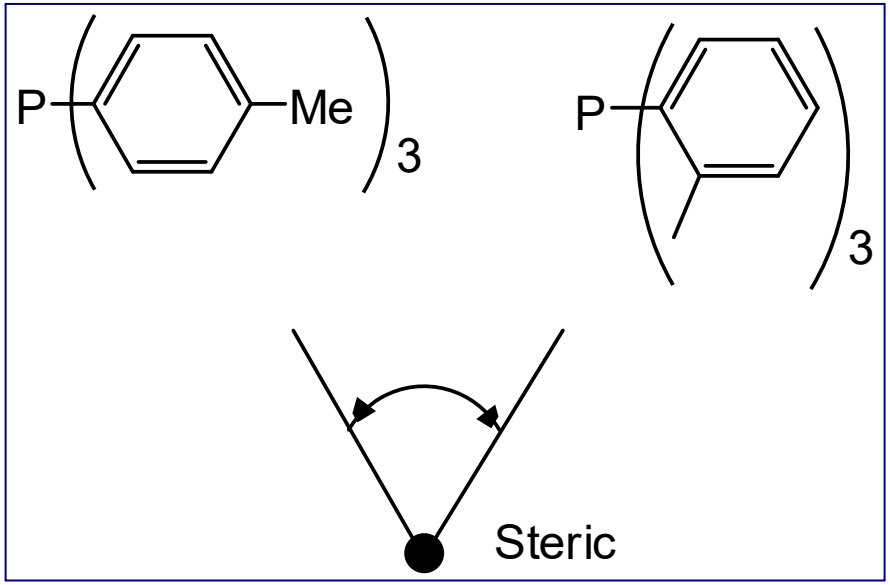
R = carbon groups { phosphine (US)
phosphane (Germany/Europe)

R = OR groups → phosphite

Changing substituents on the phosphorus(III) centre alters the electronic and steric effects of the P-atom and changes catalytic activity.

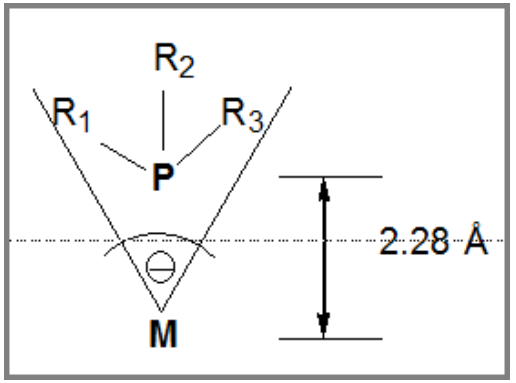
Electronic effects – transmitted along bonds, e.g. the difference in basicity of phosphines such as P(*p*-$C_6H_4OMe)_3$ and P(*p*-$C_6H_4Cl)_3$.





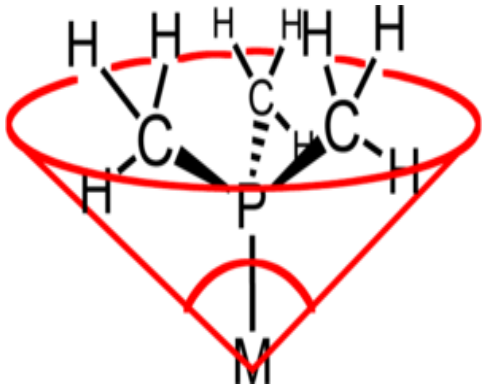
Steric effects correspond to forces (usually non-bonding) between parts of the molecule, e.g. the difference in changing the position of a substituent such as P(*p*-$C_6H_4Me)_3$ and P(*o*-$C_6H_4Me)_3$.

Tertiary phosphine ligands



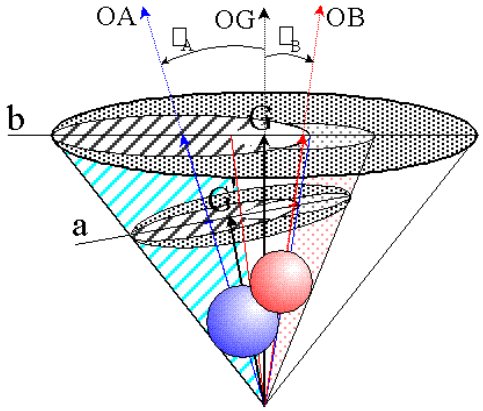
In 1977 Chad Tolman published a review covering methods that he developed for ordering a wide variety of phosphine ligands in terms of their steric bulk and electron-donating ability (*Chemical Reviews*, **1977**, *77*, 313-348).

Quantification of steric bulk – Tolman (or ligand) cone angle, Θ, is a measure of the size of a ligand. It is defined as the solid angle formed with the metal at the vertex and the hydrogen atoms at the perimeter of the cone. Tertiary phosphine ligands are commonly classified using this parameter, but the method can be applied to any ligand.



Cone angles of common phosphine ligands, PR_3 (º): H 87 F 104 OCH_3 107; CH_3 118; CH_2CH_3 132; C_6H_5 145; cyclo-C_6H_{11} 170; t-Bu 182; C_6F_5 184; 2,4,6-$Me_3C_6H_2$ 212.

Cone angles are determined from crystallographically determined structures or computed by algorithms.



(Figure by B. Craig Taverner, Structural Chemistry Group, Department of Chemistry, University of the Witwatersrand, Private Bag 3, WITS 2050, Johannesburg, South Africa.)

Steric and electronic map

If an experimental parameter is dominated by steric effects, the dependence can be readily shown by plotting it against Θ. If an experimental parameter is dominated by electronic effects, a plot against n is appropriate. In general, many experimental parameters depend on both steric and electronic effects, e.g. catalytic activity. It is possible to describe the dependence graphically in terms of its percentages of steric and electronic character. This can be done with the Steric and Electronic Map of phosphorus ligands. The position of any ligand on the map can be determined by its values of n and Θ and examples where this is important in catalysis will be given later. (Figure taken from *Chemical Reviews*, **1977**, *77*, 313)

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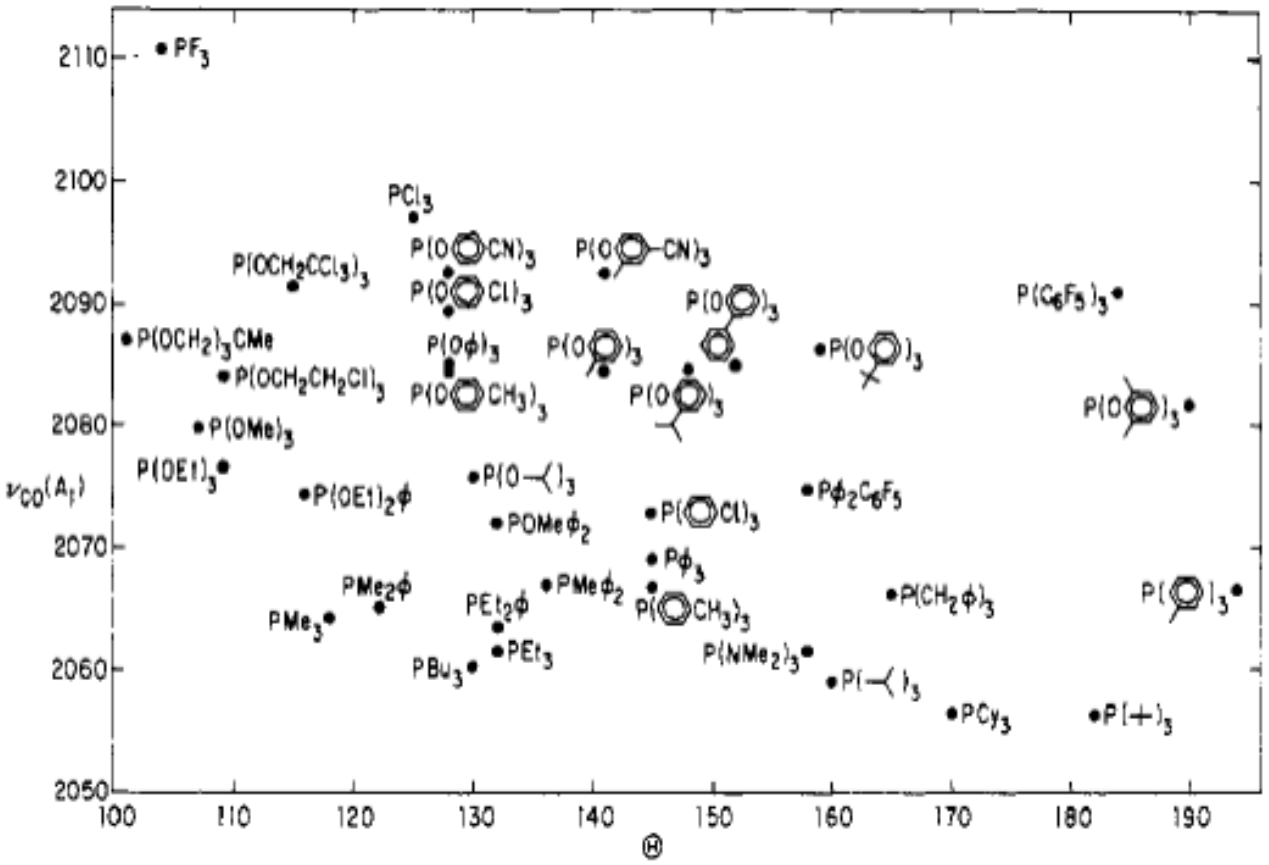
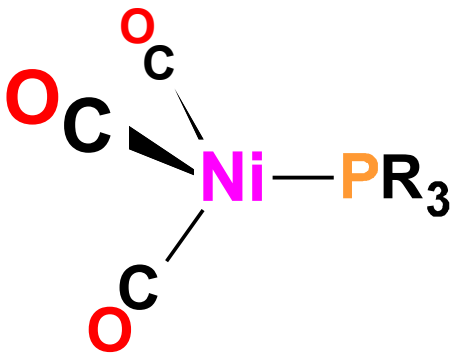


The electronic parameter, υ, or the **electron-donating ability** of a phosphine ligand was determined by reacting one equivalent of the phosphine with $Ni(CO)_4$ to make a $Ni(CO)_3$(phosphine) complex. The carbonyl υ_{CO} IR stretching frequency (the very sharp a_1 high energy mode) of the $Ni(CO)_3$(phosphine) complex was measured. The **more electron density the phosphine ligand donates** to the metal, the greater the π-backbonding to the carbonyl ligands, **weakening the C≡O triple bond**, thus **lowering the υ_{CO} IR stretching frequency**.

Lowest CO stretching frequency:

most donating phosphine



Highest CO stretching frequency:

least donating phosphine

(best π-acceptor)

Substituent	Substituent contribution†
^{t}Bu	0.0
Et	1.8
p-C_6H_4OMe	3.4
p-C_6H_4Me	3.5
m-C_6H_4Me	3.7
Ph	4.3
C_6F_5	11.2
CF_3	19.6

† Substituent contribution: more electron donating substituent gives lower υ_{CO}

Note: Alkyl groups are more electron donating than aryl groups.

Substituents on the aryl groups are important.

So how to improve Wilkinson's catalyst?

$Rh(PPh_3)_3Cl$

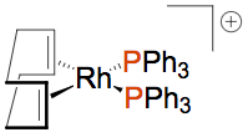
So how to improve Wilkinson's catalyst?

$Rh(PPh_3)_3Cl$

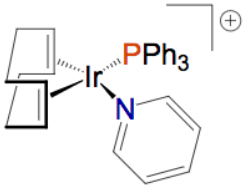
Something a bit more radical?

Cationic catalysts

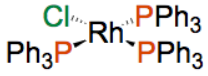
Cationic catalysts are the most active homogeneous hydrogenation catalysts developed so far:



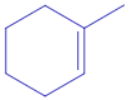
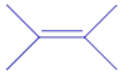
Schrock-Osborn catalyst



Crabtree's catalyst



Wilkinson's catalyst

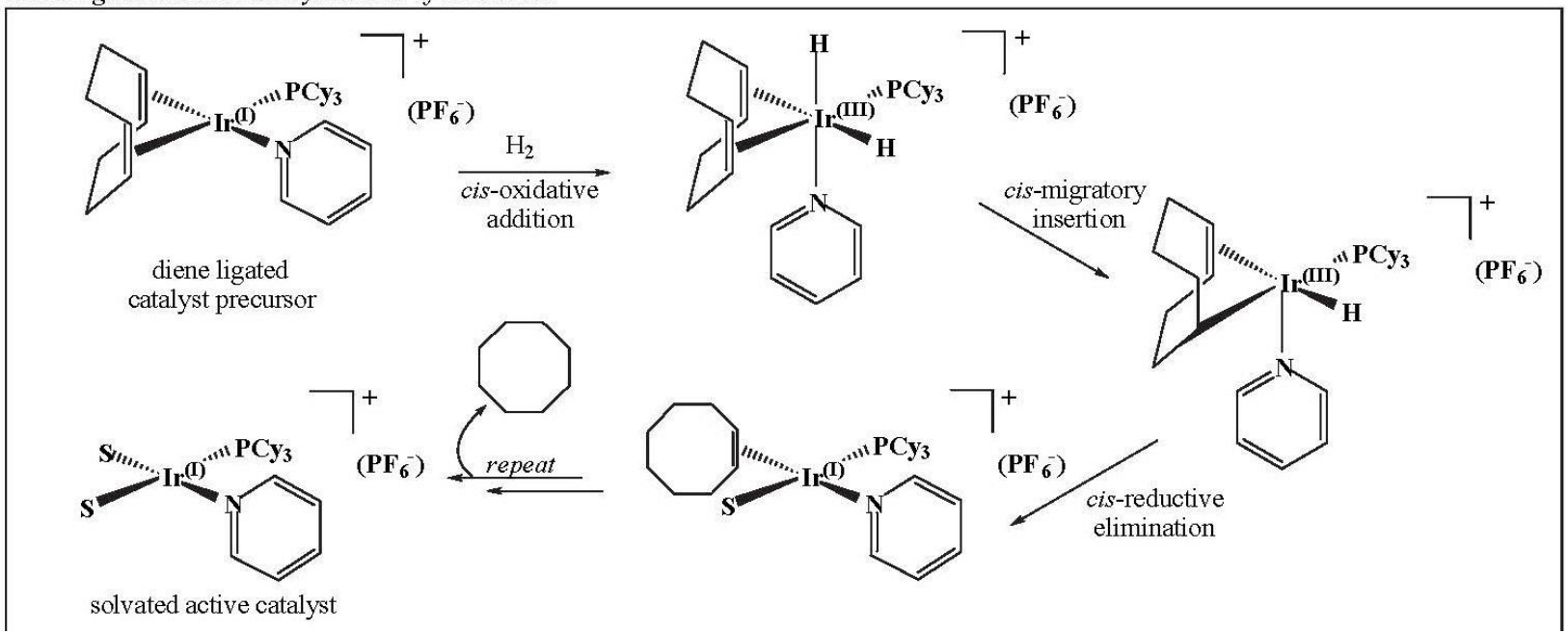
Substrates	Schrock-Osborn catalyst	Crabtree's catalyst	Wilkinson's catalyst
		TOF	
	4000	6400	700
	10	4500	650
		3800	13
		4000	

Mechanism changes from neutral to cationic catalysts !!!

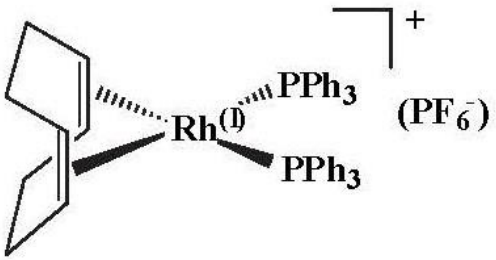
Olefin binding is before H_2 activation

Schrock- Osborn /Crabtree: Cationic catalysts

Diene ligated cationic catalysts mode of activation:

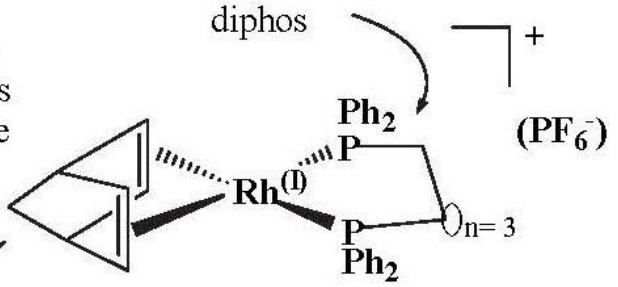


Diene ligand is removed under H_2 to give a di(solvato) complex



Schrock-Osborn catalyst

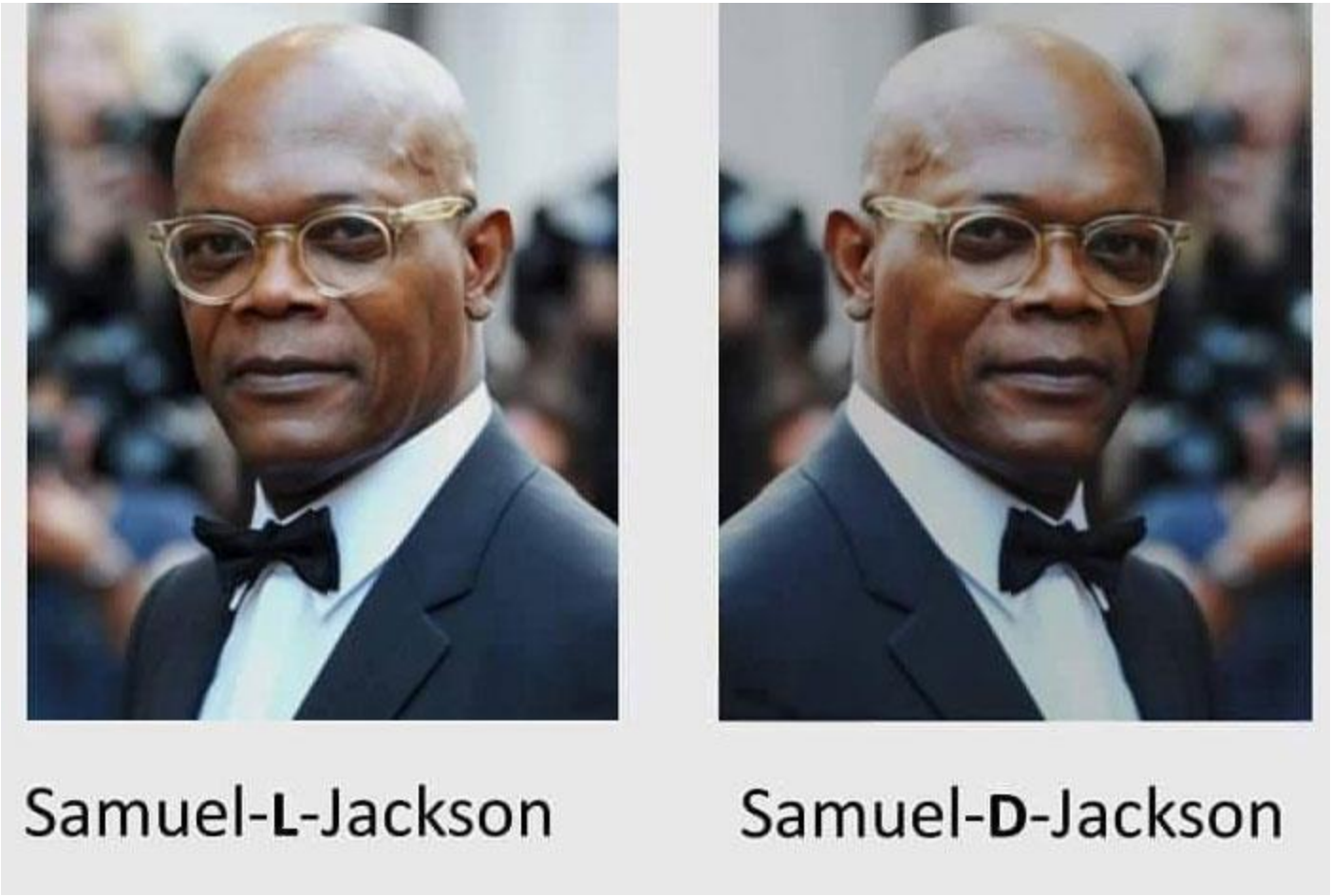
nbd
(norbornadiene)
ring strain results
in more facile
hydrogenation



Schrock-Osborn type catalyst
most commonly used:
$[Rh(nbd)(diphos\text{-}4)]BF_4$

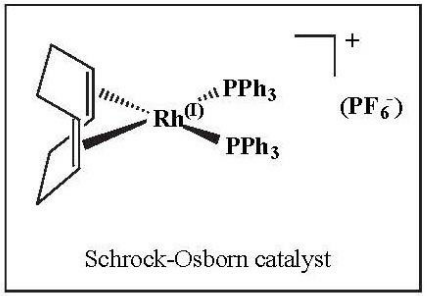
V. Asymmetric hydrogenation

Life is chiral

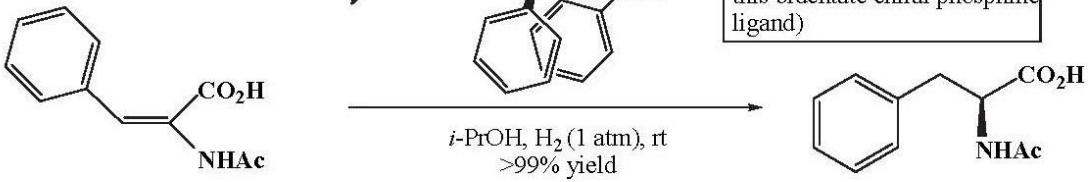


Asymmetric Hydrogenation

A bidentate, C_2 symmetric version of the cationic Schrock-Osborn catalyst affords extraordinarily high levels of enantioselectivity in the hydrogenation of achiral enamides. This was the first demonstration that a chiral transition metal complex could effectively transfer chirality to a non-chiral substrate with selectivities that rival those observed in enzymes. Recall that this led to the 1st commericalized asymmetric process using a chiral transition metal complex: Monsanto Process for the industrial production of *L*-DOPA (see Structure and Bonding, pg. 4)



Schrock-Osborn catalyst



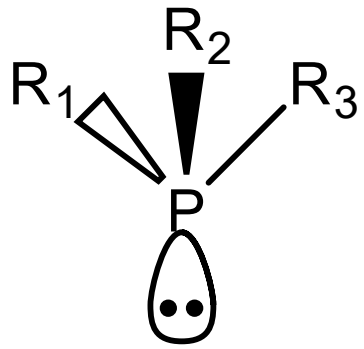
Knowles *JACS* **1975** (97) 2567.

93% ee

Chirality can be introduced into phosphines in several ways.

1. Chirality and the P-atom –

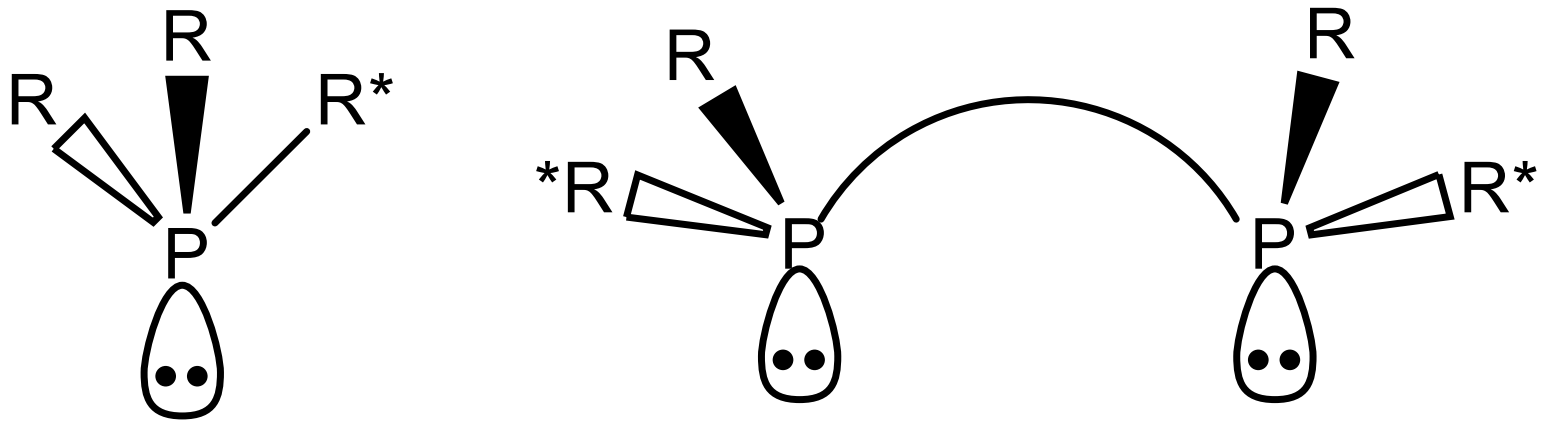
three different substituents at the P-atom:

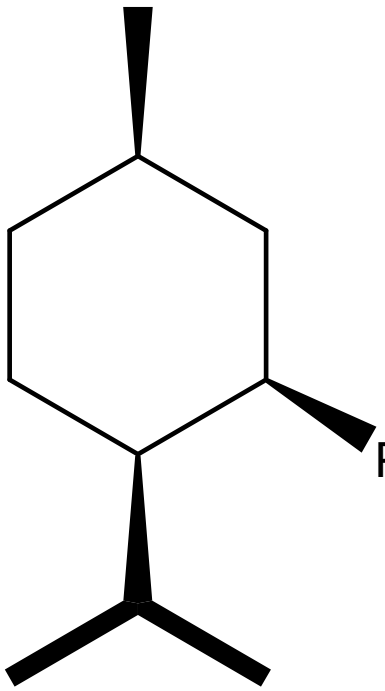


- Do not racemise (high barrier to inversion).
- Several step synthesis and resolution required.

Chirality can be introduced into phosphines in several ways.

2. Chirality not at P using a chiral substituent:



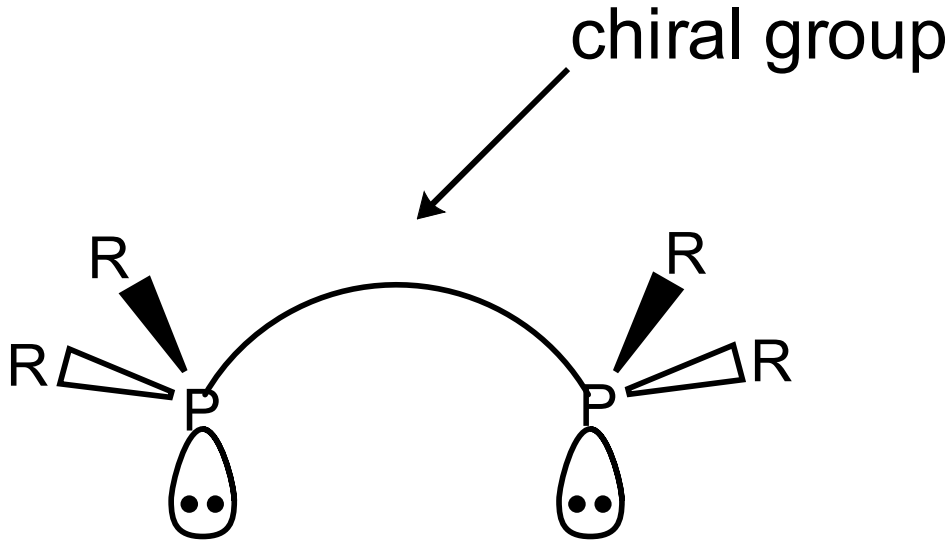


(-)NeomenthylPPh$_2$

- Easily prepared from a chiral starting material

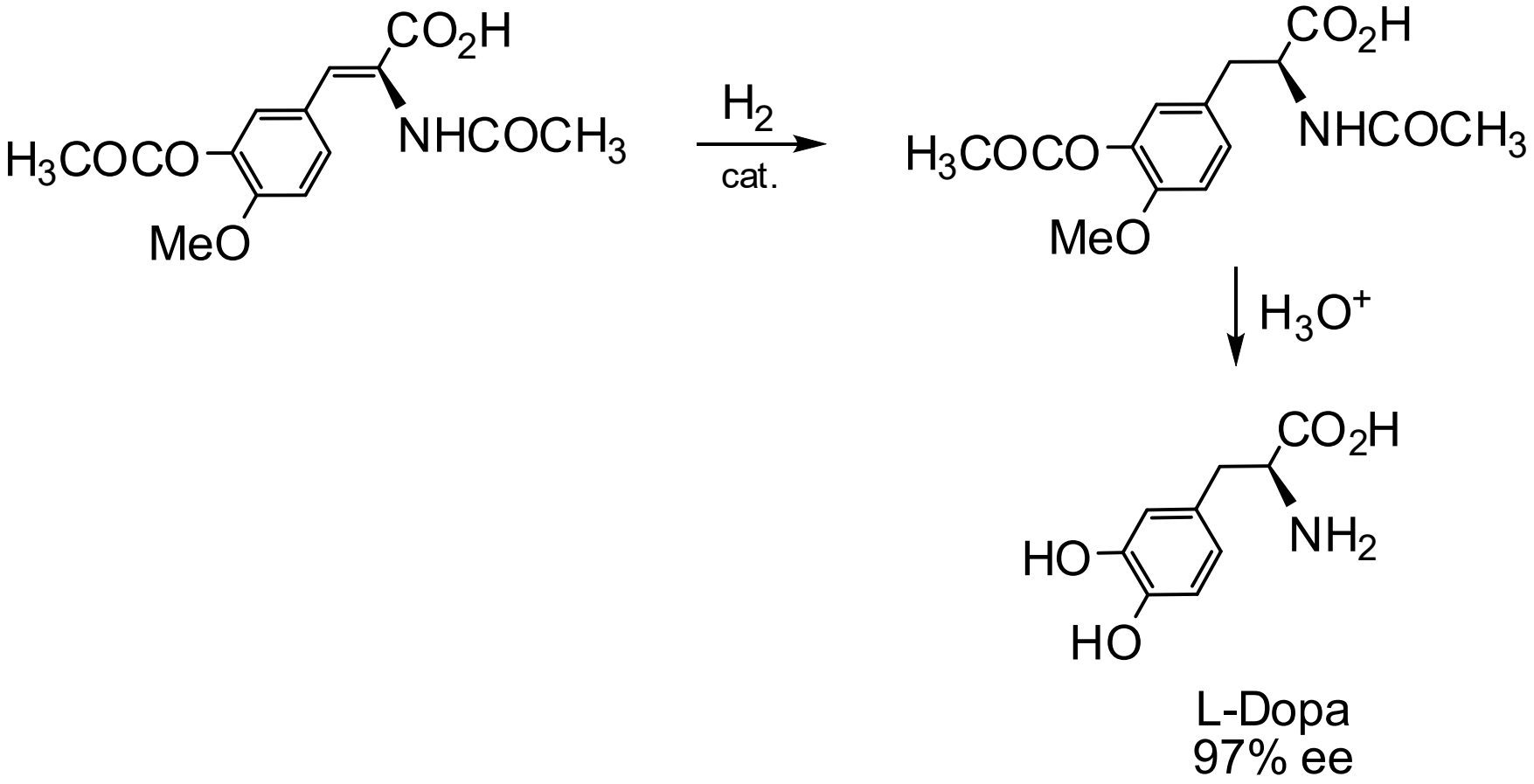
Chirality can be introduced into phosphines in several ways.

3. A chiral group in a bis-phosphine backbone:



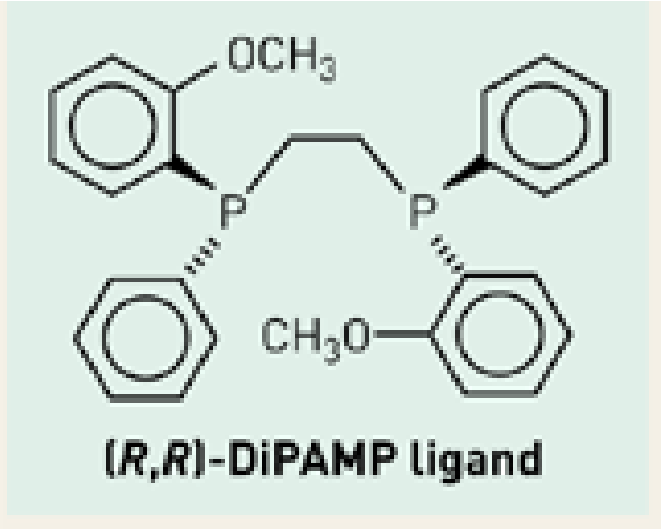
A classic example of the application of a chiral bis-phosphine is in the synthesis of L-Dopa – an intermediate in dopamine biosynthesis. L-dopa is used in the treatment of Parkinson's disease.

The key step in L-dopa synthesis is the catalytic hydrogenation of the prochiral olefin.


CO2H
NHCOCH3
H3COCO
MeO
H2
cat.
CO2H
NHCOCH3
H3COCO
MeO
H3O+
CO2H
NH2
HO
HO

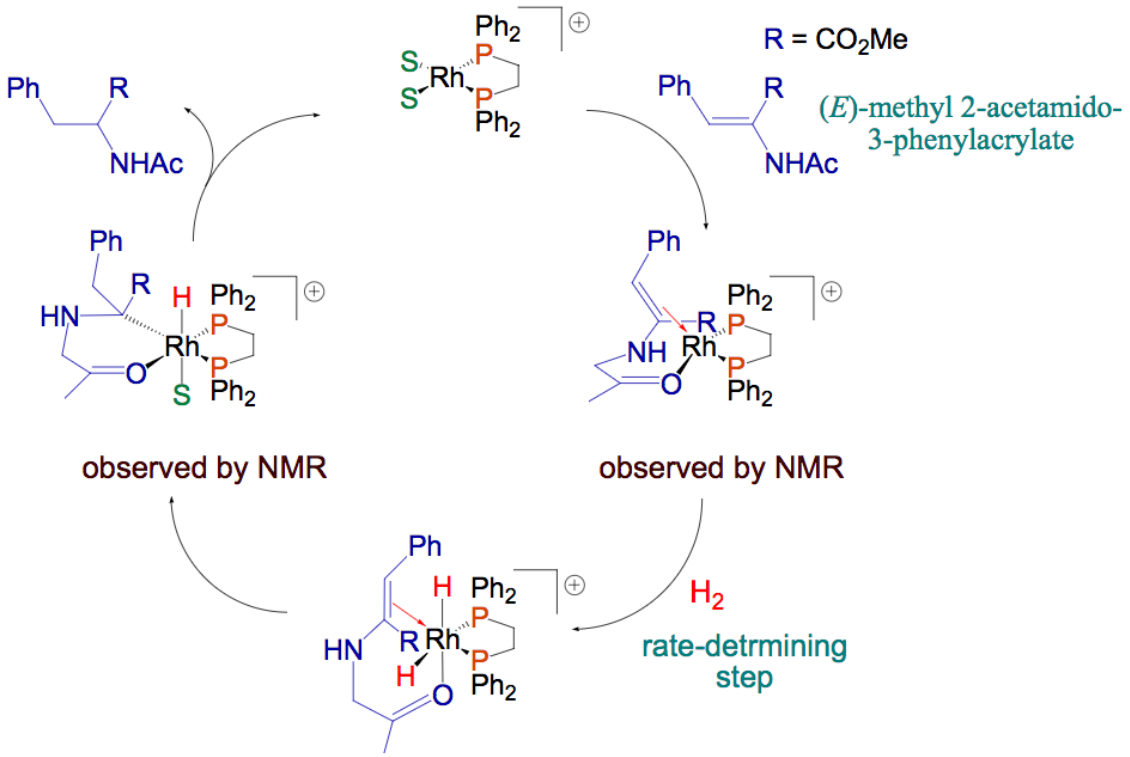
L-Dopa
97% ee

The catalyst is prepared in situ from $[Rh(COD)_2]^+$ and (R,R)-DIPAMP:



(R,R)-DIPAMP was developed by Knowles in 1970s with Monsanto, received nobel prize in 2001.

Halpern's mechanism of hydrogenation for cationic Rh catalysts with bidentate phosphines

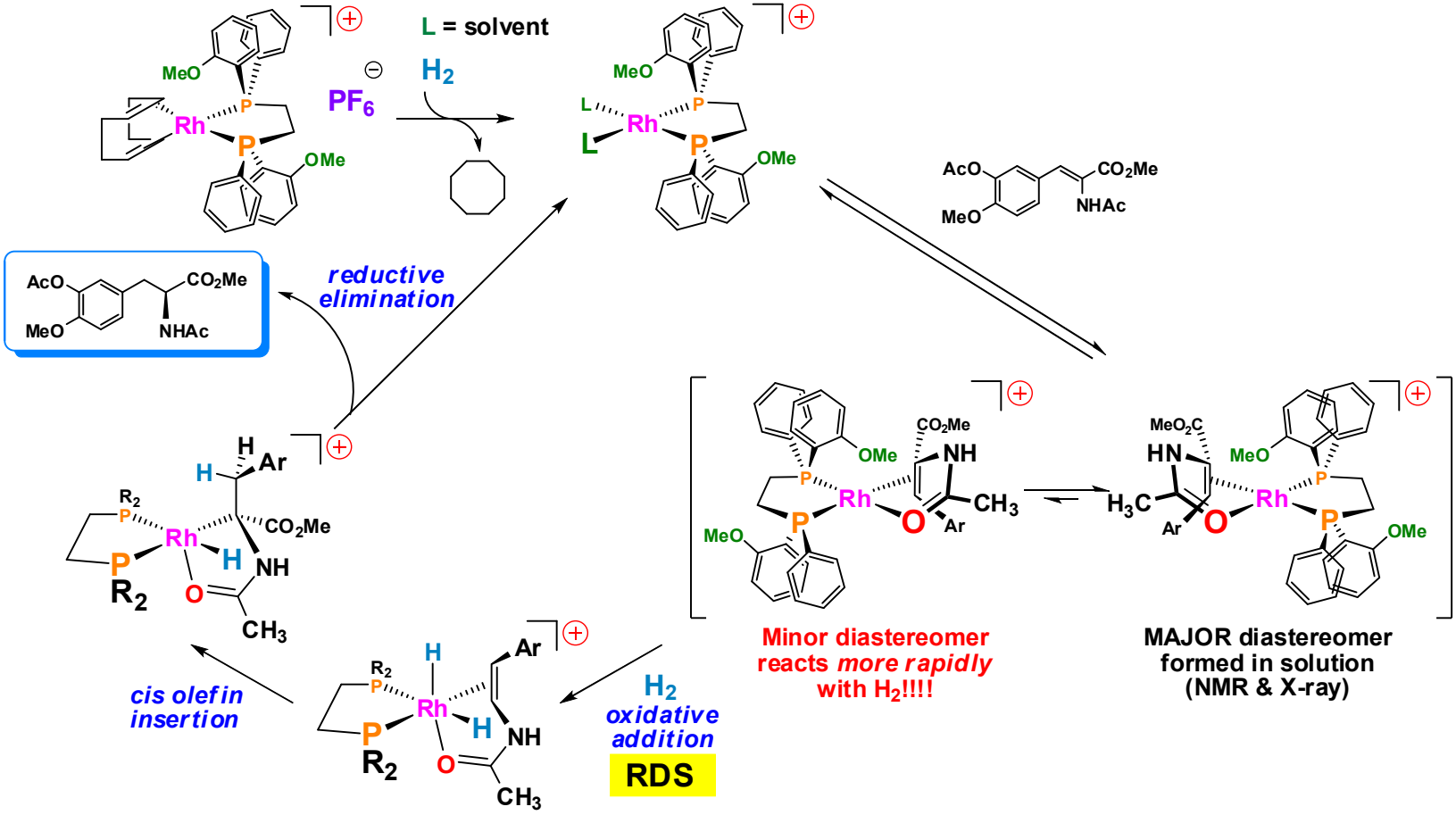


Steps: (**1**) alkene addition, (**2**) H_2 addition, (**3**) migratory insertion, (**4**) reductive elimination of the alkane, regeneration of the catalyst.

Halpern, *Science* **1982**, *217*, 401.

Mechanism for asymmetric hydrogenation

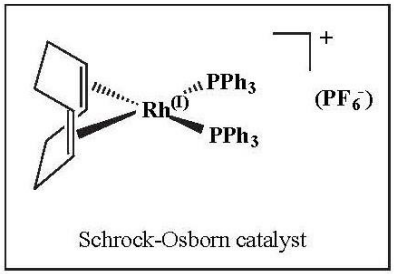
Halpern *Science* **1982**, *217*, 401



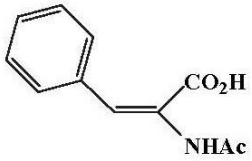
Olefin association occurs before oxidative addition of H_2 and this oxidative addition is the rate-limiting step. What is even more amazing is that the major olefin complex diastereomer, which was isolated and characterized by NMR and X-ray techniques, gives the WRONG product. In elegant mechanistic studies, Halpern showed that the *minor diastereomer (olefin complex)* REACTS 580x FASTER to give the final hydrogenated chiral product in a 60:1 ratio!

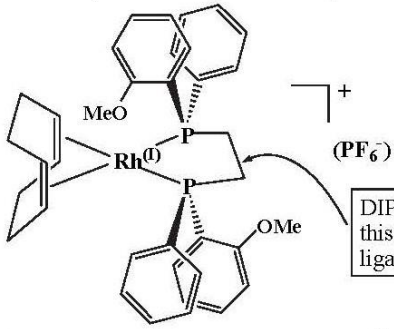
Asymmetric Hydrogenation

A bidentate, C_2 symmetric version of the cationic Schrock-Osborn catalyst affords extraordinarily high levels of enantioselectivity in the hydrogenation of achiral enamides. This was the first demonstration that a chiral transition metal complex could effectively transfer chirality to a non-chiral substrate with selectivities that rival those observed in enzymes. Recall that this led to the 1st commericalized asymmetric process using a chiral transition metal complex: Monsanto Process for the industrial production of *L*-DOPA (see Structure and Bonding, pg. 4)



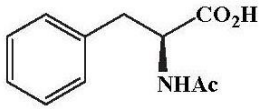
Schrock-Osborn catalyst





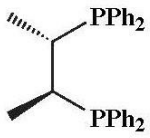
DIPAMP (common name for this bidentate chiral phosphine ligand)

i-PrOH, H_2 (1 atm), rt
>99% yield

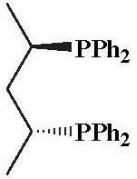


Knowles *JACS* **1975** (97) 2567. ***93% ee***

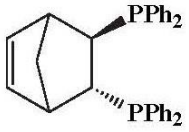
A variety of bidentate chiral phosphines have since been synthesized and used to effect the hydrogenation of aromatic enamides (important substrates for the efficient generation of amino acids):



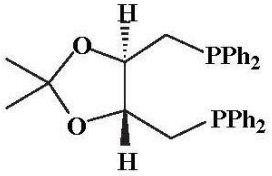
Chiraphos (99% ee)



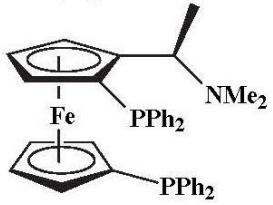
SKEWPHOS (92% ee)



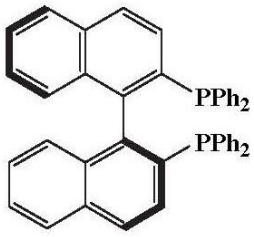
NORPHOS (95% ee)



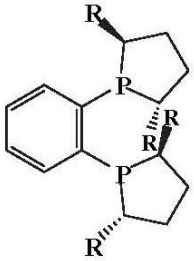
DIOP (85% ee)



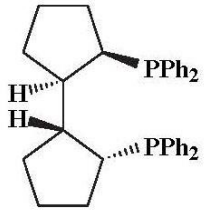
BPPFA (93% ee)



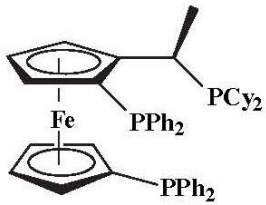
BINAP (100% ee)



DuPHOS (99% ee)



BICP (97% ee)



JOSIPHOS (96% ee)

We'll see these ligands again effecting asymmetry in a wide assortment of mechanistically unrelated metal catalyzed reactions with prochiral substrates. "Privileged ligand class": ligands that communicate asymmetry effectively with a transition state localized at the metal center, irrespective of the nature of the transition state.

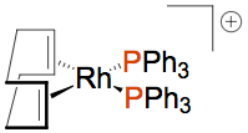
E.N. Jacobsen;
personal communication

E. N. Jacobsen. Chem 153 notes. Spring 2001.
For review on DuPhos: **Burk** *Acc. Chem. Res.* **2000** (33) 363.

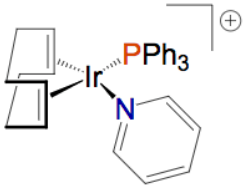
VI. Cationic catalysts for asymmetric hydrogenation

Cationic catalysts

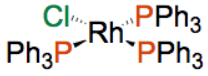
Cationic catalysts are the most active homogeneous hydrogenation catalysts developed so far:



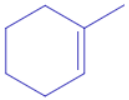
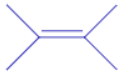
Schrock-Osborn catalyst



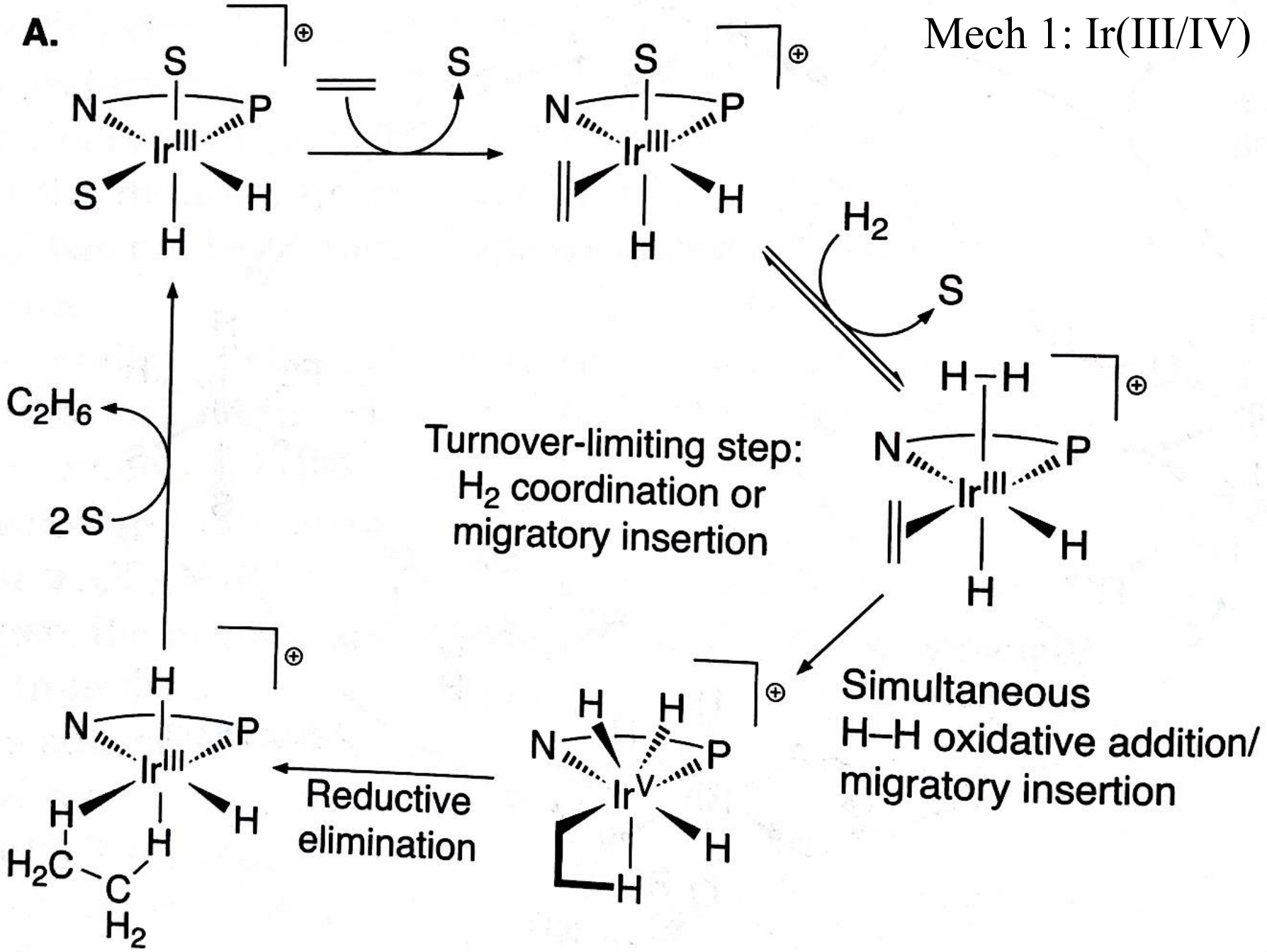
Crabtree's catalyst

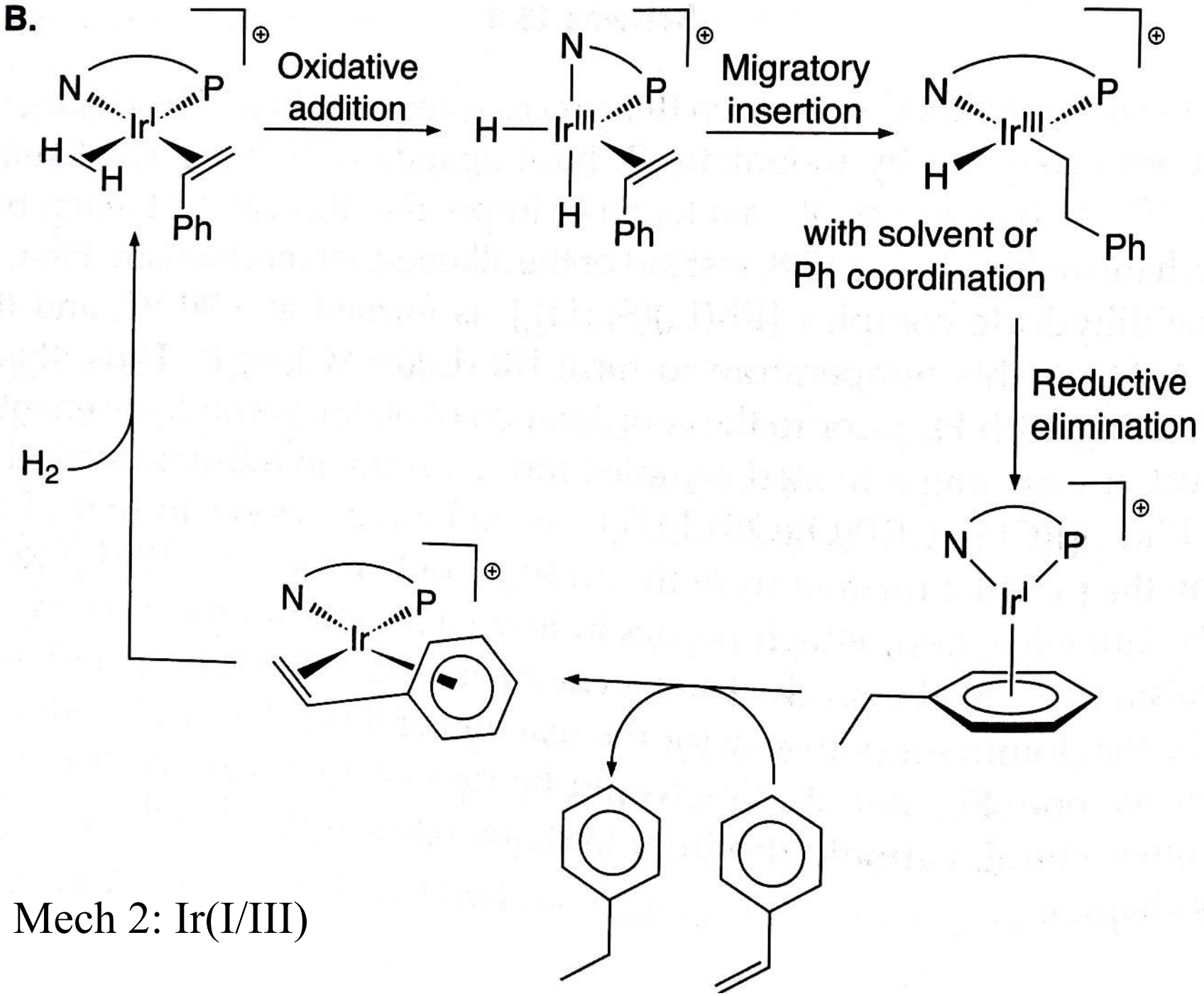


Wilkinson's catalyst

Substrates	Schrock-Osborn catalyst	Crabtree's catalyst	Wilkinson's catalyst
		TOF	
	4000	6400	700
	10	4500	650
		3800	13
		4000	

Mech 1: Ir(III/IV)



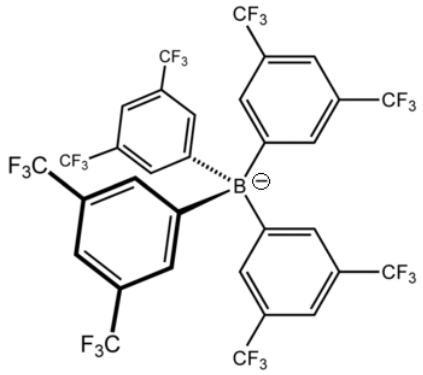


Mech 2: Ir(I/III)

Crabtree-type catalyst:

The high reactivity of Crabtree's catalyst can be explained by the fact that the alkene does not have to compete with dissociated phosphine or coordinating solvent molecules for a free site on the metal

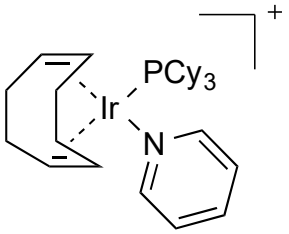
Requires non-coordinating solvents; activity improved by using bulky, non-coordinating anions, such as BArF



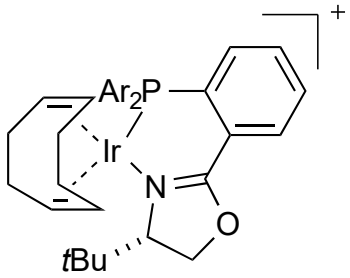
Crabtree's catalyst is highly active towards highly-substituted alkenes, for which other catalysts are inactive.

Olefins with no coordinating functionalities, especially tri- and tetrasubstituted, have been identified as the most difficult substrates for asymmetric hydrogenation. These olefins are particularly difficult to hydrogenate due to the absence of the polar group which is required for Rh or Ru catalysts to obtain high catalytic activity and enantioselectivity.

Several groups in 1990's and 2000's have developed Ir based catalyst systems with chiral P-N ligands based on Crabtree's catalyst, which has been reported as an efficient catalyst for the reduction of unfunctionalized alkenes.

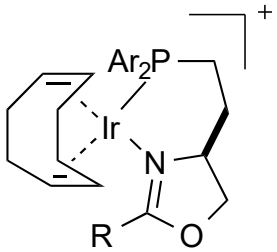


Crabtree's catalyst

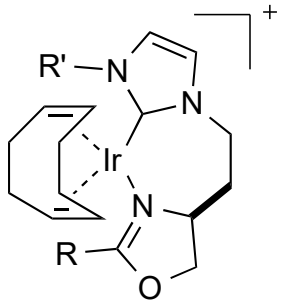


Ir-PHOX

typical Pfaltz' catalyst

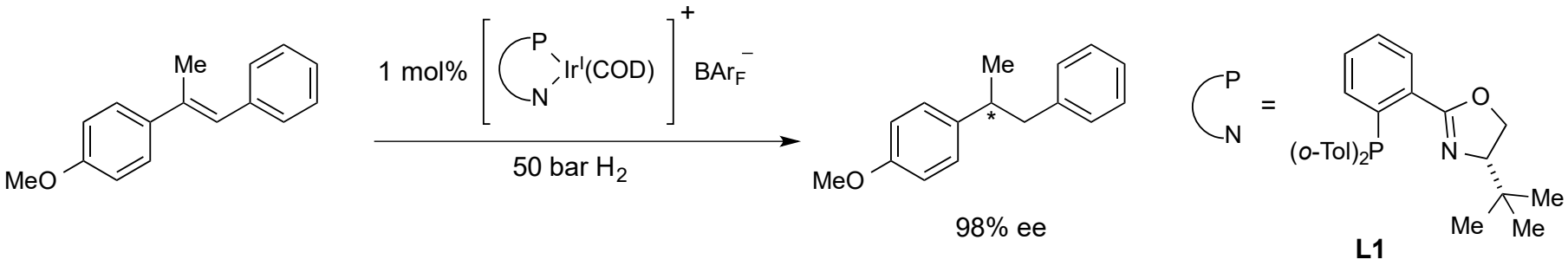


JM Phos catalyst



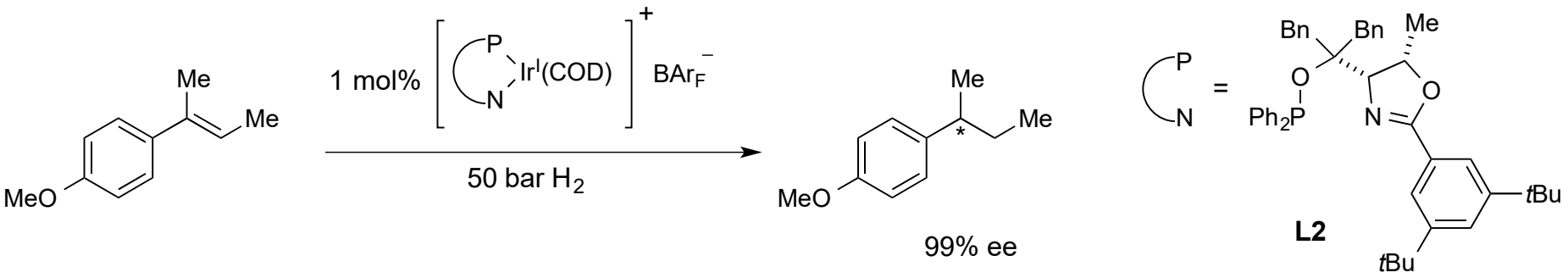
Burgess' catalyst

Ir-PHOX (Phosphinooxazoline) catalyst developed by Andreas Pfaltz in 1990's. The versatile library of PHOX ligands can be prepared easily in 2 to 4 steps depending on the structural features of the ligand.

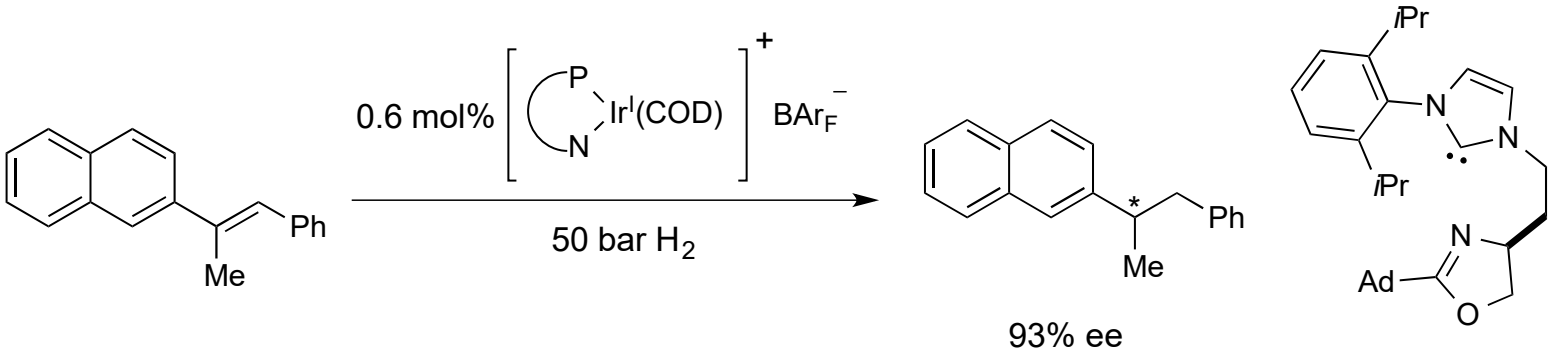


Pfaltz *Adv. Synth. Catal.* **2003**, *345*, 33

For different substrates the reaction requires a screening for the ligands to obtain the best enantioselectivity. In the following case **L2** afforded product in 99% ee, while the **L1** provided only 81% ee.



Burguss reported a new class of iridium catalysts with a NHC-ligand, which were able to hydrogenate trisubstituted aryl alkenes in good ee.



Burgess *J. Am. Chem. Soc.* **2003**, *125*, 113

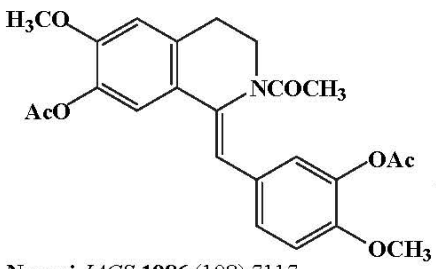
What is the rational of using NHC ligands?

VII. Ru catalysts for asymmetric hydrogenation

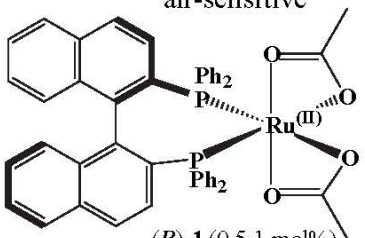
Changing now to Ru?

BINAP-Ru complexes: Noyori increases the substrate scope for asymmetric hydrogenations

The first report: asymmetric hydrogenation of (Z)-enamides

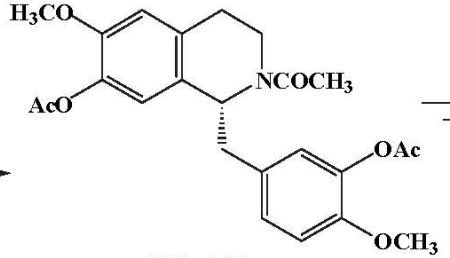


air-sensitive

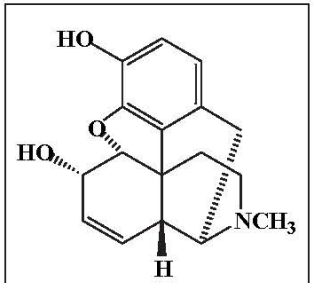


(*R*)-**1** (0.5-1 mol%)

EtOH:CH_2Cl_2 (5:1), H_2 (4 atm), 23°C



92% yield
95% *ee*

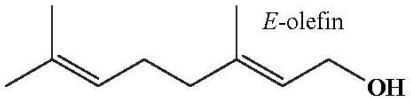


morphine

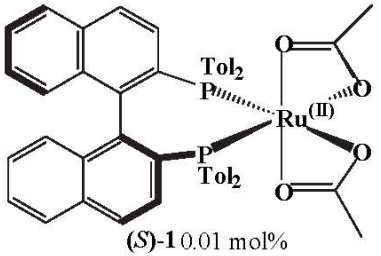
Interestingly, *E*-enamides are completely unreactive towards these hydrogenation conditions. No rationale for this has been presented.

Noyori *JACS* **1986** (108) 7117.
Noyori *ACIEE* **2002** (41) 2008.

Asymmetric hydrogenation of allylic and homoallylic alcohols:



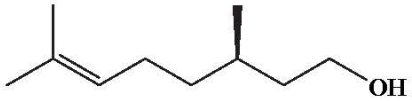
geraniol



(*S*)-**1** 0.01 mol%

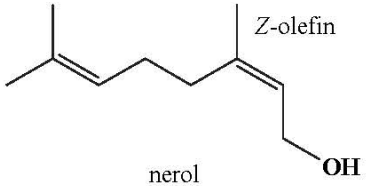
MeOH, H_2, 18-20°C

97 to >99% yields



(*R*)-citronellol
96% *ee*

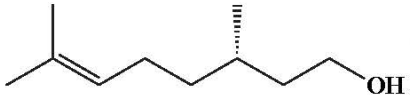
regioselectivity: allylic and homoallylic alcohols are hydrogenated whereas bis homoallylic and higher analogues are left untouched.



nerol

(*S*)-**1** 0.2 mol%

MeOH, H_2, 18-20°C

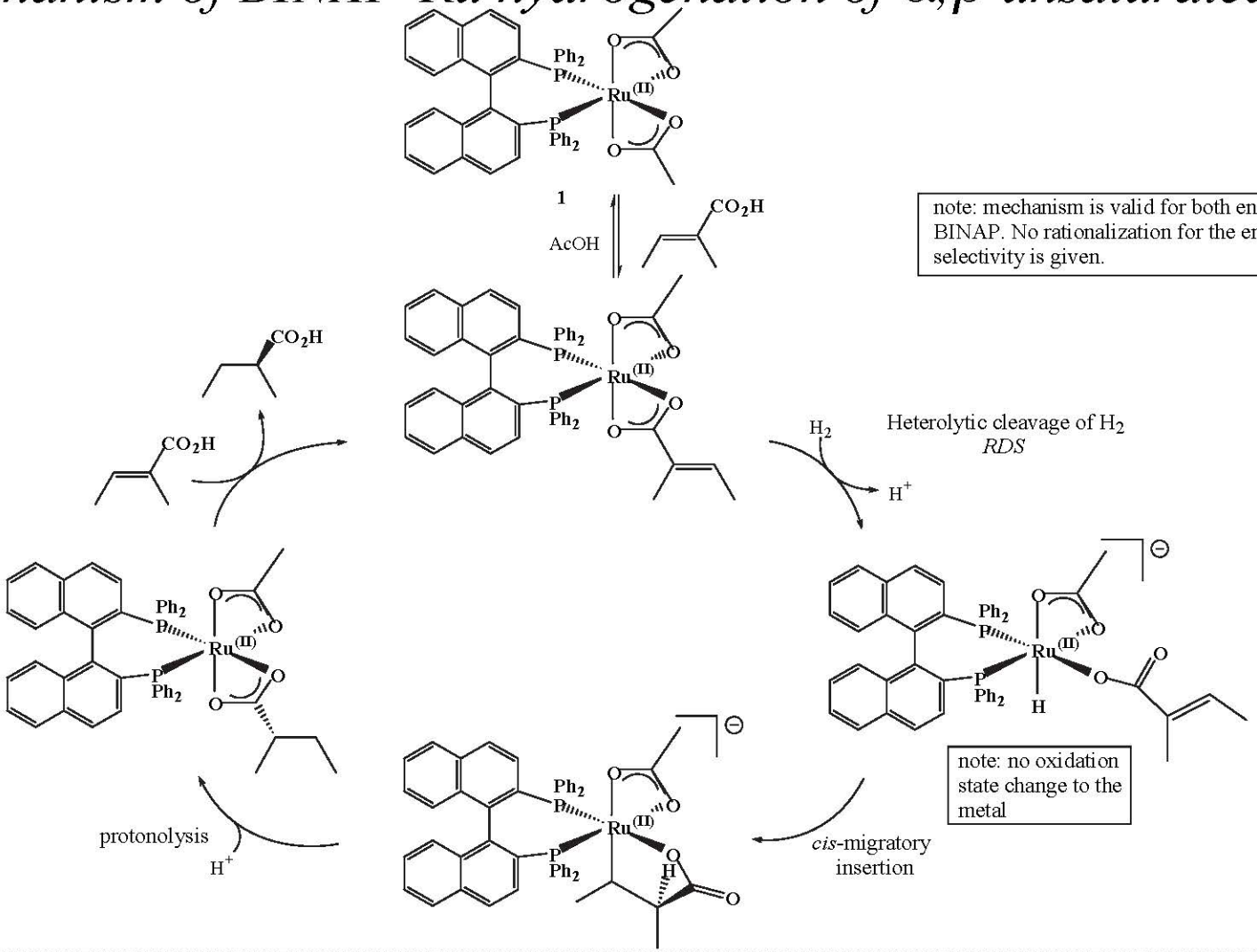


(*S*)-citronellol
98% *ee*

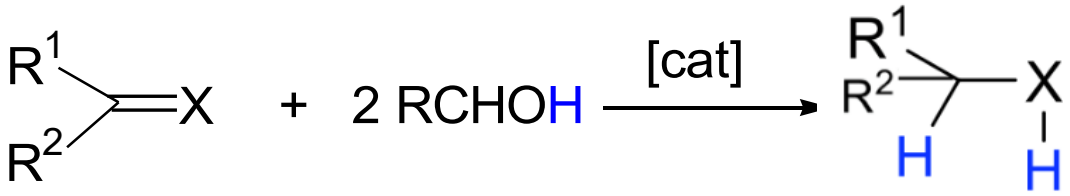
allylic olefin geometry may dictate the stereochemical outcome of the hydrogenation. Practical consequence: to obtain high ee's must start with stereochemically pure olefins.

Noyori *JACS* **1987** (109) 1596.

Mechanism of BINAP-Ru hydrogenation of α,β-unsaturated acids



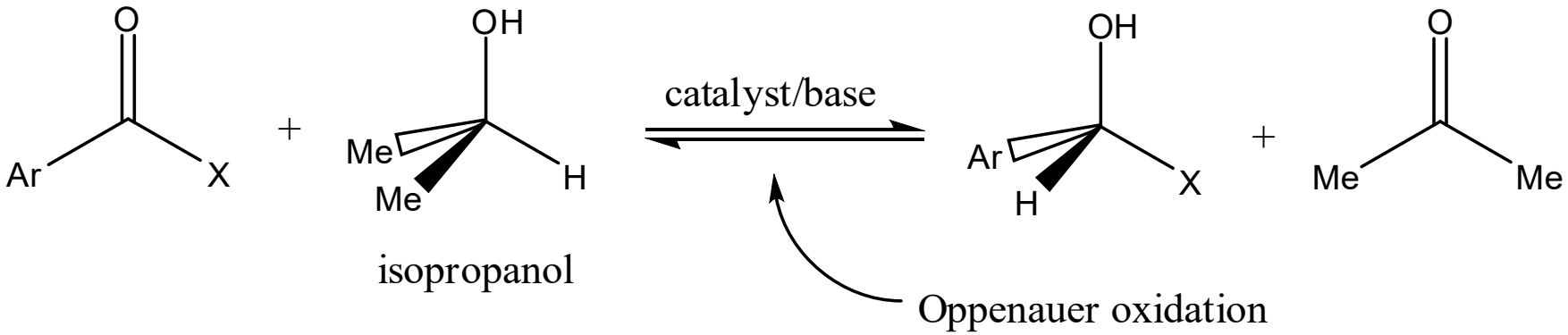
Transfer hydrogenation of alcohols



Advantages: Avoids use of H_2 gas. Allows for molecular diversity in the reducing agent.

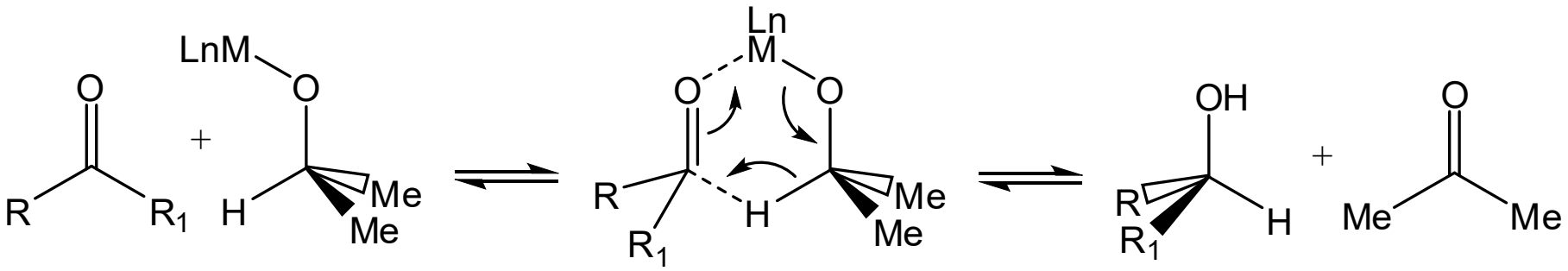
Disadvantages: Formation of a co-product from the dehydrogenation of the hydrogen donor. Reversibility.

Classic reaction



If uses a strong base such as aluminium isopropoxide,
Oppenauer oxidation

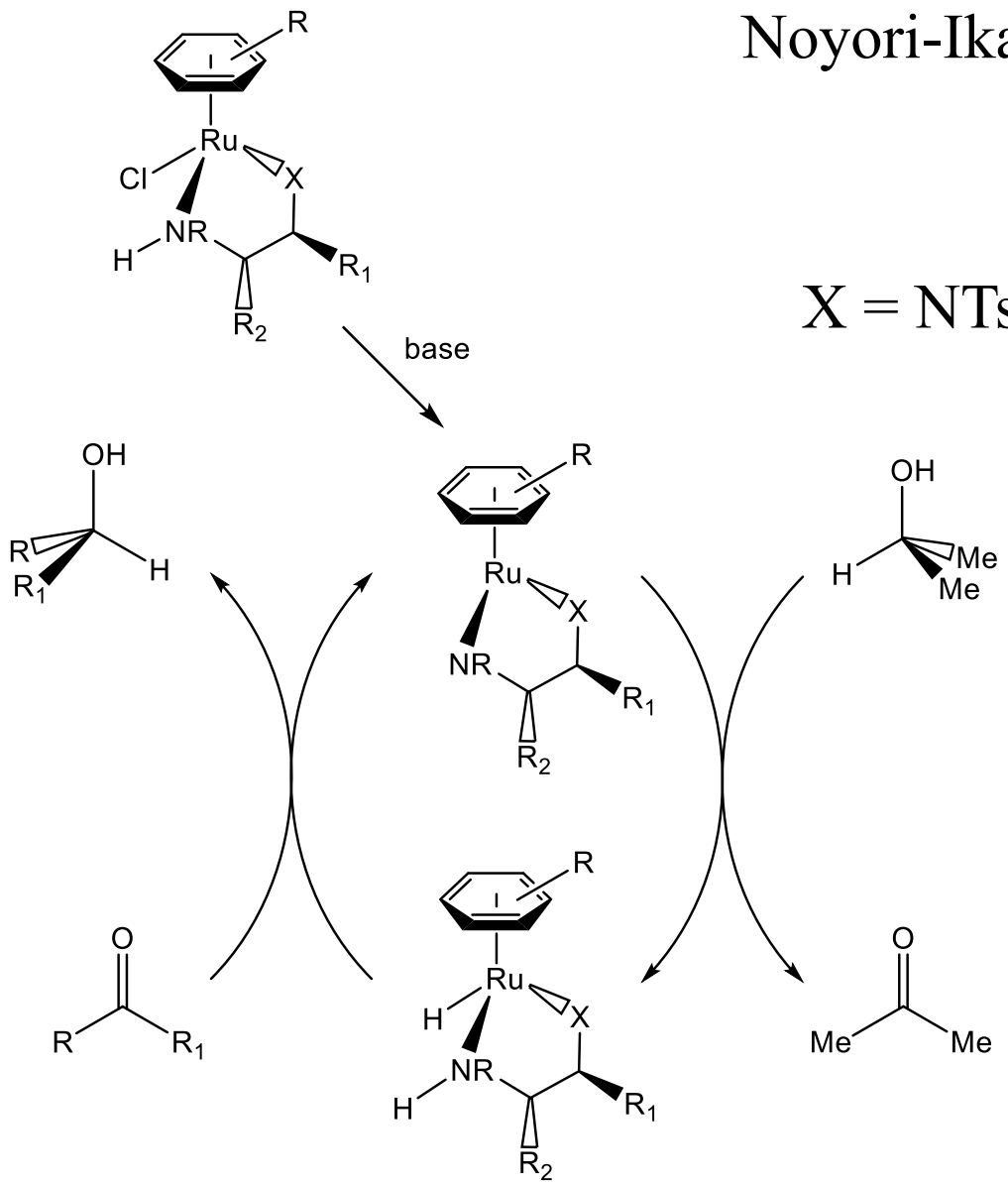
Mechanism 1: direct H transfer



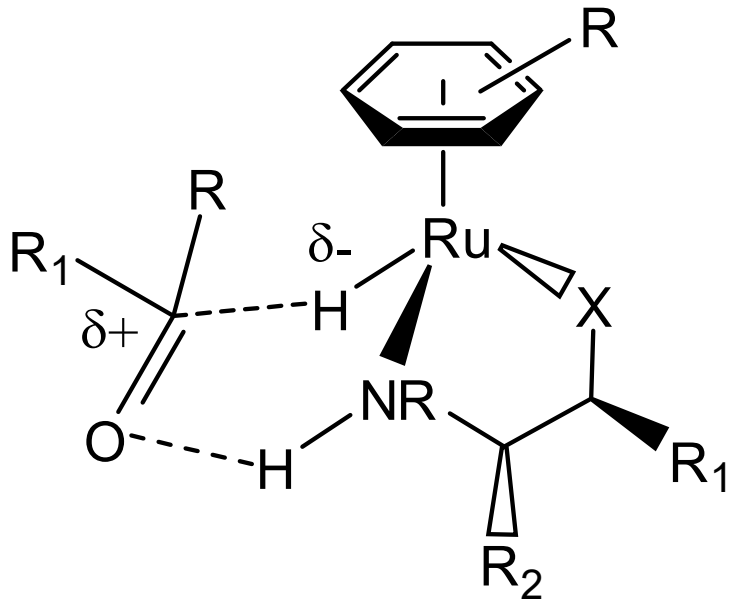
Mechanism 2: metal-hydride transfer

Noyori-Ikayira catalyst

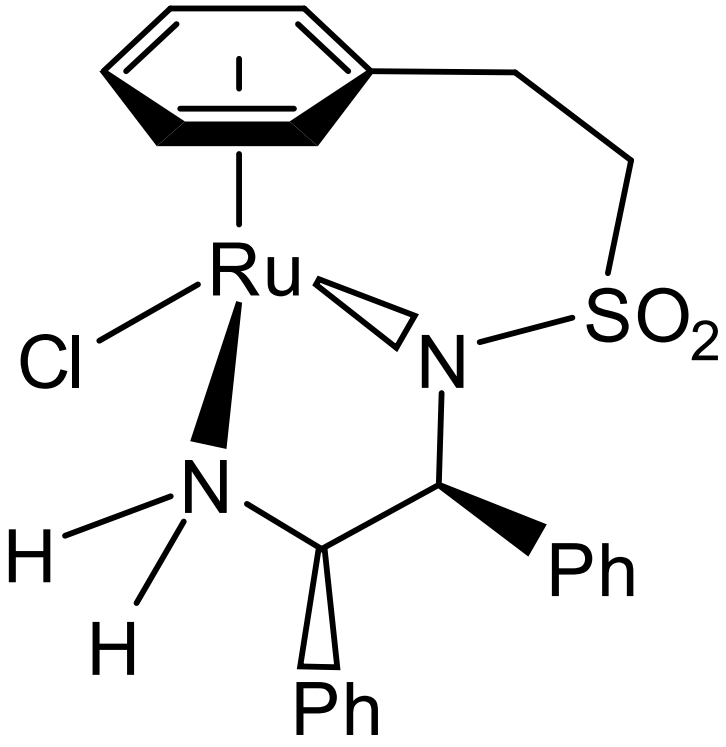
X = NTs, O



Mechanism 2: outer-sphere reaction; key intermediate

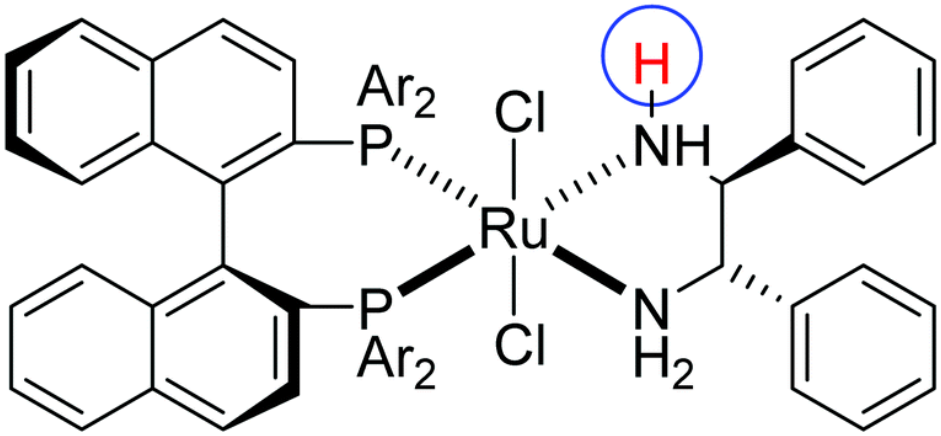


The main problem with these catalysts is that high loadings are required as their stability is low – i.e. the catalysts decompose during reaction. Tethered systems have been developed that have increased stability:



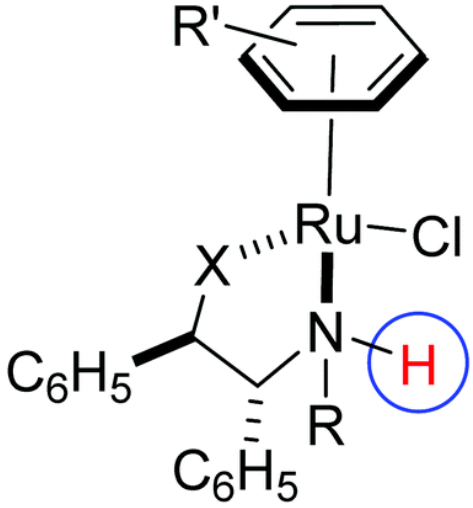
Noyori catalysts: Efficient for simple ketones

Noyori, 1995



1

Noyori–Ikariya, 1995



X = O, NTs

2

Summary

- From heterogeneous to homogeneous
- Understanding and improving Wilkinson's catalysts
- Different classes of catalysts for asymmetic hydrogenation