Green Synthesis

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What is Green Synthesis?

Principles of Green Chemistry/Synthesis

1. Prevent waste

   It is better to prevent waste than to treat or clean up waste after it is formed.

2. Atom economy

   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less hazardous synthesis

   Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Safer chemicals

   Chemical products should be designed to preserve efficacy of function while reducing toxicity.

What is Green Synthesis?

Principles of Green Synthesis

5. Safer solvents and auxiliaries

   The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.

6. Energy efficiency

   Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7. Renewable feedstocks

   A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.

8. Reduce derivatives

   Unnecessary derivatization should be avoided whenever possible.

What is Green Synthesis?

Principles of Green Synthesis

9. Catalysis

Catalytic reagents are superior to stoichiometric reagents.

10. Design for degradation

Chemical products should be designed so that at the end of their function they do not persist in the environment.

11. Real-time analysis for pollution prevention

Analytical methodologies need to be real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently safer chemistry for accident prevention

Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

What is Green Synthesis?

Most important

Risk and function,
Balance the risks and the benefits

Major contributors

Catalysis

All types of catalysis (principles 1, 2, 4, 5, 6, 8, 9, 12)

Unusual forms of energy

Ultrasounds, microwaves

Unusual solvents

water, fluorous solvents, supercritical fluids, ionic liquids.

Green Synthesis 1

Catalytic Methods

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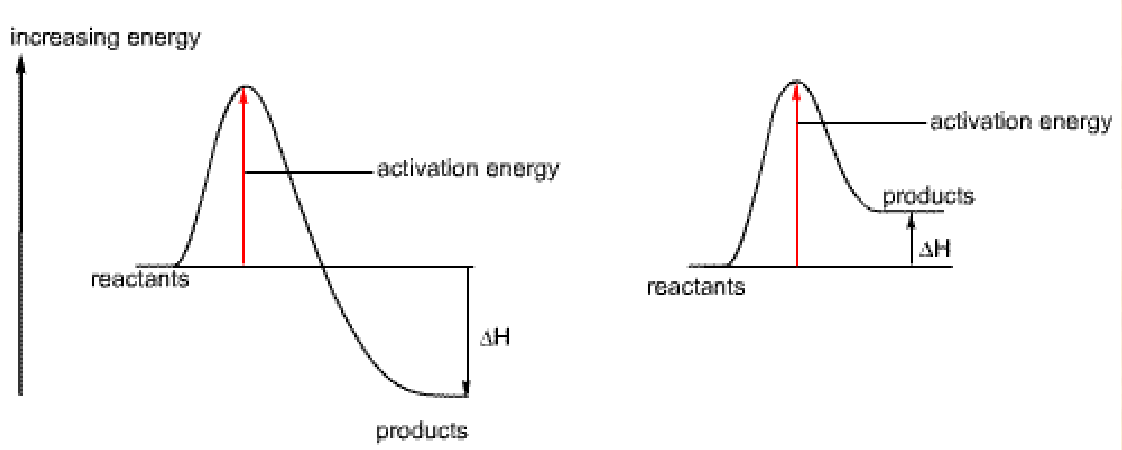
Catalysis - Effect on Rate

Catalysts increase the rate of a reaction without being used up in the process. In order for a reaction to occur bonds in the reactants must be broken - this requires energy, and new bonds must be made, releasing energy. This is called the activation energy.



Catalysts reduce the activation energy, increases the rate by a factor of up to several 1000. The catalyst causes this increase in rate by reducing the activation energy of the reaction.

Some enzymes can increase rates by up to 10^{20} times.

Catalysis - Effect on Activation Energies

A catalyst reduces the activation energy for both reactions, leaving the equilibrium position unchanged.

$2HI(g) \rightleftharpoons H_2(g) + I_2(g)$

if uncatalysed, E_A=185 kJ mol-1 in the forward direction and 164 kJ mol^{-1} in the reverse direction. With a platinum catalyst E_A=59 kJ mol^{-1} (forward direction).

A variety of different kinds of catalyst can be effective, as shown for the decomposition of hydrogen peroxide

$2H_2O_2 \rightleftharpoons 2H_2O + O_2$

catalyst	**E_a/ kJmol^{-1}**
none	73
iodide ion	54
Pt surface	46
iron(III)	40
catalase	4

Catalysis - Effect on Activation Energies

How does a catalyst change the activation energy?

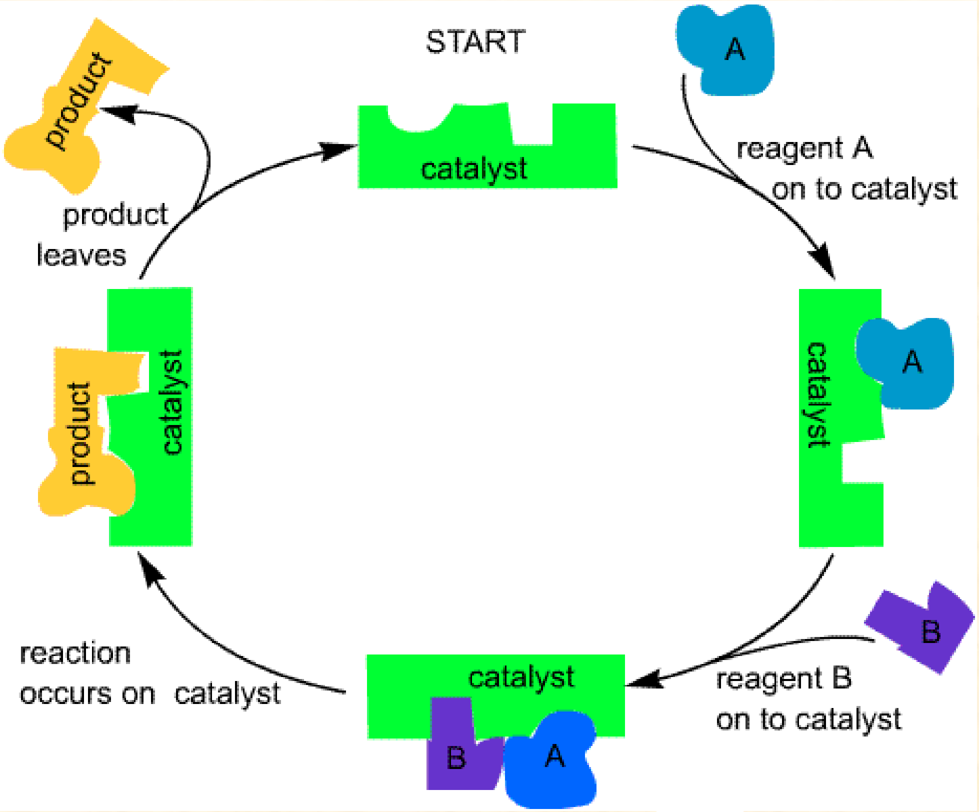
(1) It forms bonds with one or more of the reactants and so reduces the energy needed by the reactant molecules in order to complete the reaction

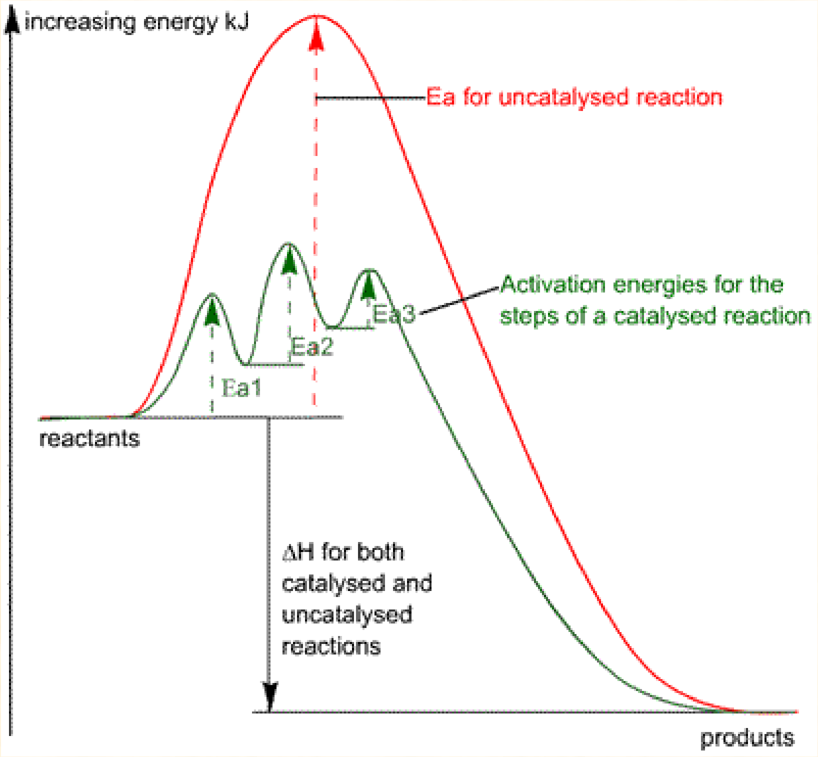
(2) It brings the reactants together and holds them in a way that makes reaction more likely..

In other words catalysts change the path of a reaction; they change its mechanism.

Catalysis - Mechanisms

Catalytic Cycle





Types of Catalysis

(1) Homogeneous

(a) Metal Complex Catalysis

(b) Organocatalysis

(2) Enzyme

(3) Heterogeneous

Homogeneous Catalysis – Metal Complexes

Homogeneous Catalysis:

The catalyst and reactants are in the same phase, usually liquid.

- transition metal ions
- transition metal complexes
- inorganic acids and bases
- enzymes (separate section)

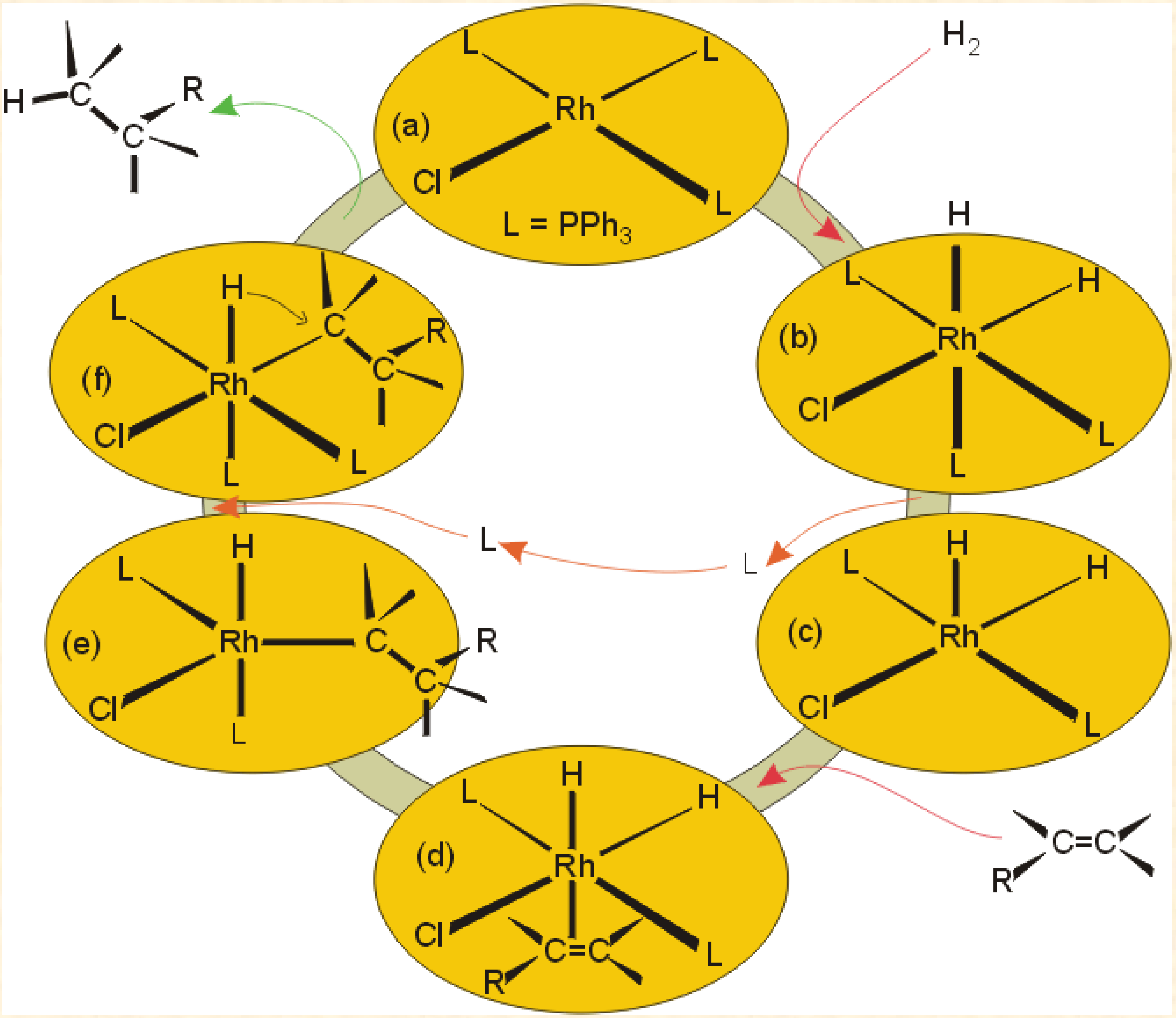
Advantages

- good contact with reactants so a great effective concentration of catalyst
- achieves the same rate under milder conditions which comes with greater selectivity.
- at the research and development stage it is often quicker and simpler to work with homogeneous catalysts

Disadvantages

- catalyst separation after reaction could be difficult
- catalyst recovery difficult
- catalyst stability, handling
- sometimes very toxic

Homogeneous Catalysis – Metal Complexes



Ernst O. Fischer

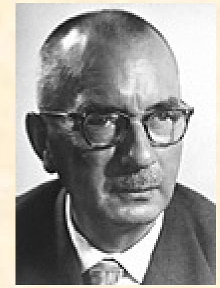
Geoffrey Wilkinson

Nobel Prize
1973

Homogeneous Catalysis – Metal Complexes

first polyethylene by accident – top secret material

For insulation (airborne radar, WWII)



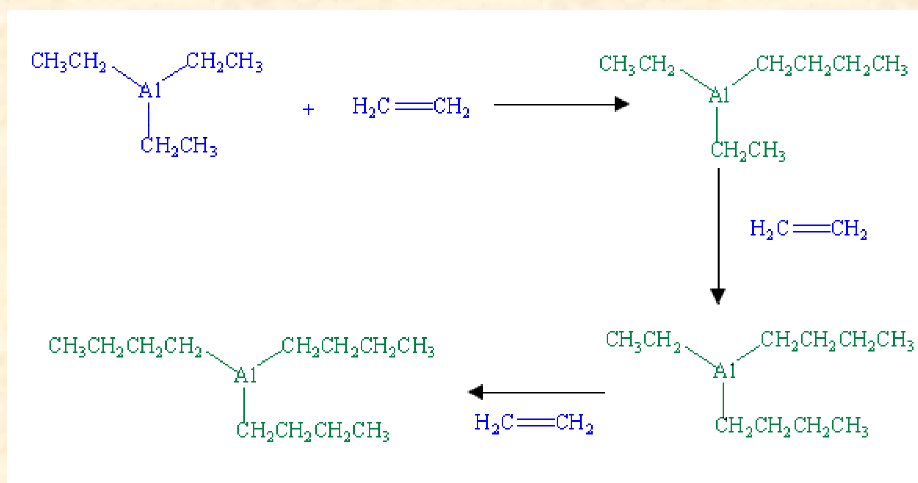
Karl Ziegler

Giulio Natta

Nobel Prize 1963

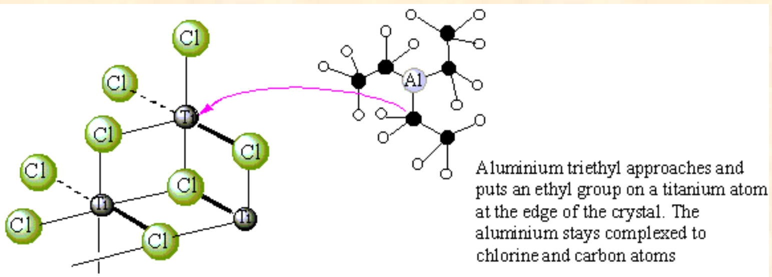
A Ziegler catalyst has two components.

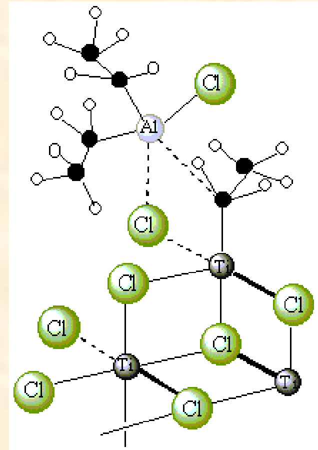
1. a titanium compound, $TiCl_4$ or $TiCl_3$ - the catalyst
2. an organoaluminium compound as cocatalyst

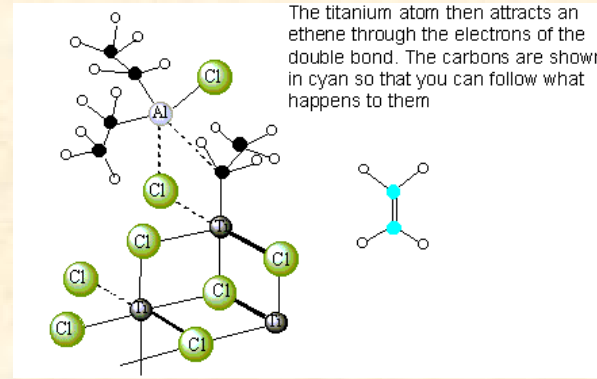


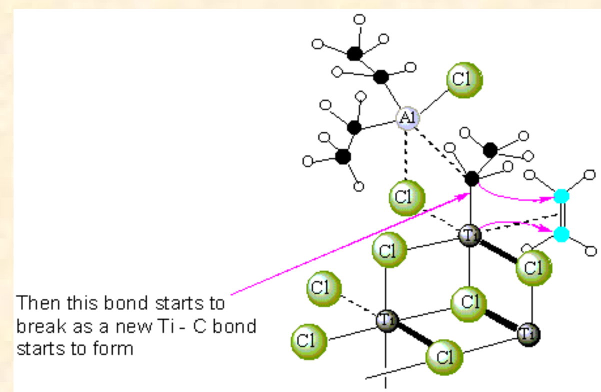
Homogeneous Catalysis – Metal Complexes

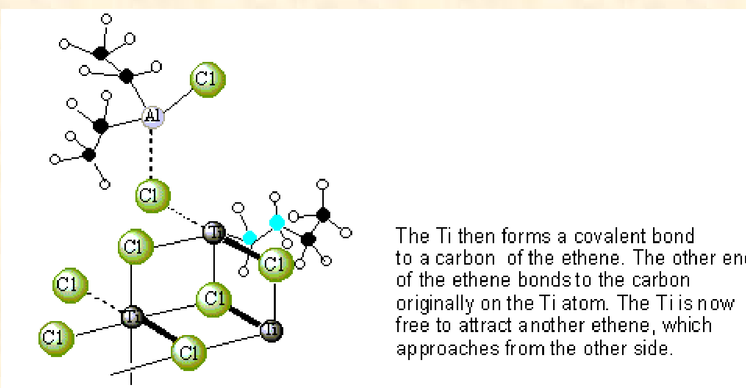
How the Ziegler Catalysts Work





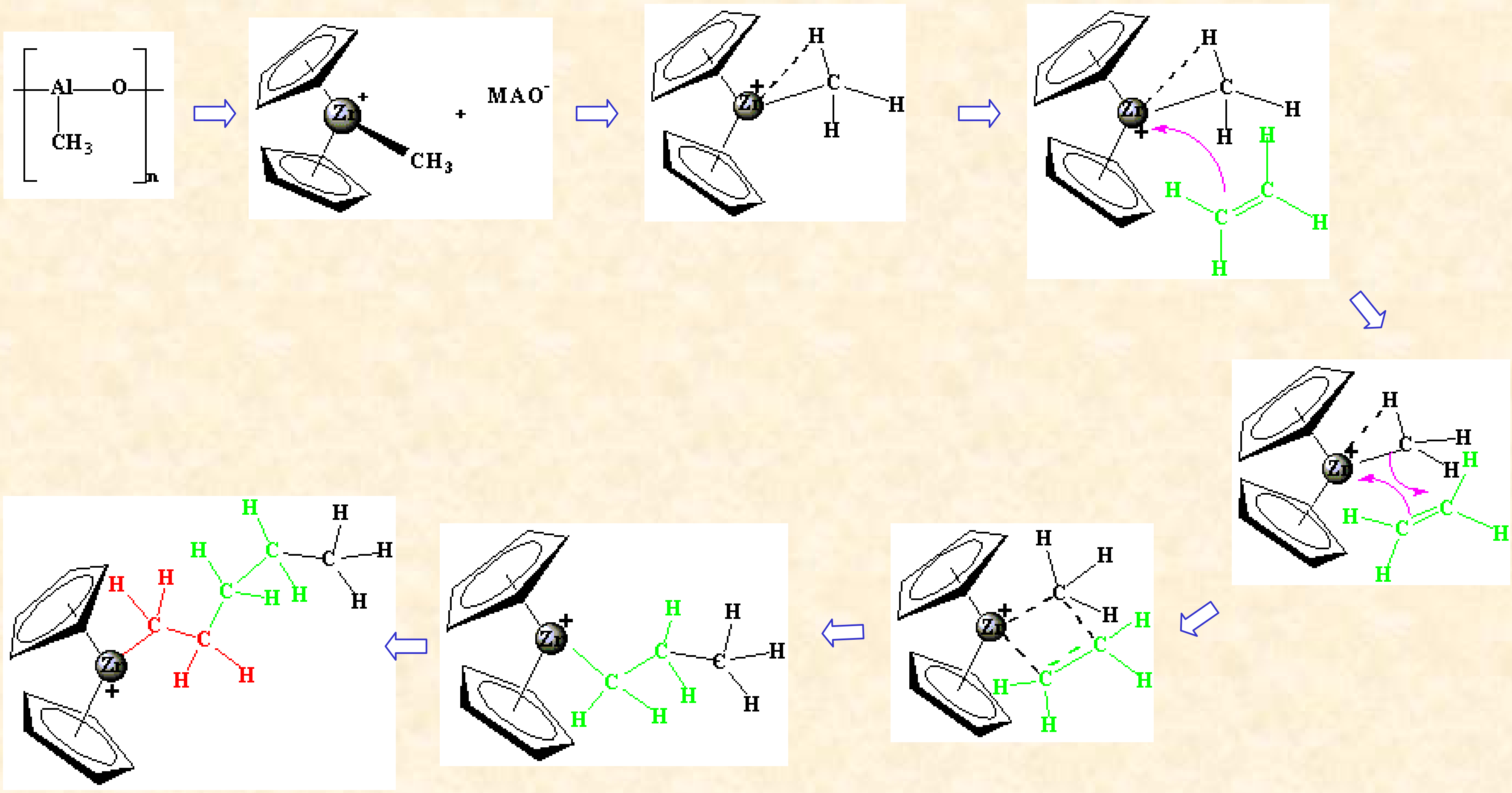




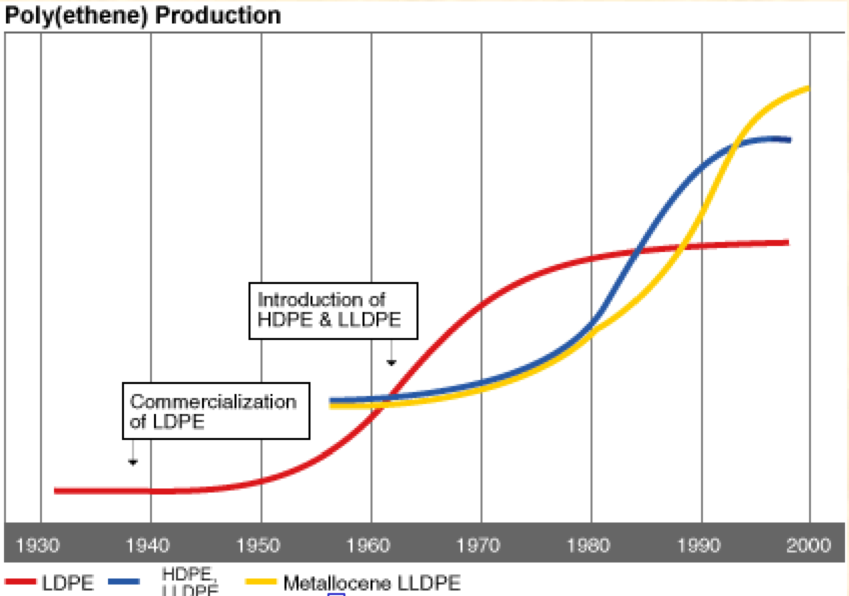


Homogeneous Catalysis – Metal Complexes

The Kaminsky Catalyst

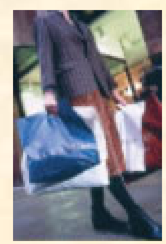


Homogeneous Catalysis – Metal Complexes



damp-proof membrane in building applications

As a barrier for clothing and hygiene in a medical environment, where post-use disposal is essential, it has the advantage of being low-cost



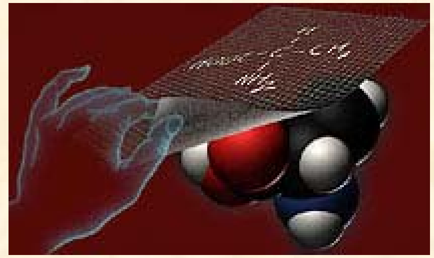
Poly(ethene) film can be coloured and printed, useful for aesthetic purposes in some applications

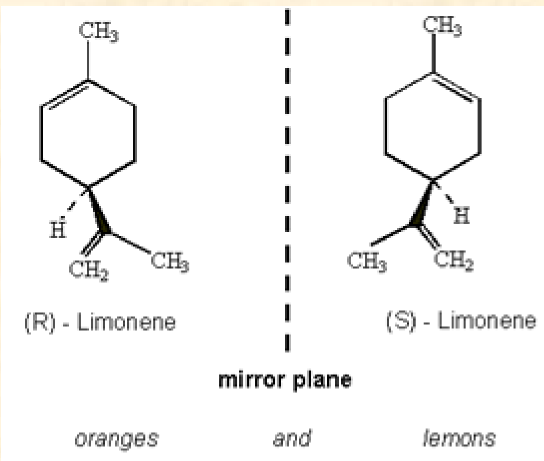
Plastic films can be designed to shrink when heated, enabling "shrink wrap" packaging, which is very economical

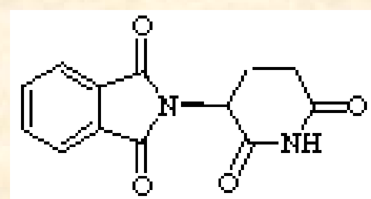
The addition of light-filtering additives make ldpe ideal as an alternative to glass for horticultural use

Homogeneous Catalysis – Metal Complexes

The Importance of Chirality







The “wrong” example

Thalidomide: (*R*) or (*S*)

Homogeneous Catalysis – Metal Complexes

Routes to chiral compounds

Chiral Resolution	Chiral Synthesis
⇩	⇩
Chiral derivatization agent	Stoichiometric and Catalytic Methods
⇩	⇩
Chiral Product	Chiral Product
(up to 50% yield and 100% ee)	(up to 100% yield and 100% ee)

ee – enantiomeric excess ($ee\ \% = \frac{|[R] - [S]|}{[R] + [S]} \times 100$)

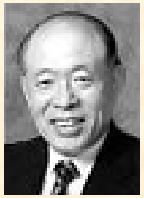
Homogeneous Catalysis – Metal Complexes

Asymmetric Catalysis

The most effective way for the preparation of chiral compounds

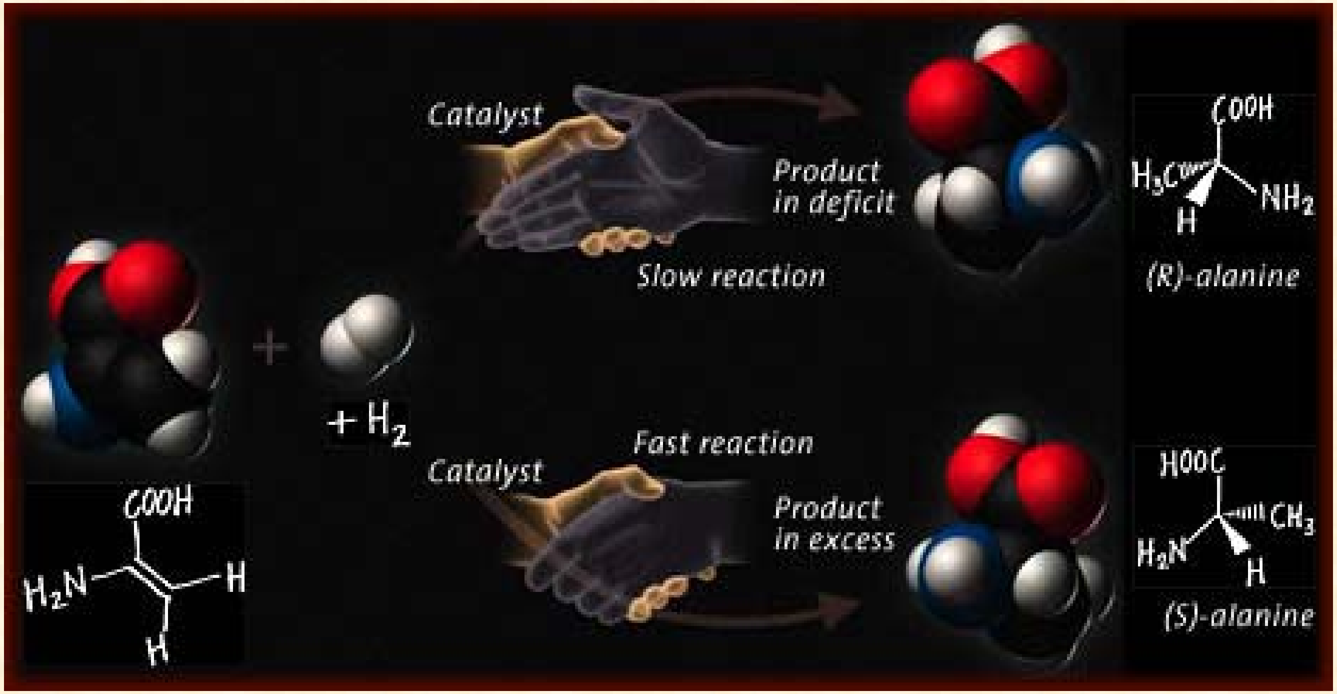
Nobel Prize in Chemistry, 2001

•William S. Knowles



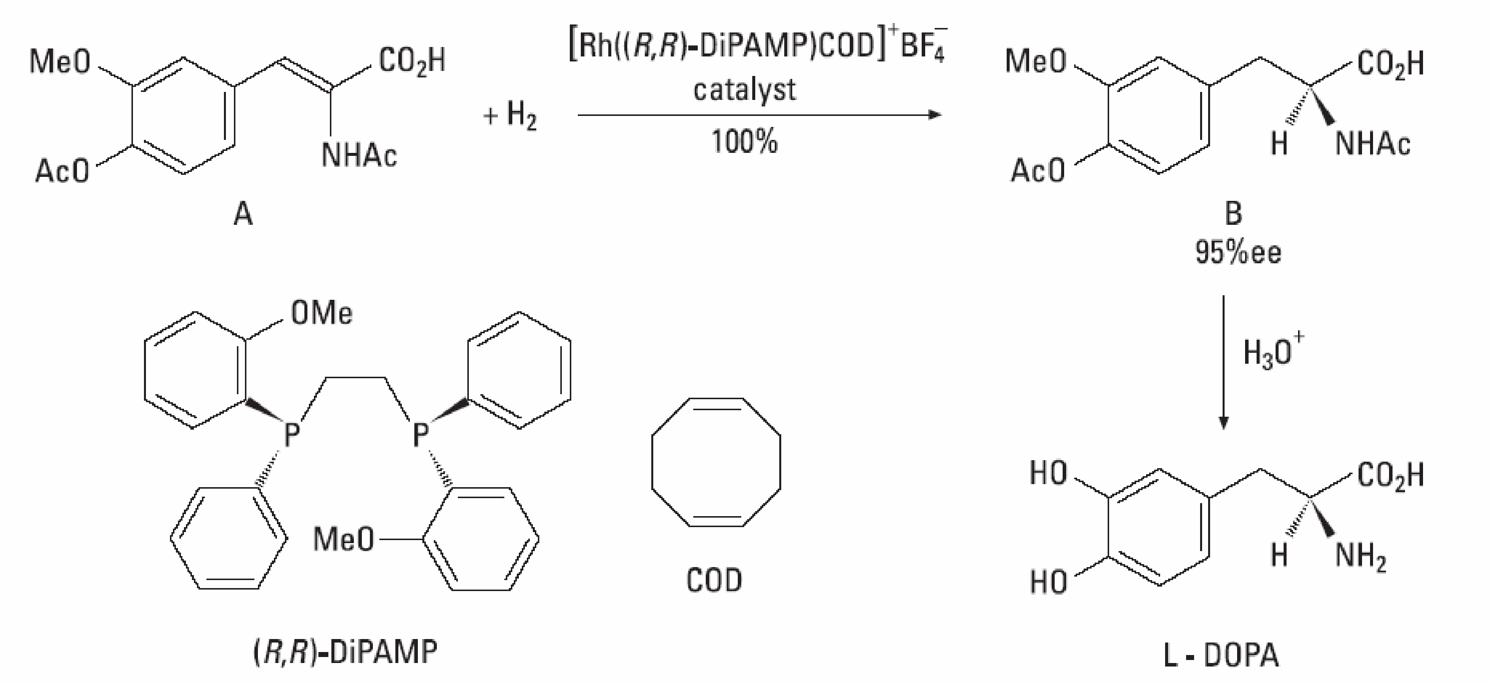
•Ryoji Noyori

•K. Barry Sharpless



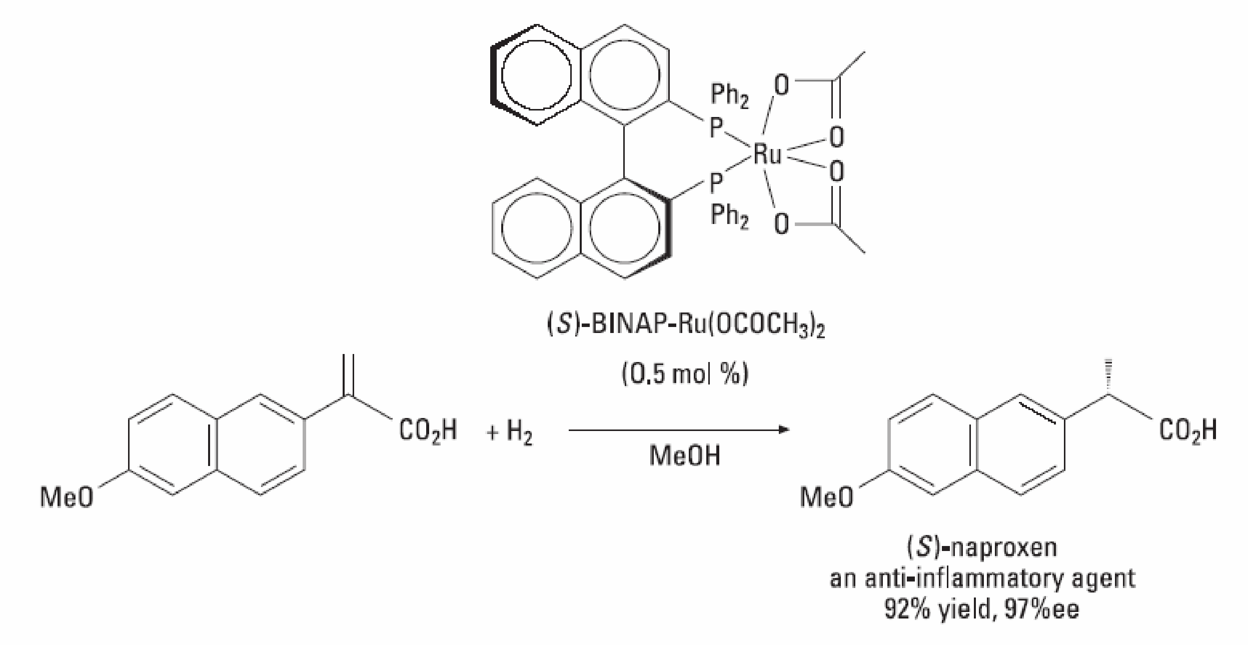
Homogeneous Catalysis – Metal Complexes

First industrial catalyst (Knowles, MONSANTO)



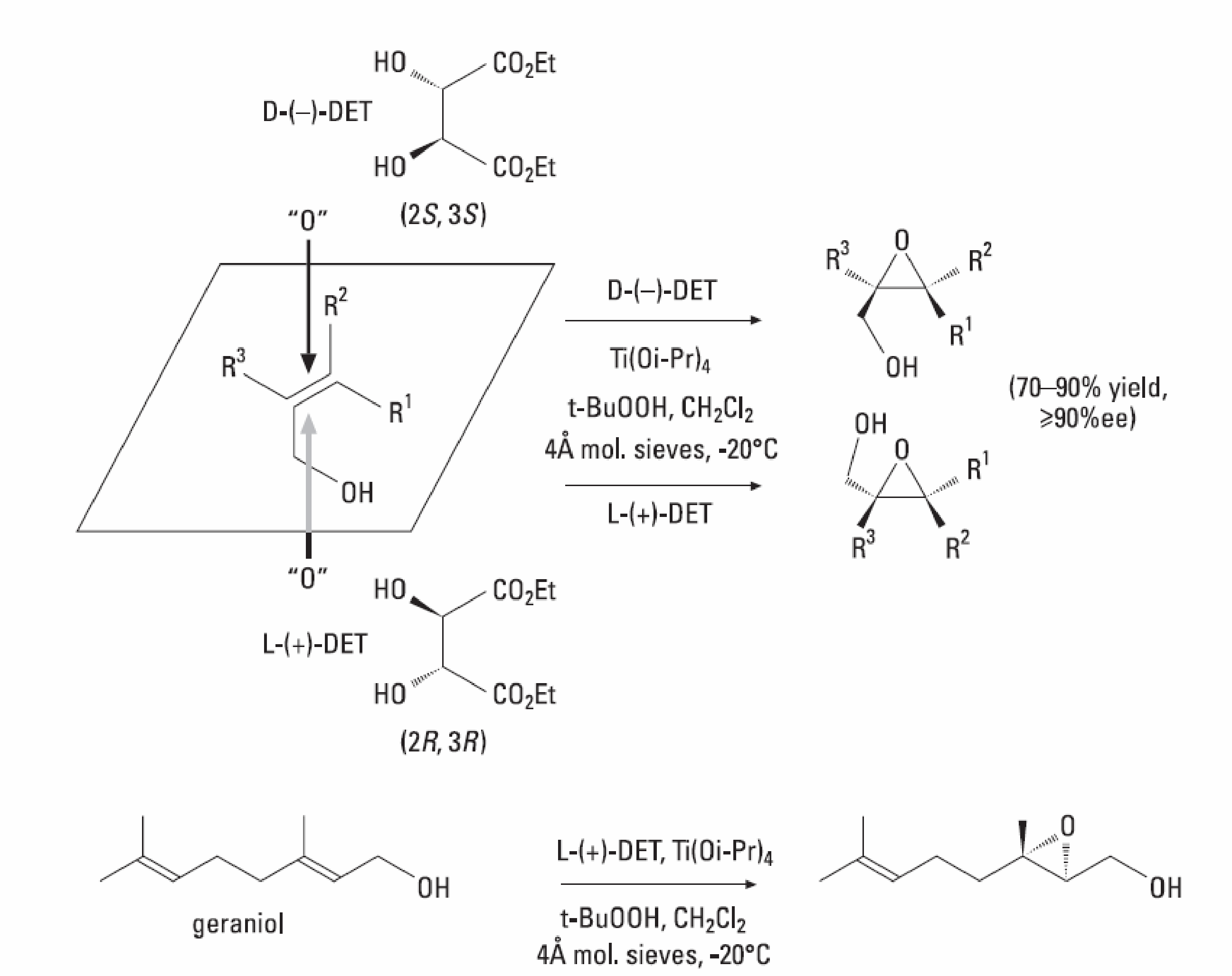
Homogeneous Catalysis – Metal Complexes

BINAP catalyst (Noyori, TAKASAGO)

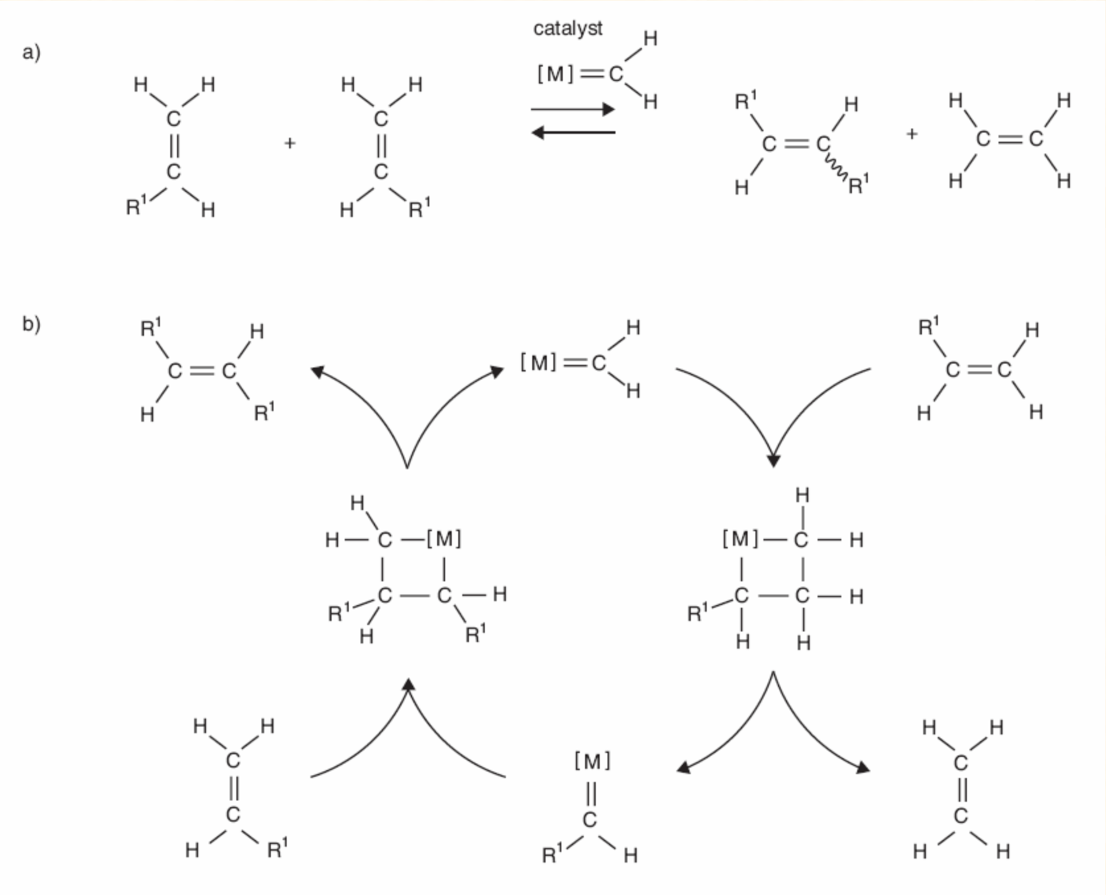


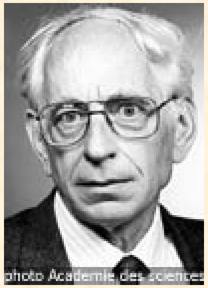
Homogeneous Catalysis – Metal Complexes

Catalytic enantioselective oxidations (Sharpless)



Homogeneous Catalysis – Metal Complexes





Yves Chauvin

Robert H. Grubbs

Richard R. Schrock

Nobel Prize in Chemistry, 2005

(a) Metathesis of alkenes catalysed by a metal alkylide.

(b) Chauvin's mechanism for olefin metathesis. In the catalytic cycle on the way to the products rings with four atoms are formed – three carbons and one metal.

Homogeneous Catalysis – Metal Complexes

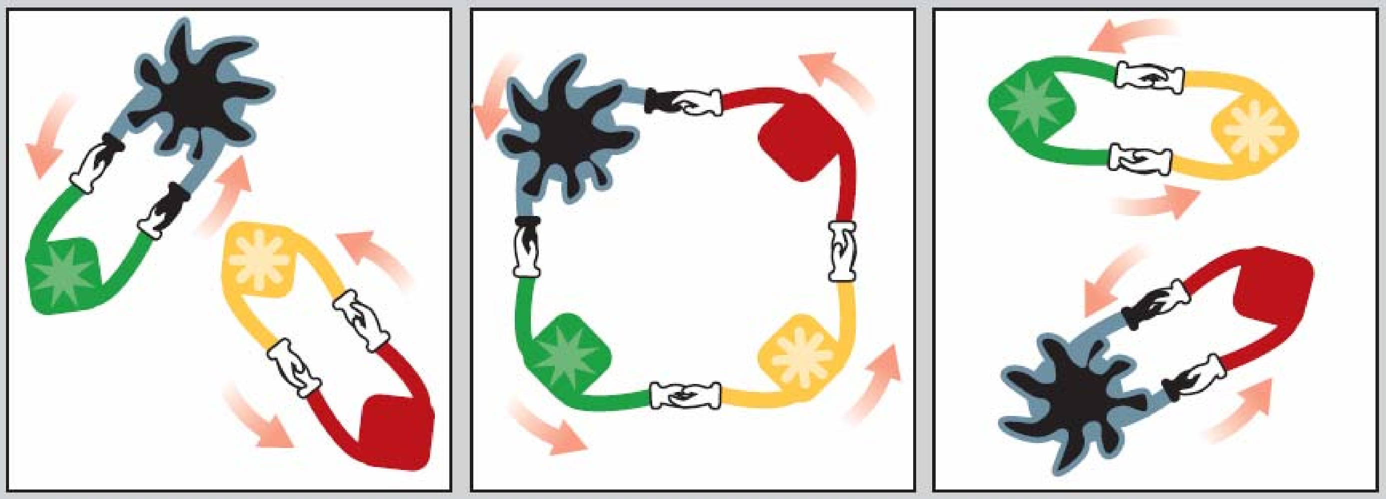
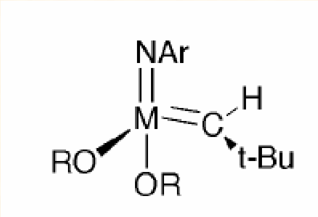
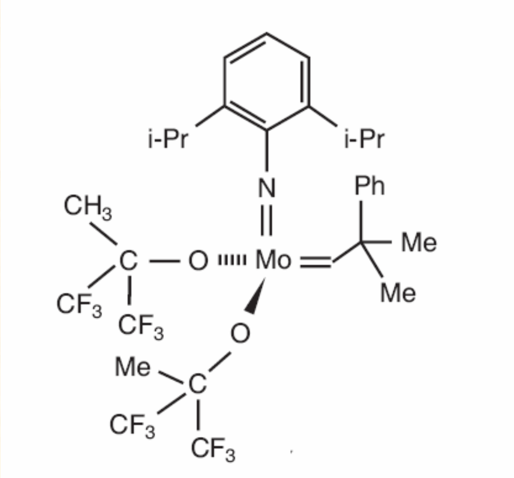


Figure 4. Chauvins' mechanism described above can be viewed as a dance in which the "catalyst pair" and the "alkene pair" dance round and change partners with one another. The metal and its partner hold hands with both hands and when they meet the "alkene pair" (a dancing pair consisting of two alkylides) the two pairs unite in a ring dance. After a while they let go of each other's hands, leave their old partners and dance on with their new ones. The new "catalyst pair" is now ready to catch another dancing "alkene pair" for a new ring dance or, in other words, to continue acting as a catalyst in metathesis.

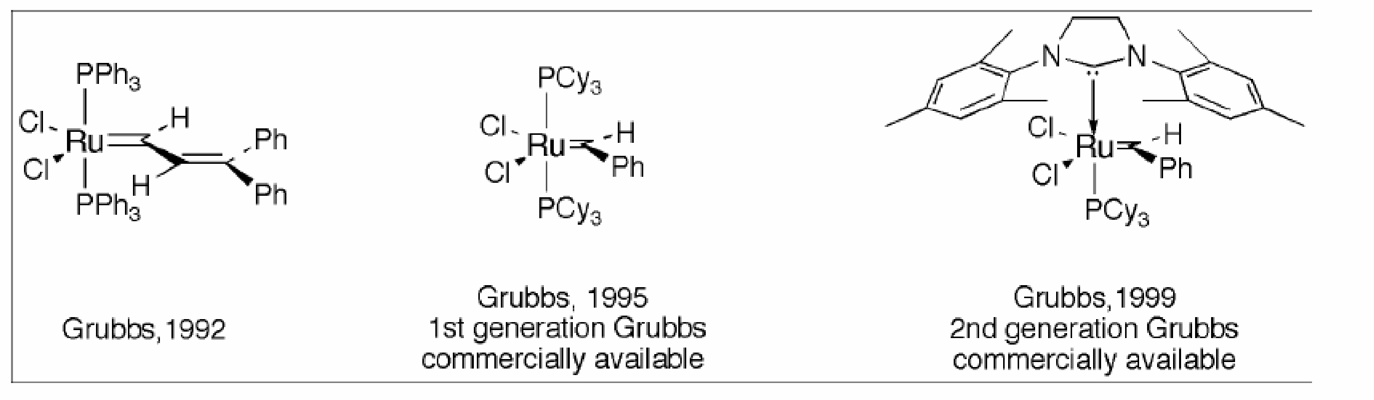
Homogeneous Catalysis – Metal Complexes



General formula of Schrock's catalysts (M= Mo, W, R and Ar are bulky substituents)

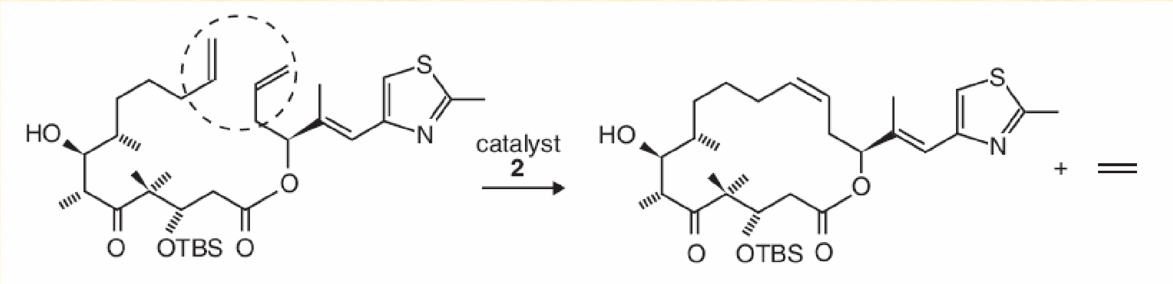


A commercially available Schrock's catalysts

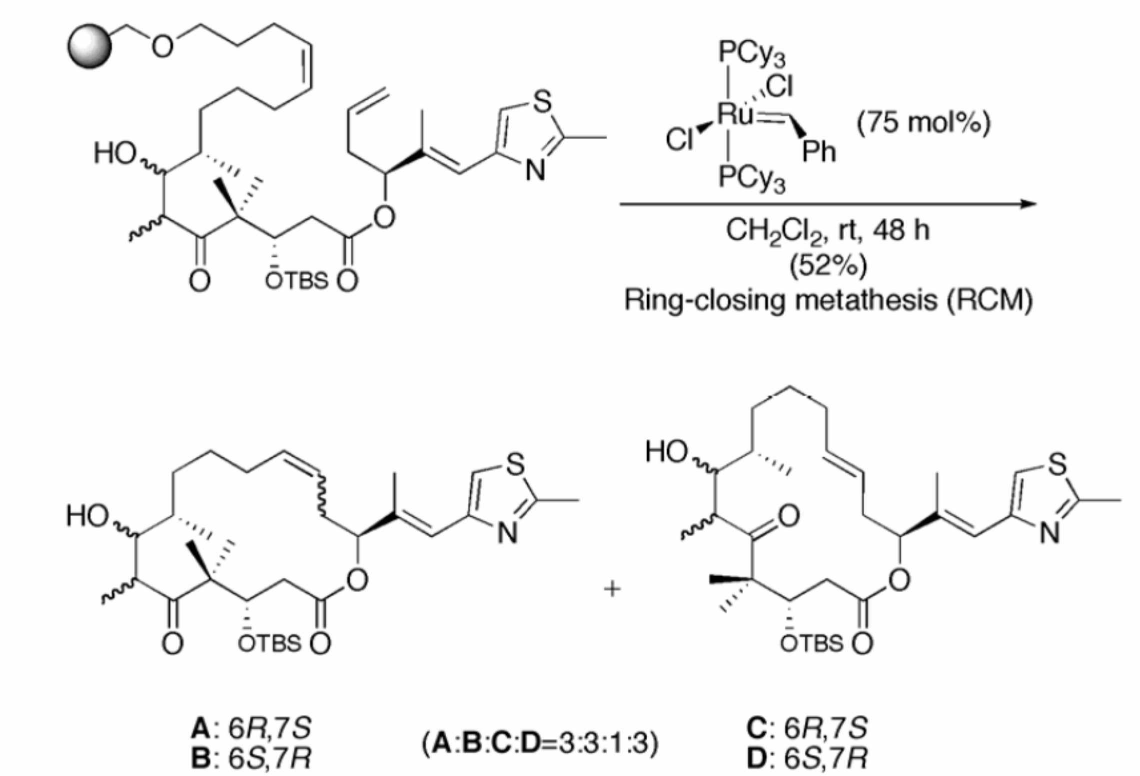


Ruthenium catalysts developed by Grubbs

Homogeneous Catalysis – Metal Complexes



Synthesis with
one of Grubbs' catalysts.



Synthesis of epothilone A
(Nicolaou)

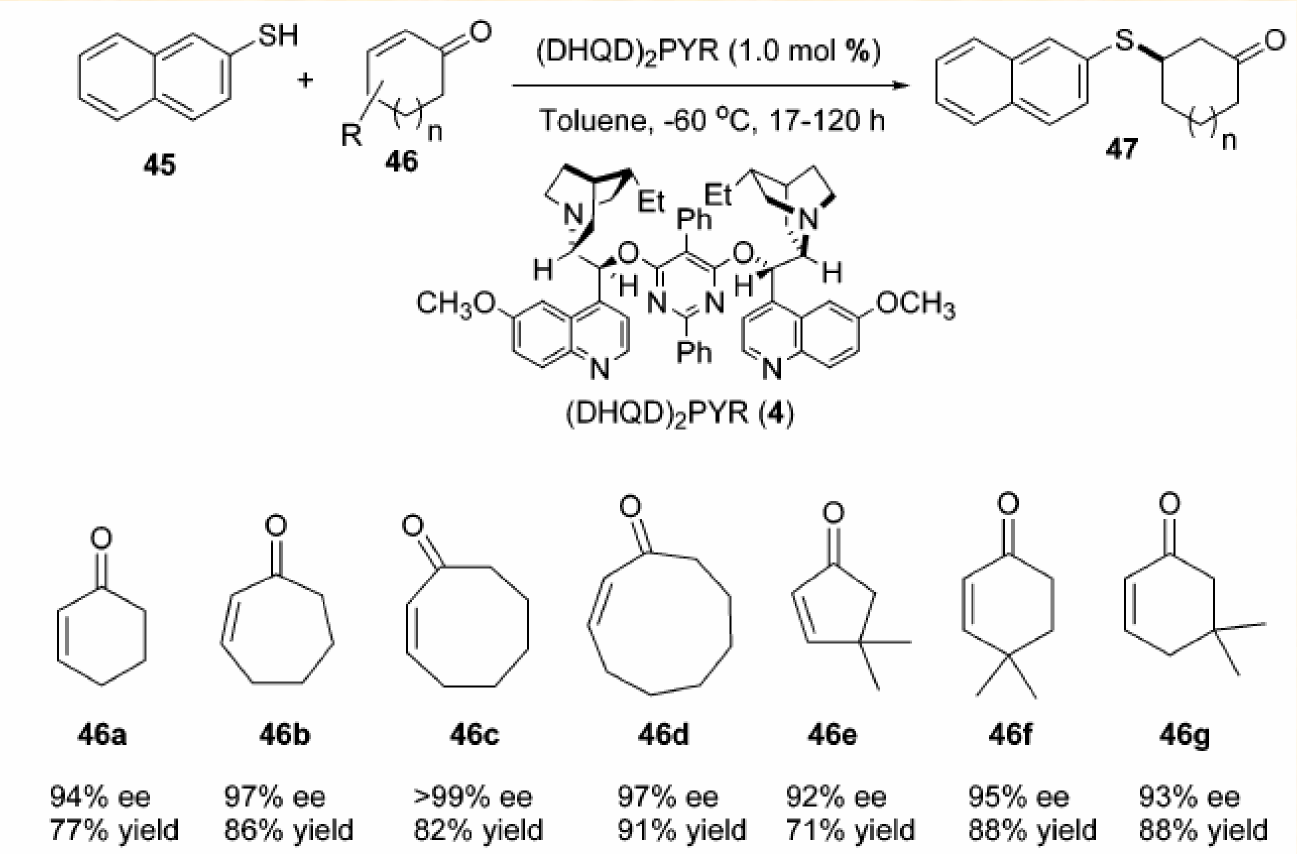
Homogeneous Catalysis – Organocatalysis

Organocatalysis

- Economic and available catalyst (usually natural products)
- High optical purity
- Easy and complete removal from the product
- No metal impurities in the product

Homogeneous Catalysis – Organocatalysis

Cinchona alkaloids



Homogeneous Catalysis – Organocatalysis

Cinchona alkaloids

Table 3: Enantioselective hydroxyalkylation of substituted indoles with ethyl 3,3,3-trifluoropyruvate in ether at −8 °C catalyzed by cinchona alkaloids.

Reactant	R^1	R^2	R^3	Catalyst	Product	Yield [%][a]	*ee* [%][b]
1a	H	H	H	CD	3a	99	95
	H	H	H	CN	4a	99	90
1b	H	H	5-Me	CD	3b	98	93
	H	H	5-Me	CN	4b	99	92
1c	H	H	6-Me	CD	3c	97	95
	H	H	6-Me	CN	4c	98	90
1d	H	H	5-F	CD	3d	97	92
	H	H	5-F	CN	4d	98	86
1e	H	H	5Cl	CD	3e	96	90
	H	H	5-Cl	CN	4e	98	86
1f	H	H	5-Br	CD	3f	97	87
	H	H	5-Br	CN	4f	96	85
1g	H	H	5-I	CD	3g	97	87
	H	H	5-I	CN	4g	97	85
1h	H	H	5-COOMe	CD	3h	96	88
	H	H	5-COOMe	CN	4h	97	85
1j	H	H	5-OMe	CD	3j	98	83
	H	H	5-OMe	CN	4j	96	83

[a] Isolated yields. [b] Average of five parallel reactions.

Homogeneous Catalysis – Organocatalysis

Amino Acids
(mostly proline and derivatives)

Scheme 13. Enamine Mechanism of the Direct Catalytic Asymmetric Aldol Reaction Catalyzed by L-Proline

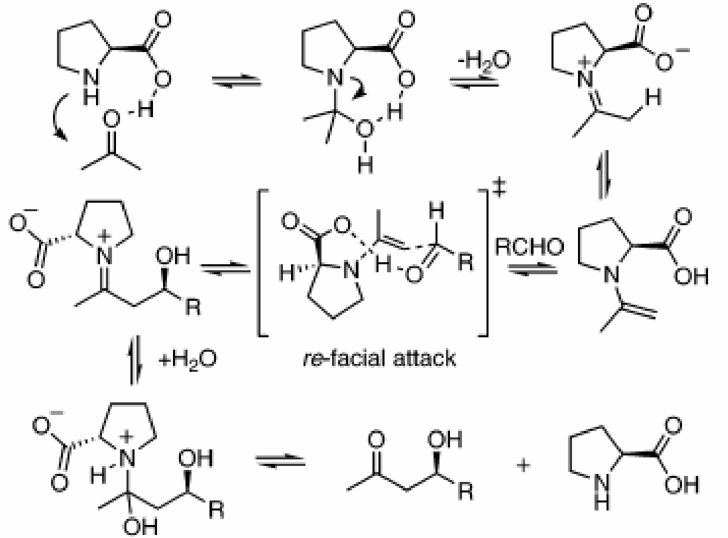
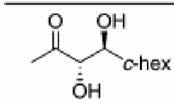
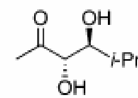
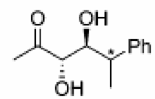
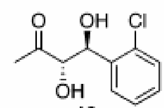
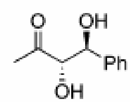
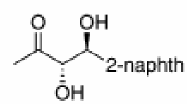
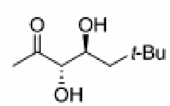
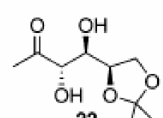
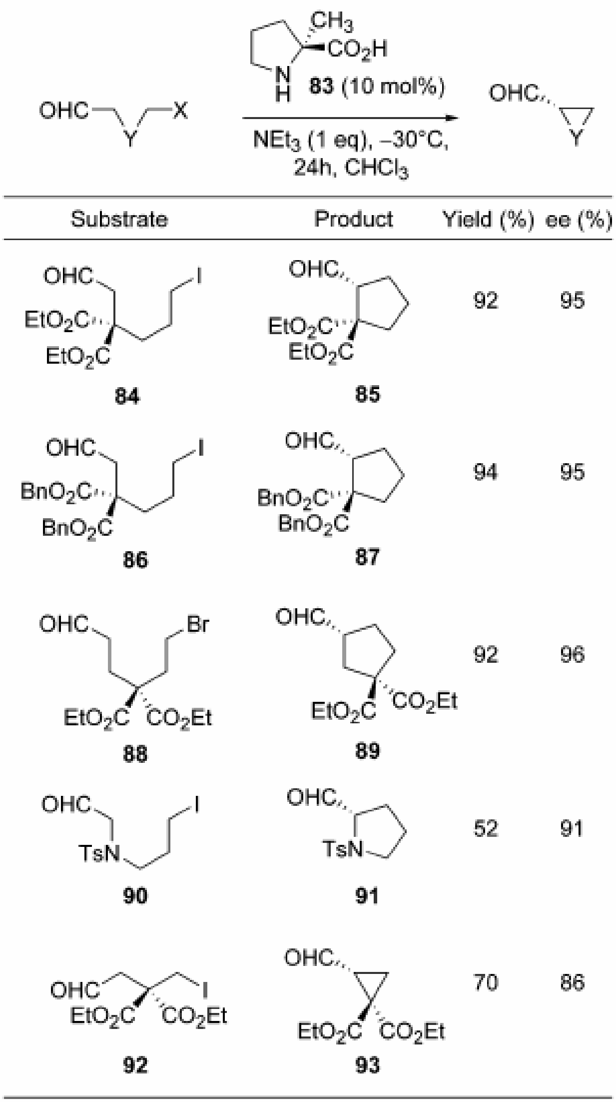


Table 3. Synthesis of Anti Diols from Hydroxyacetone

Product	Catalyst	anti:syn	Yield	ee
 **15**	(*L*)-Pro	>20:1	60%	>99%
	DMTC	>20:1	45%	95%
 **16**	(*L*)-Pro	>20:1	62%	>99%
	DMTC	n.d.	<5%	n.d.
 **17a** + **17b** (2:1)	(*L*)-Pro	>20:1	51%	>95%
	DMTC	n.d.	<5%	n.d.
 **18**	(*L*)-Pro	3:2	95%	67% (32%)
	DMTC	3:2	60%	92% (76%)
 **19**	(*L*)-Pro	1:1	83%	80% (n.d.)
	DMTC	1:1	52%	95% (50%)
 **20**	(*L*)-Pro	3:1	62%	79% (33%)
	DMTC	1:1	57%	91% (36%)
 **21**	(*L*)-Pro	1.7:1	38%	>97% (84%)
	DMTC	n.d.	<5%	n.d.
 **22**	(*L*)-Pro	2:1	40%	>97% (97%)
	DMTC	n.d.	<5%	n.d.

Homogeneous Catalysis – Organocatalysis

Scheme 20. Catalytic Asymmetric α-Alkylation of Aldehydes



Scheme 13. Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction