
聲明

本檔案之內容僅供下載人自學或推廣化學教育之非營利目的使用。並請於使用時註明出處。
[如本頁取材自○○○教授演講內容]。

Green Chemistry
綠色化學

工業界綠色永續合成實例

Cases of Green, Sustainable Synthesis in Industrial World

2010 永續合成化學工作坊
Feb 1, 2010, Taipei, TAIWAN



朝陽科技大學

周德璋

Green Chemistry

The design, development, and implementation of chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment.

[為縮減或淘汰對人類健康和環境具有危害性的物質的使用，而進行化學產品和製造過程的設計、開發與執行。]

Anastas PT, Kirchhoff MM,
Origins, Current Status, and Future Challenges of Green Chemistry

Acc. Chem. Res. 2002, 35. 686.

Anastas PT, Warner JC, editors. *Green Chemistry: theory and practice.*

Oxford: Oxford University Press; 1998.



The Twelve Principals of Green Chemistry

1. Prevent waste:

Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

2. Design safer chemicals and products:

Design chemical products to be fully effective , yet have little or no toxicity.

3. Design less hazardous chemical syntheses:

Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

4. Use renewable feedstocks:

Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.



The Twelve Principles of Green Chemistry

- 5. Use catalysts, not stoichiometric reagents:** *Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.*
- 6. Avoid chemical derivatives:** *Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.*
- 7. Maximize atom economy:** *Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.*
- 8. Use safer solvents and reaction conditions:** *Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.*
- 9. Increase energy efficiency:** *Run chemical reactions at ambient temperature and pressure whenever possible.*



The Twelve Principles of Green Chemistry

10. Design chemicals and products to degrade after use:

Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

11. Analyze in real time to prevent pollution: Include *in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.***12. Minimize the potential for accidents:** *Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.*

*Originally published by Paul Anastas and John Warner in
Green Chemistry: Theory and Practice
(Oxford University Press: New York, 1998).*



“Underlying the Green Chemistry approach is the recognition that all we have to work with on Earth is matter and energy.”

[綠色化學方法之基礎是，認知到我們在地球上所能夠使用的，就是物質和能量。]

“Green Chemistry seeks to design and invent the next generation of matter (material) that is the basis of our society and our economy so that it minimizes adverse consequences to human health and the environment.”

[綠色化學的目的是，設計和發明下一代我們的社會和經濟能夠賴以立基，並能夠對人類健康和環境有最小不利後果的物質（材料）。]

J. B. Manley, P. T. Anastas, B. W. Cue Jr.

Frontiers in Green Chemistry: meeting the grand challenges for sustainability in R&D and manufacturing,

J. Cleaner Production 16 (2008) 743.



**Webster's definition of chemistry,
“the study of matter and all of its transformations.”**

Transformations are carried out by chemical synthesis.

“Synthetic chemistry in the 21th century is not just a great intellectual challenge, it is essential for addressing the many challenges that face humanity.”[#] [21 世紀的合成化學並不只是一個重大的智力挑戰，有必要解決人類面臨的種種挑戰。]

*[#] Prof. Peter B. Dervan, California Institute of Technology,
2009 Welch Symposium on the Frontiers of Organic Synthesis*



The most critical challenge is global sustainability.

“The challenges of global sustainability are most complex and definitionally the most consequential of any that civilization has or can encounter.”

“The three elements of sustainability, environmental, social, and economic must be recognized in the context shown in Fig. 1.”

“....., we must understand that the economy exists within society and the society exists within the environment.

“The true long-term goal must be to ensure that the goals of environment, society, and economy are working in concert in a synergistic way.” →→→ **Toward global sustainability.**

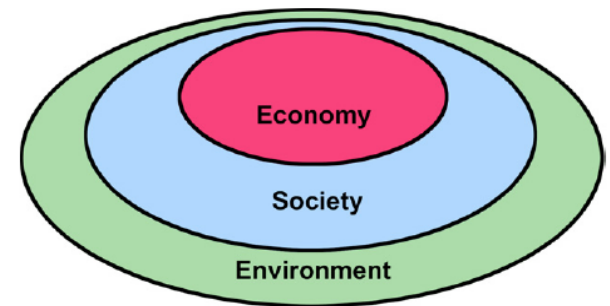


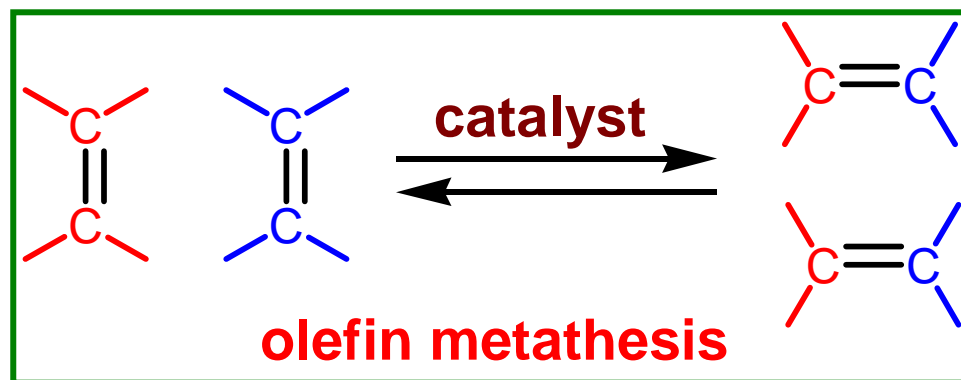
Fig. 1. A sustainable community [3].

J. B. Manley, P. T. Anastas, B. W. Cue Jr. *J. Cleaner Production* 16 (2008) 743.



“Americans Robert H. Grubbs and Richard R. Schrock and France's Yves Chauvin won the 2005 Nobel Award for their development of the **metathesis** method in organic synthesis.”

“This represents a great step forward for **green chemistry**, reducing potentially hazardous waste through smarter production. **Metathesis** is an example of how important basic science has been applied for the benefit of man, society and the environment,.....”



What is the ideal synthesis

1. Convenient and practical -- Simple
2. High yield (100%!)
3. Short (1 step!)
4. Mild conditions (room temperature or 37 °C)
5. Starting materials easy to obtain (natural or commercial)
6. Available controlled stimulus (mild reagents or catalysts)
7. Cheap and safe solvent (water!)
8. Easy isolation of products
9. Isolation of intermediates unnecessary (one-pot reaction)
10. Display novel chemistry or new applications

As Mother Nature Does!





Green Chemistry is focused on the design, manufacture, and the use of chemicals and chemical processes that have little or no pollution potential or environmental risk.

Sustainable Chemistry not only includes the concepts of **green chemistry**, but also expands the definition to a larger system than just the reaction. Also considers the effect of processing, materials, energy, and economics.



To process chemists

Process chemists and engineers in industry generally feel that green chemistry is an academic pursuit - until green chemistry considerations can lower the cost of goods. As Canales Clariond* said, “The world doesn’t move because of idealism... It moves because of economic incentives.”

Editorial: *Organic Process Research & Development* **2008**, 12, 1019.

**Fernando Canales Clariond, former Mexican secretary of the economy: steps new reactions and new technologies are important, The Los Angeles Times, July 10, 2008:*

<http://articles.latimes.com/2008/jul/10/business/fi-seafarm10>.

13



Lower the Cost of Goods (COG) and the Environment

- ✓ **Minimize waste**
 - ▶ **Achieving higher yields**
reduces the environmental quotient (EQ) of waste production.
 - ▶ **Processing using fewer unit operations and under more concentrated conditions**
reduce waste, cycle times, and labor costs.
- ✓ **Designing routes that require fewer steps**
require smaller quantities of starting materials, solvents, and reagents and less labor; less waste and reduced costs for waste disposal.
- ✓ **Review and consider older approaches and replaced with new reactions and new technologies.**



- ✓ **Support new synthetic initiatives and encourage unbiased researchers from academia to invent new approaches to existing compounds.**
- ✓ **Provide feedback to drug discovery.**
 - ▶ **Is the most potent or bioavailable compound selected?**
 - ▶ **Can the compound be prepared in the fewest steps?**
 - ▶ **Is the chiral center of the prodrug really necessary?**
- ✓ **Selecting different starting materials through designing and redesigning routes to lower the COG**

關心 COG
必能關心我們的環境



Twelve more principles of green chemistry

(Winterton N, *Green Chemistry* 2001, G73)

- 1. Identify and quantify byproducts**
鑑定並定量所有的副產物
- 2. Report conversions, selectivities and productivities**
記錄所有的轉換率、選擇性和產量
- 3. Establish full mass balance for process**
建立製程中完整的質量平衡
- 4. Measure catalyst and solvent losses in air and aqueous effluent**
測量空氣和水的流出物中催化劑和溶劑的耗損量
- 5. Investigate basic thermochemistry**
查悉基本熱化學
- 6. Anticipate heat and mass transfer limitations**
預估傳熱與傳質的限制



Twelve more principles of green chemistry

7. **Consult a chemical or process engineer**
諮詢化學或製程工程師
8. **Consider effect of overall process on choice of chemistry**
考量整個製程對選擇化學的影響
[化學反應和方法的選擇要依據整體製程]
9. **Help develop and apply sustainability measures**
協助開發和應用永續發展的措施
10. **Quantify and minimize use of utilities**
量化並減少使用通用性器材（水、電、煤氣等）
11. **Recognize where safety and waste minimization are incompatible**
認知安全和廢棄物減化在（製程中）何處會是不相容的[不能兼顧的]
12. **Monitor, report and minimize laboratory waste emitted.**
監控、記錄和減少實驗室的廢棄物排放



Material Efficiency: The Concept of Atom Economy

Professor Barry M. Trost, Stanford University,
The winners of the *Academic Award* in
the US Presidential **Green Chemistry** Challenge Awards, **1998**
for the Development of the Concept of Atom Economy



● How many of the atoms of the reactant are incorporated into the final product and how many are wasted?

[究竟有多少反應物的原子被合併到最終產品，有多少被浪費？]

$$\% \text{ Atom Economy} = \frac{\text{FW of atoms utilized}}{\text{FW of all reactants}} \times 100$$

Trost BM (1991)

The atom economy: A search for synthetic efficiency.

Science 254:1471–1477.

$$\text{Atom Economy} = \frac{\text{molecular wt. of desired product}}{\text{molecular wt. of all products}} \times 100\%$$

Chao-Jun Li and Barry M. Trost, *PNAS*, 2008, 105 (36), 13197–13202.

$$\text{Reaction Yield} = \frac{\text{quantity of product isolated}}{\text{theoretical quantity of product}} \times 100\%$$



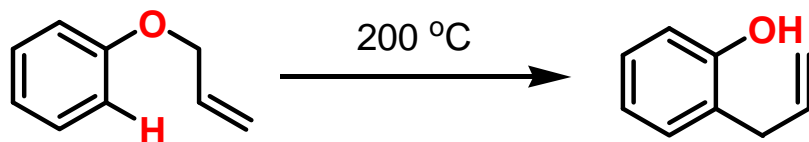
The Concept of Atom Economy

Examples

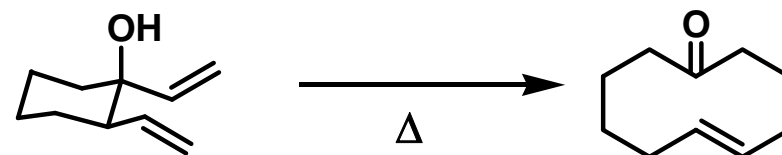
● Isomerization

% atom economy = 100%

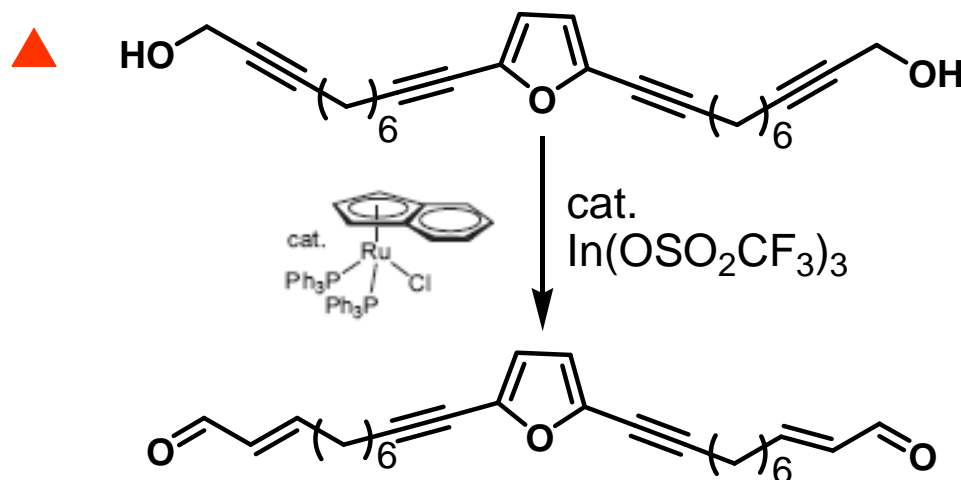
▲ Claisen Rearrangement

% atom economy = $(134.18/134.18) \times 100\% = 100\%$

▲ Oxy-Cope Rearrangement



% atom economy = 100%

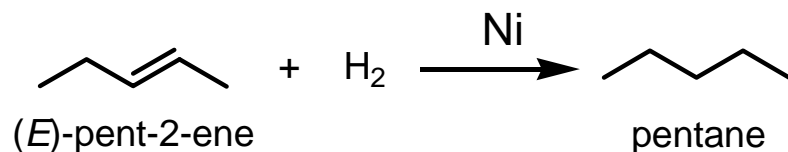


The Concept of Atom Economy

● Addition

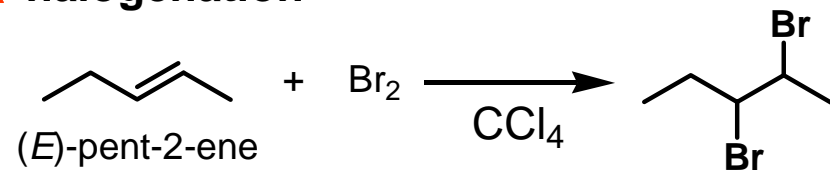
% atom economy = 100%

▲ hydrogenation



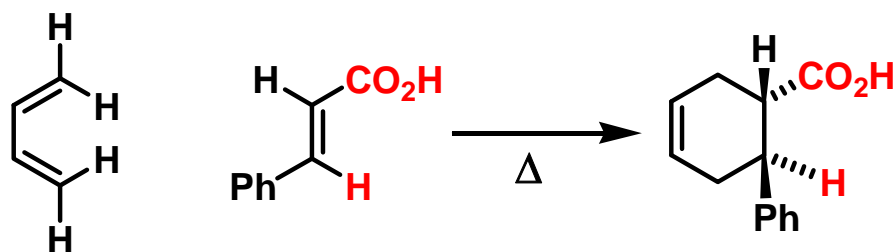
$$\% \text{ atom economy} = [72.15 / (70.13 + 2.02)] \times 100\% = 100\%$$

▲ halogenation

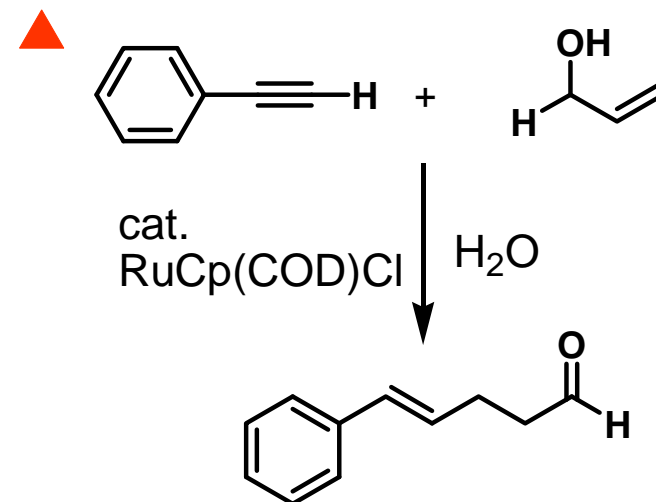


$$\% \text{ atom economy} = 100\%$$

▲ Diels-Alder reaction



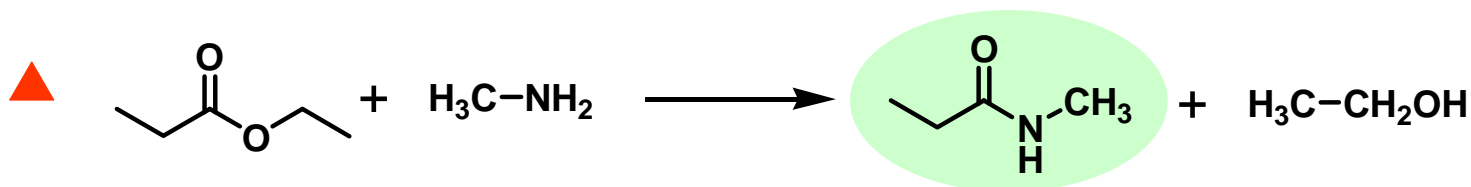
$$\% \text{ atom economy} = [202.25 / (54.09 + 148.16)] \times 100\% = 100\%$$



The Concept of Atom Economy

● **Substitution**

% atom economy < 100%



<u>Reactants</u>		<u>Utilized</u>		<u>Unutilized</u>	
<i>Formula</i>	<i>FW</i>	<i>Formula</i>	<i>FW</i>	<i>Formula</i>	<i>FW</i>
$C_5H_{10}O_2$	102.132	C_3H_5O	57.057	C_2H_5O	45.061
CH_3NH_2	31.057	CH_4N	30.049	H	1.008
$C_6H_{15}NO_2$	133.189	C_4H_9NO	87.106	C_2H_5OH	46.069

$$\% \text{ atom economy} = (87.106/133.189) \times 100\% = 65.4\%$$



The E Factor

[Environmental factor]

E-Factor = Total Waste (kg) / Product (kg)
(廢料總量 / 產物總量)

E-Factor = Raw materials-Product / Product (kg)
(原料總量-產物總量 / 產物總量)

Raw materials: substrate compounds, reagents, solvents, acid and base, catalyst, and even materials for producing energy.

Products: target compounds (goods) and materials that are recovered.

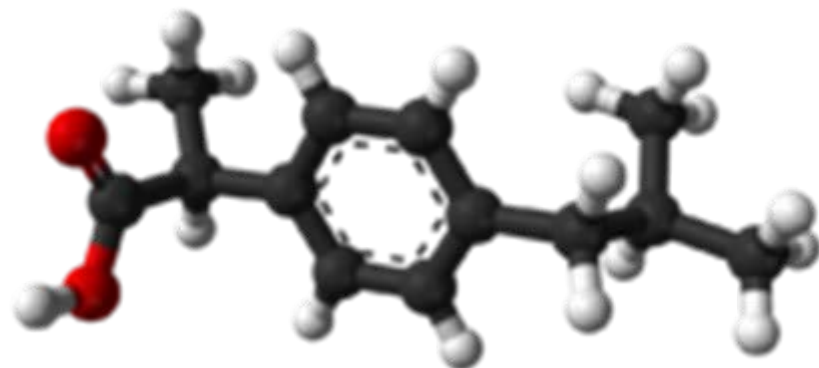
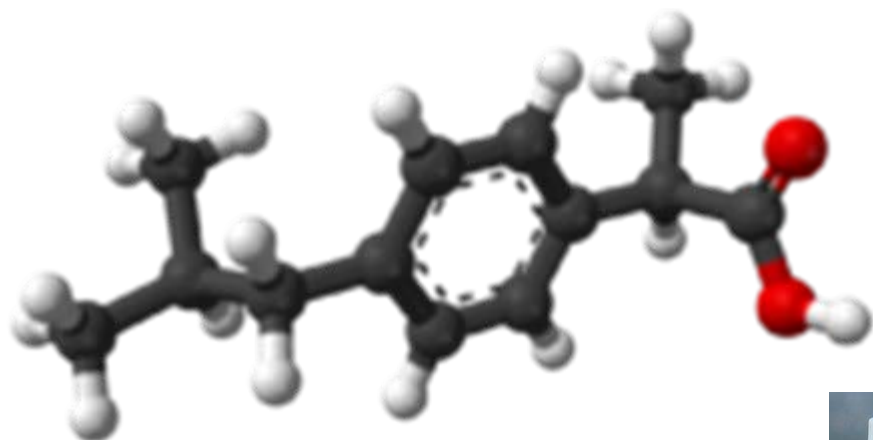
Waste: Anything that enters and causes “burden” to the environment.



Case 1.

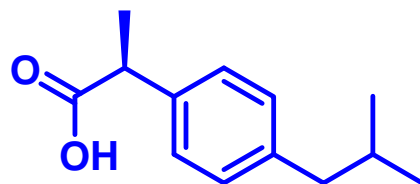
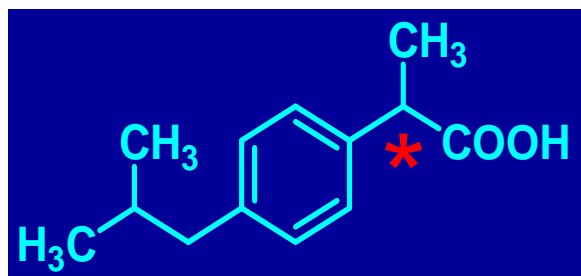
實例1

Ibuprofen

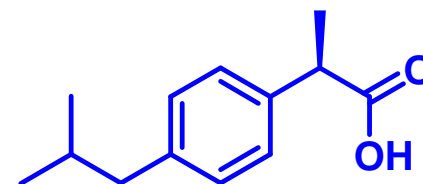


ibuprofen

What is ibuprofen?



(S)-ibuprofen



(R)-ibuprofen

(S)-2-(4-isobutylphenyl)propanoic acid, (S)-ibuprofen, is active form both *in vitro* and *in vivo*.

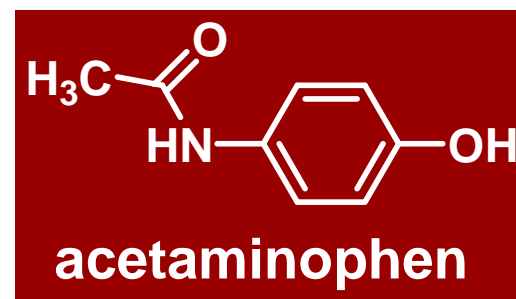
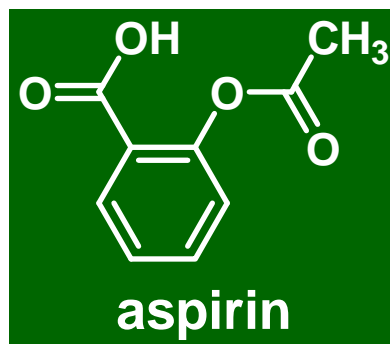
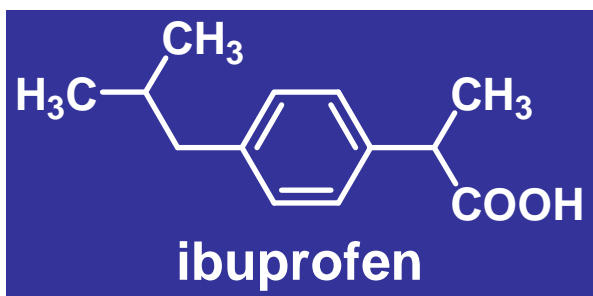


marketed as **racemic mixtures**.

ibuprofen



- One of core non-steroidal anti-inflammatory medicines (非類固醇消炎藥) in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system ---- *Over-the-Counter* (不需處方可出售的) medicine.
[others: aspirin, paracetamol (acetaminophen)]



- Discovered by S. Adams, with J. Nicholson, A. R. M. Dunlop, J. B. Wilson & C. Burrows (Boots Company), and was patented in 1961. Dr. Adams initially tested the drug on a hangover (宿醉).



- It was launched in 1969 as a medication for the treatment of rheumatoid arthritis [風濕性關節炎] in the UK and in 1974 in the USA.
- The Boots Group was awarded **Queen's Award for Technical Achievement** for the development of ibuprofen in 1987.
- 具解熱、消炎和鎮痛的作用，可治療發燒、疼痛和發炎。
- 減輕關節炎(arthritis)，原發型痛經(primary dysmenorrhea)，發燒(fever)，等症狀；作為止痛劑(analgesic)；具抑制血小板凝集效應(antiplatelet effect)。
- Active ingredient in “Motrin”, “Advil”, Medipren”....， “炎熱消”(水液)，“普服芬”(錠劑)，宜痛炎錠，伊普®鎮痛，...



◆ synthesis

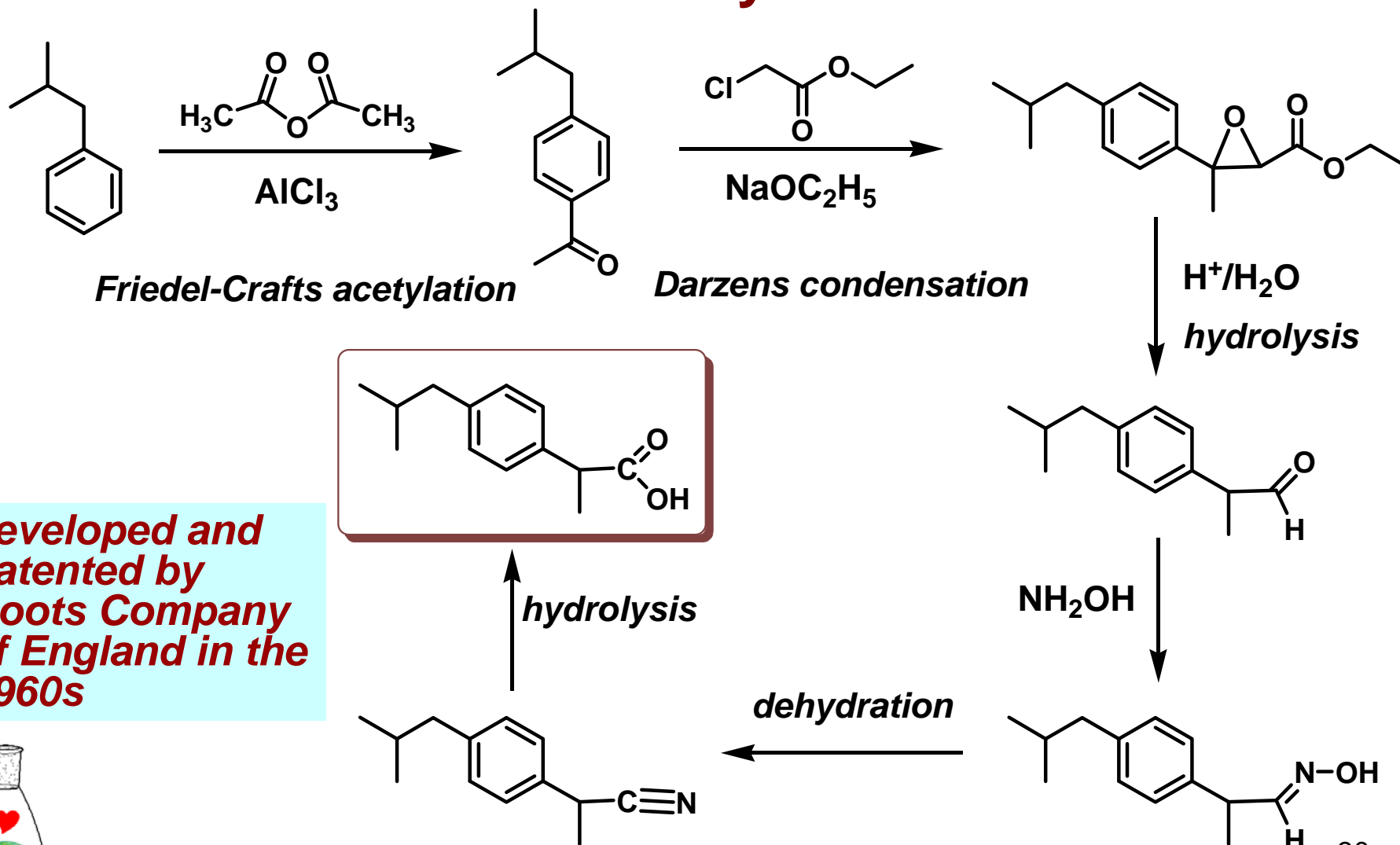
- The industrial synthesis was developed and patented by Boots Company of England in 1961. --- ***brown synthesis***
- A new greener industrial synthesis was developed and implemented by the BHC Company (now BASF Corporation) in 1991. --- ***green synthesis***
- BHC won Presidential Green Chemistry Challenge Awards (USA) ---- ***Greener Synthetic Pathways Award*** in 1997.

BHC = **B**oots + **H**oechst **C**elanese



Boots synthesis of ibuprofen

--- brown synthesis



developed and patented by Boots Company of England in the 1960s



ibuprofen

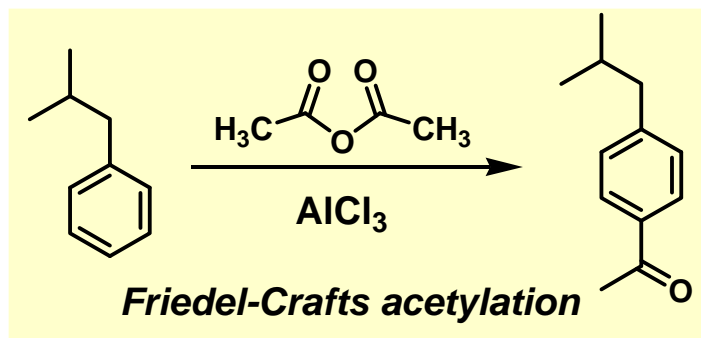
	Reagent		Used in ibuprofen		Unused in ibuprofen	
	Formula	Mw	Formula	Mw	Formula	Mw
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3	24	$C_2H_3O_3$	75
2	$C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
	C_2H_5ONa	68		0	C_2H_5ONa	68
3	H_3O	19		0	H_3O	19
4	NH_3O	33		0	NH_3O	33
6	H_4O_2	36	HO_2	33	H	3
	Total		Ibuprofen		Waste products	
	$C_{20}H_{42}NO_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5

▶ = $(206)/(514.5) \times 100 = 40\%$

Table 1. Atom economy in the Boots' synthesis of ibuprofen



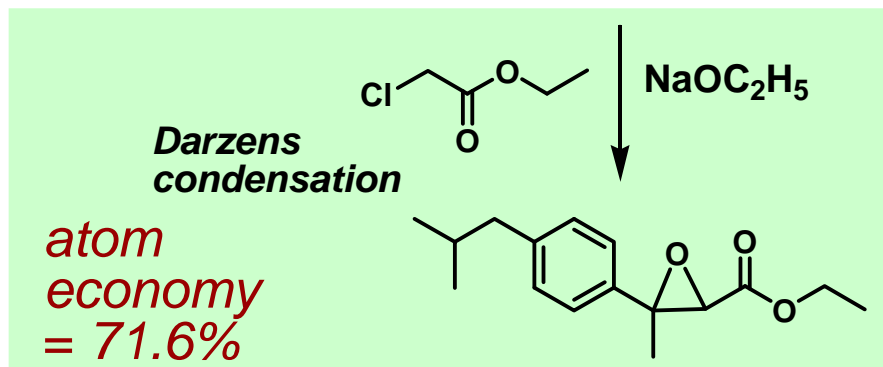
Problems with Boots synthesis of ibuprofen



atom economy = 74.5%

HCl AcOH Al

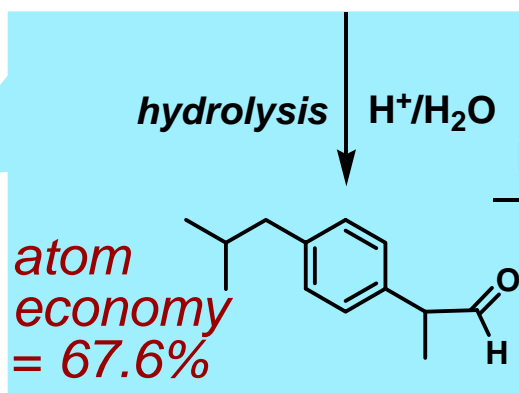
aluminium trichloride, AlCl_3 , is not a true catalyst. it is changed into a hydrated form, $\text{Al}(\text{OH})_3/\text{H}_2\text{O}$, that has to be disposed of – usually in landfill sites.



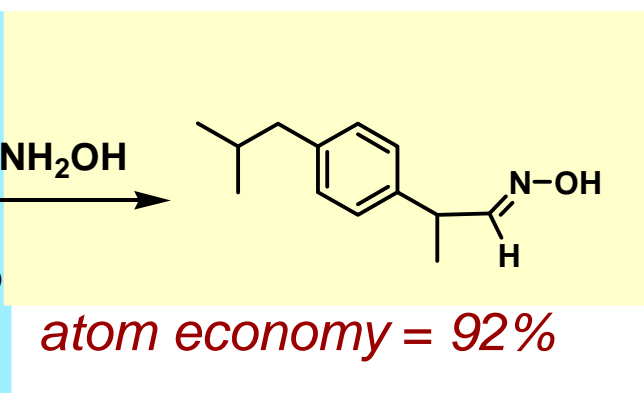
atom economy = 71.6%

NaCl C₂H₅OH

CO₂
C₂H₅OH



atom economy = 67.6%

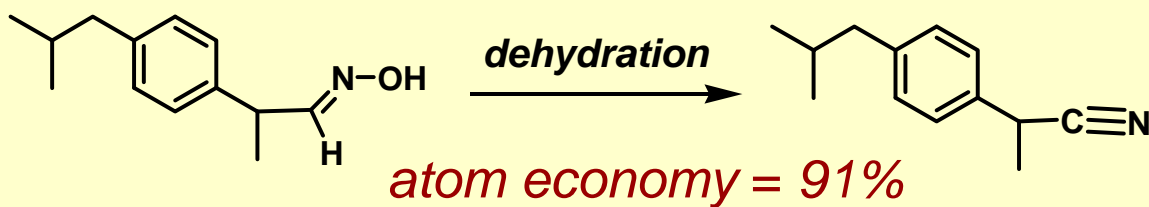
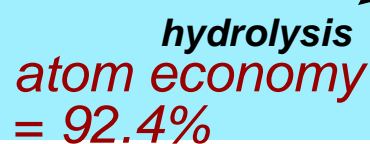


atom economy = 92%

H₂O



ibuprofen

H₂ONH₃

- **6 steps!**

If 90% yield for each step, then overall yield is 53%.

- **atom economy is 40%!**

*thus every 1 kg of **ibuprofen** produced is accompanied with more than 1.5 kg of waste.*

- **UK market for ibuprofen is about 3,000,000 kg per year!**

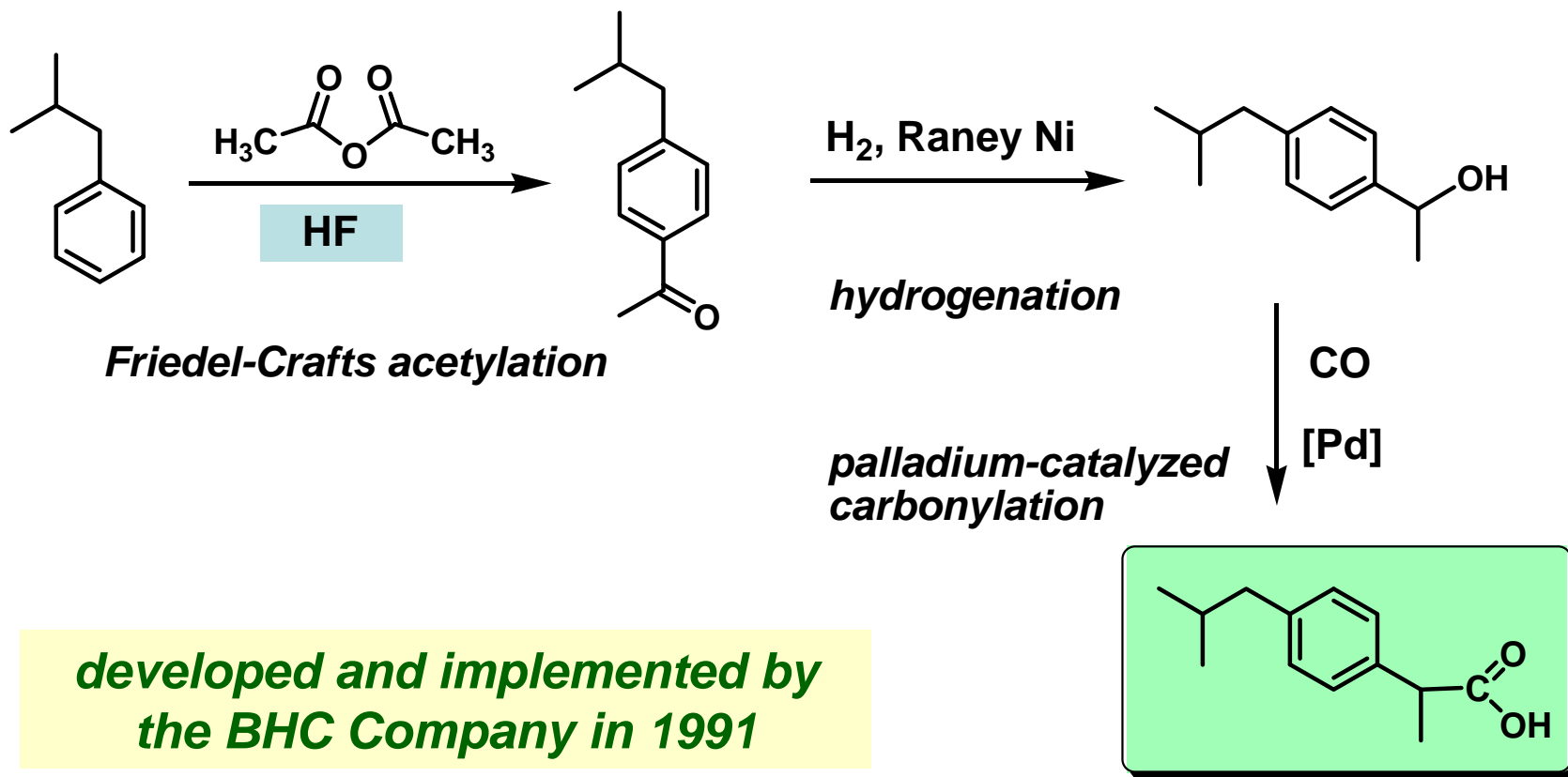
- *about 4,500,000 kg of waste are produced.*
- *a typical tablet contains 200 mg of ibuprofen, then 15,000,000,000 (1.5×10^{10}) tablets are produced.*



BHC synthesis of ibuprofen

--- green synthesis

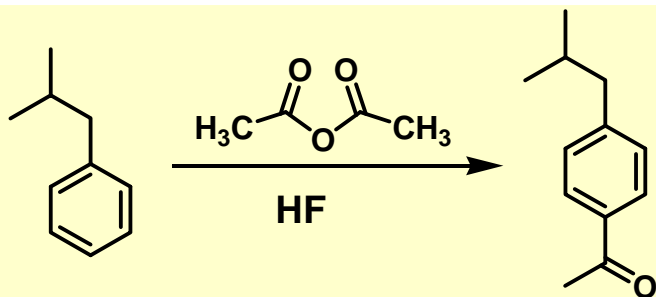
(USA) Presidential Green Chemistry Challenge Awards
Greener Synthetic Pathways Award in 1997



	Reagent		Used in ibuprofen		Unused in ibuprofen	
	Formula	Mw	Formula	Mw	Formula	Mw
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
2	H_2	2	H_2	2		0
3	CO	28	CO	28		0
	Total		Ibuprofen		Waste products	
	$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60
atom economy = $(206)/(266) \times 100 = 77.4\%$						

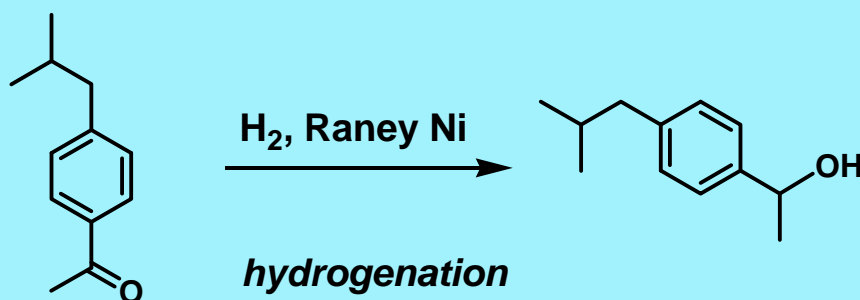
Table 2. Atom economy in the BHC synthesis of ibuprofen





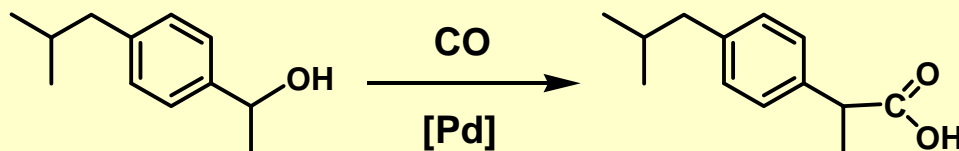
Friedel-Crafts acetylation

atom economy = 74.5%



hydrogenation

atom economy = 100%



palladium-catalyzed carbonylation

atom economy = 100%

HF AcOH

- Anhydrous hydrogen fluoride used as both catalyst and solvent ; it can be recovered (>99%) and reused.
- Acetic acid is recovered (>99%) and re-used.

- *Raney Ni is a spongy form of nickel made by dissolving the aluminium out of an Al-Ni alloy to leave holes.*

- Palladium is recovered and re-used.



Economic and Environmental Advantages of BHC Synthesis

- Greater overall yield (three steps vs. six steps)
- Greater atom economy (uses less feedstocks)
- Fewer auxiliary substances (products and solvents separation agents)
- **Less waste:** greater atom economy, catalytic vs. stoichiometric reagents, recovery of byproducts and reagents, recycling, and reuse, lower disposal costs.

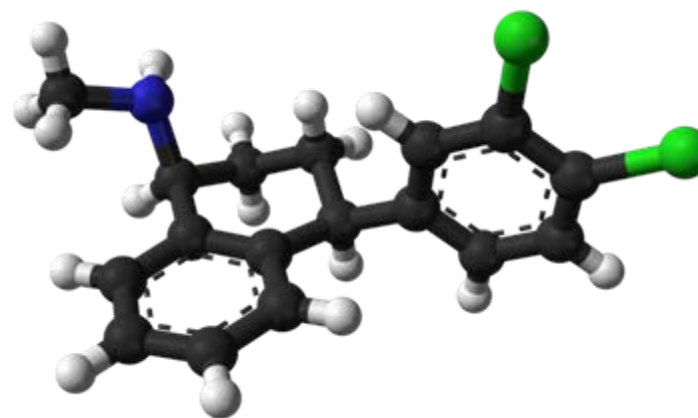
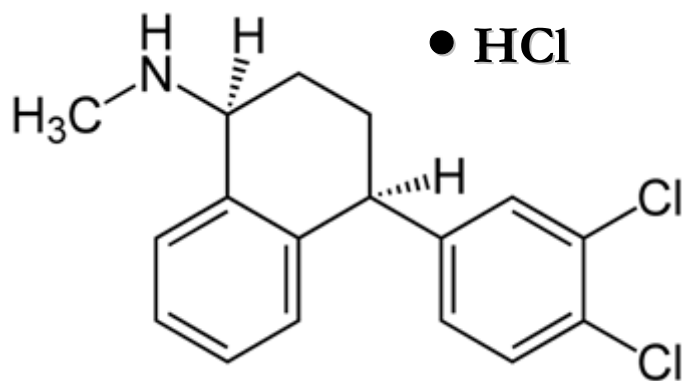
The BHC ibuprofen process is an innovative, efficient technology that has revolutionized bulk pharmaceutical manufacturing.



Case 2.

實例2

Sertraline hydrochloride



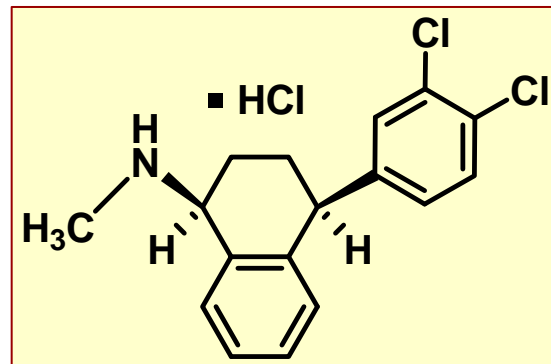
(1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine



◆ What is Sertralin Hydrochloride?

精神科藥物 Zoloft (樂復得)

- The empirical formula $C_{17}H_{17}NCl_2 \cdot HCl$ is represented by the structural formula:



2 個掌心
4 個立體異構物
2 對鏡像異構物

- Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) (選擇性血清素再吸收抑制劑).

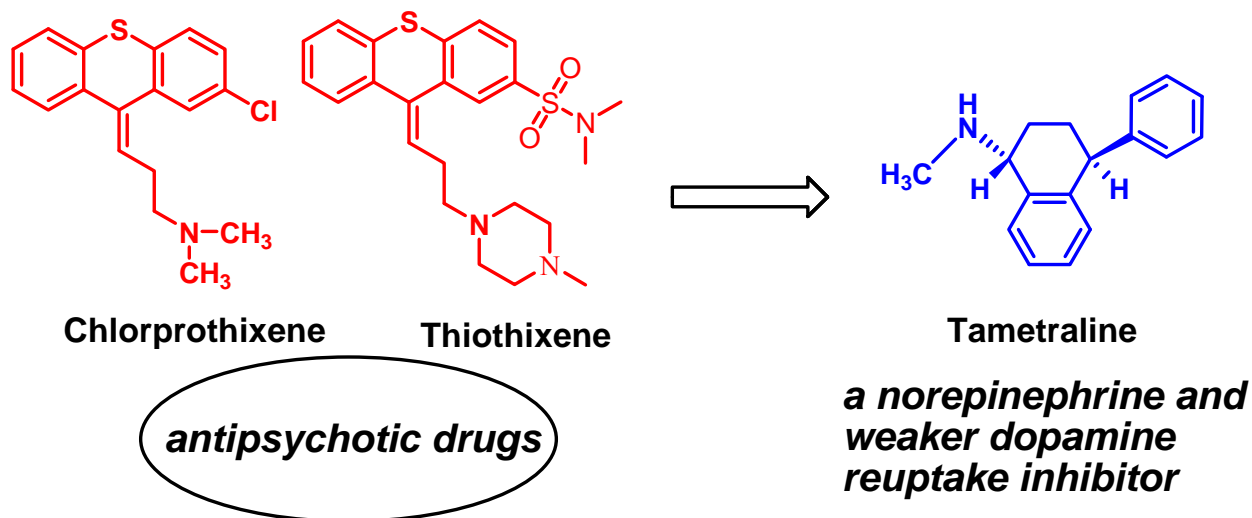


- It is an antidepressant (抗憂鬱症的) drug, used for treatment of major depression, panic disorder, obsessive-compulsive disorder, and posttraumatic stress disorder.
- It is sold by commercial name **Zoloft**[®] (Pfizer, Inc.).
- Approved for use in the U.S. in the early 1990s, it is the most prescribed drug of its class.
- It is used to treat an illness (depression) that each year strikes 20 million adults in the United States, and that costs society \$43.7 billion (1990 dollars).
- As of February 2000, more than 115 million Zoloft[®] prescriptions had been written in the United States.



◆ synthesis

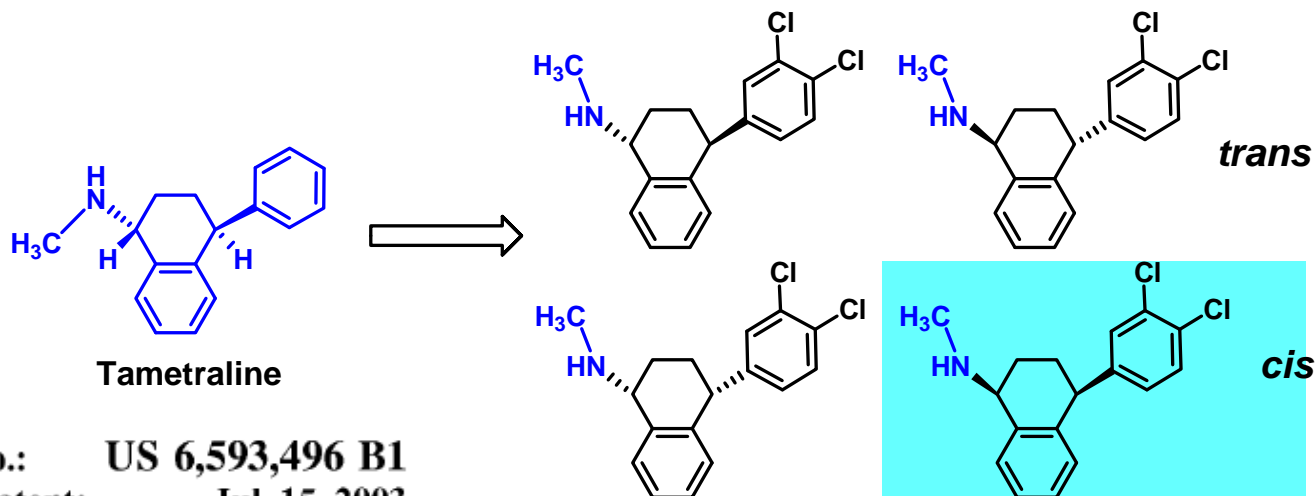
- ▶ Early 1970s, Pfizer chemist Reinhard Sarges invented a novel series of psychoactive compounds based on the structures of neuroleptics **chlorprothixene** and **thiothixene**, leading to **tametriline**, a *norepinephrine* and weaker *dopamine reuptake inhibitor*.
- ▶ Development of **tametriline** was stopped because of undesired stimulant effects observed in animals.



* A norepinephrine reuptake inhibitor (NRI, NERI) or adrenergic reuptake inhibitor (ARI), is a type of drug which acts as a reuptake inhibitor for the neurotransmitters norepinephrine (noradrenaline) and epinephrine (adrenaline) by blocking the action of the norepinephrine transporter (NET).



- ▶ In 1977, pharmacologist K. Koe, after studying the structural features of a variety of reuptake inhibitors, became interested in the **tametriline** series.
- ▶ W. Welch was asked to synthesize some previously unexplored **tametriline** derivatives and found one representative of the generally inactive **cis-analogs** was a **serotonin reuptake inhibitor**.
- ▶ The most potent and selective (+)-isomer was taken into further development and eventually named **sertraline**--- **an antidepressant** of the SSRI type.
- ▶ The discovery of the **sertraline** molecule was **serendipitous**.



Tametriline

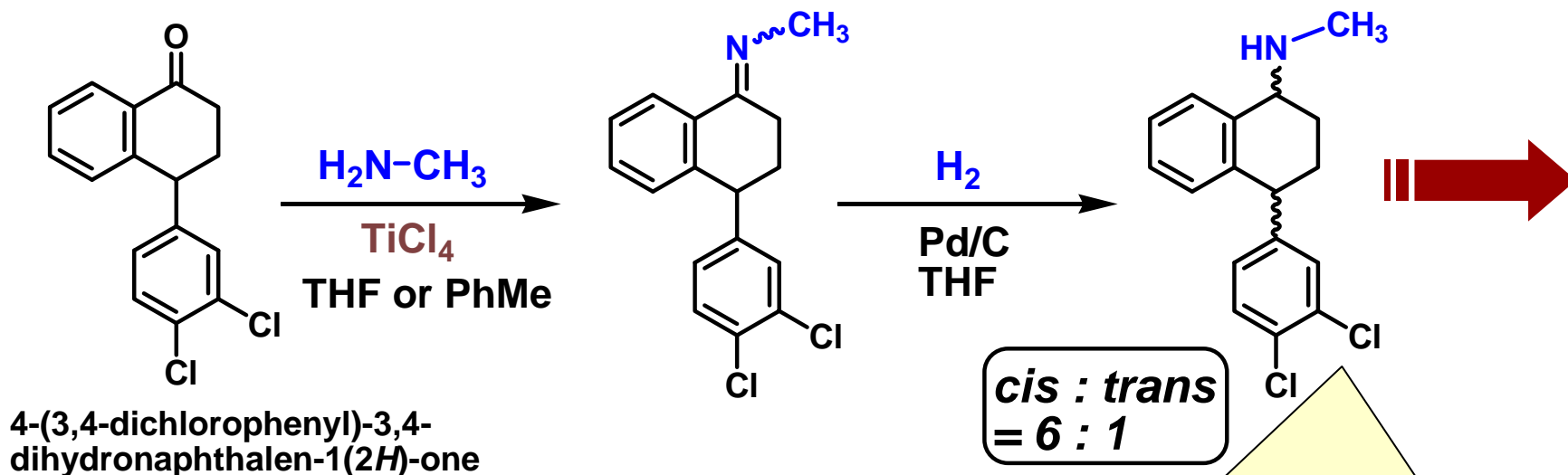
*trans**cis*

Patent No.: US 6,593,496 B1
Date of Patent: Jul. 15, 2003

Sertraline hydrochloride

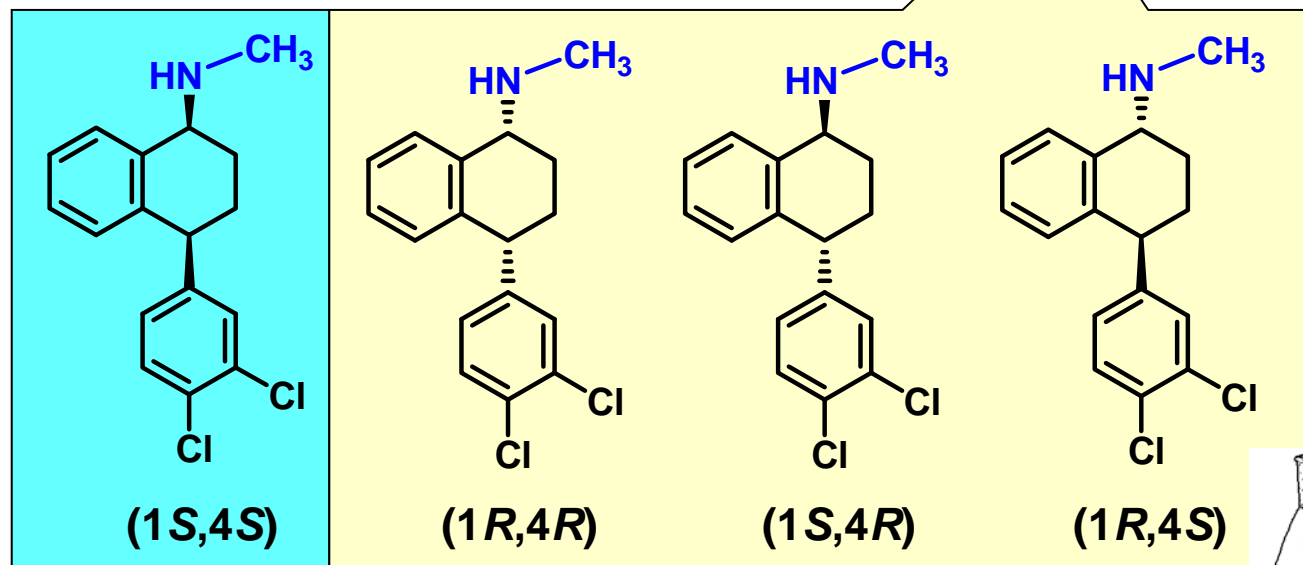


The original three-step process

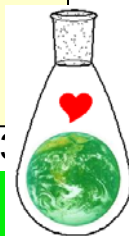


Sources

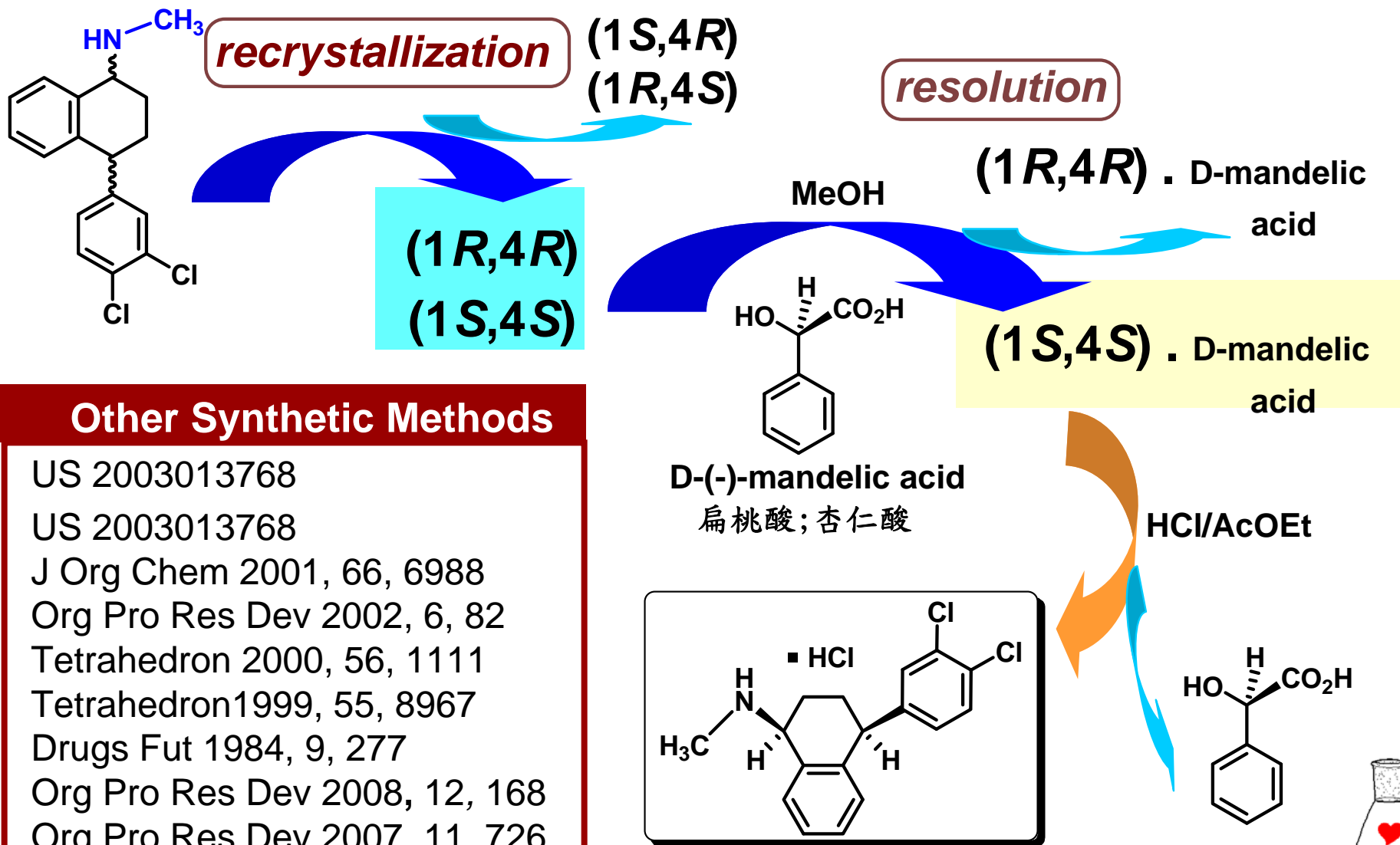
EP 0030081;
JP 1981086137;
US 6,232,500,
2001
Chem. Eng. News
2002, 80 (16), 30.
Org Proc Res Dev
2004, 8, 385



Sertraline hydrochloride



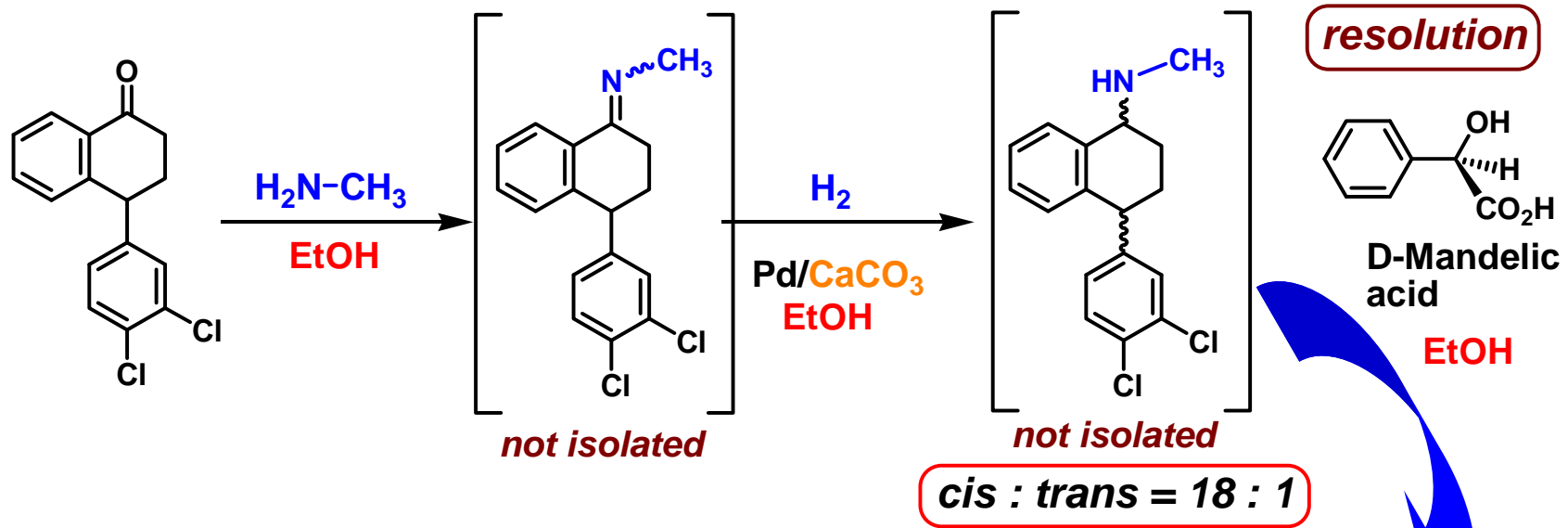
Resolution Process



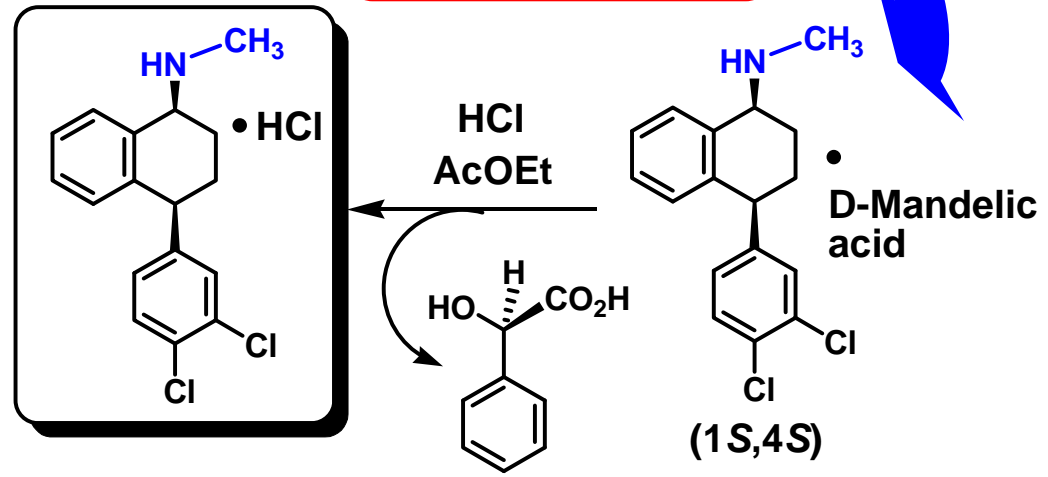
Sertraline hydrochloride



New Sertraline Process (Zoloft®, Pfizer)



developed by Pfizer process chemists G. Taber, J. Colberg, and D. Pfisterer.



The “greener” features for the new sertraline process

- 3-step, 1-pot process without isolating intermediates.
- Introduction of EtOH as solvent.
(→ reduce the solvent requirement from 60,000 to 6,000 gal/ton).
- Elimination of the need to use, distill, and recover four solvents (methylene chloride, tetrahydrofuran, toluene, and hexane).
- Elimination of using excess NH_2CH_3 (5 eq)
(The imine formation is an equilibrium reaction; imine is sparingly soluble in EtOH, favoring equilibrium toward its formation → → cut down raw material used).



- Elimination of TiCl_3 (used as dehydrating agent).
(\rightarrow eliminating 440 tons of TiO_2 , 150 tons 35% HCl , 100 tons 50% NaOH per year).
- Replacement of Pd/C with Pd/CaCO_3 .
(\rightarrow higher selectivity \rightarrow \rightarrow higher yield).
- Doubled the overall yield nearly to 37%.
(\rightarrow cut raw materials by about 60, 45, and 20% for methylamine, dichlorophenyltetralone, and D-mandelic acid, respectively.)
- Reduction of energy and water use.
- Increases worker safety.

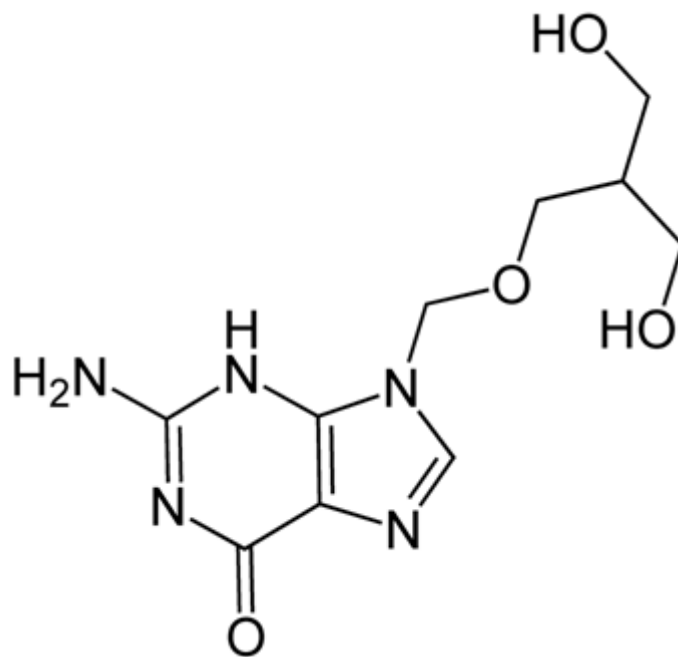
The **2002** US Presidential **Green Chemistry** Challenge Awards
in the category of
Greener Synthetic Pathways Award



Case 3.

實例3

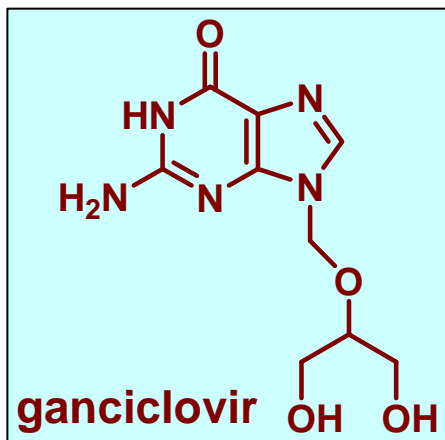
The Cytovene[®] [ganciclovir]



2-amino-9-[[[(1,3-dihydroxypropan-2-yl)oxy]methyl]-6,9-dihydro-3*H*-purin-6-one
ganciclovir



What is ganciclovir [“更昔洛韋”]?



Chemical Formula: $C_9H_{13}N_5O_4$

Exact Mass: 255.09675

Molecular Weight: 255.23062

IUPAC name:

2-amino-9-[[(1,3-dihydroxypropan-2-yl)oxy] methyl]-6,9-dihydro-3*H*-purin-6-one

- Ganciclovir is a prescription medication that belongs to the family of drugs known as “antivirals”.
[“更昔洛韋” 是屬於抗病毒的處方藥劑]

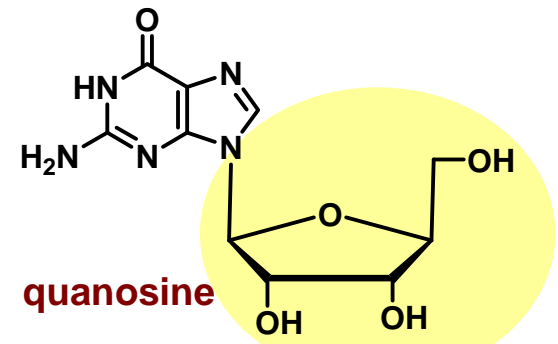
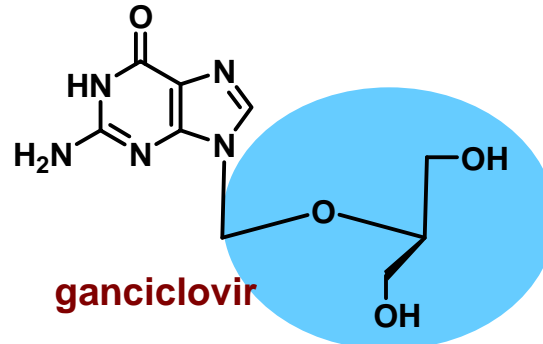
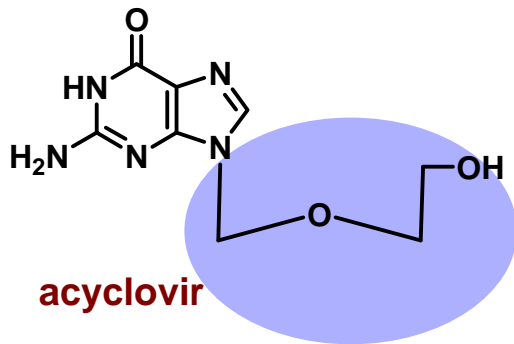


- Ganciclovir works by inhibiting cellular DNA polymerase that is associated with viral infections.
[更昔洛韋的作用是抑制與病毒感染有相關聯的細胞DNA聚合酶。]
- Ganciclovir is used to treat for cytomegalovirus (CMV) retinitis infections in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS) or patients undergoing chemotherapy.
[“更昔洛韋”是用於治療免疫損害患者中的巨細胞病毒 (CMV) 視網膜炎，包括後天免疫缺乏症候群（愛滋病）或化療病人。]
- Cytovene®, the registered trade name by the Roche Pharmaceuticals, contains ganciclovir sodium as the medicinal ingredient.
[Cytovene®是羅氏藥廠註冊的商標名稱，含更昔洛韋鈉鹽作為其藥用成分。]



◆ synthesis

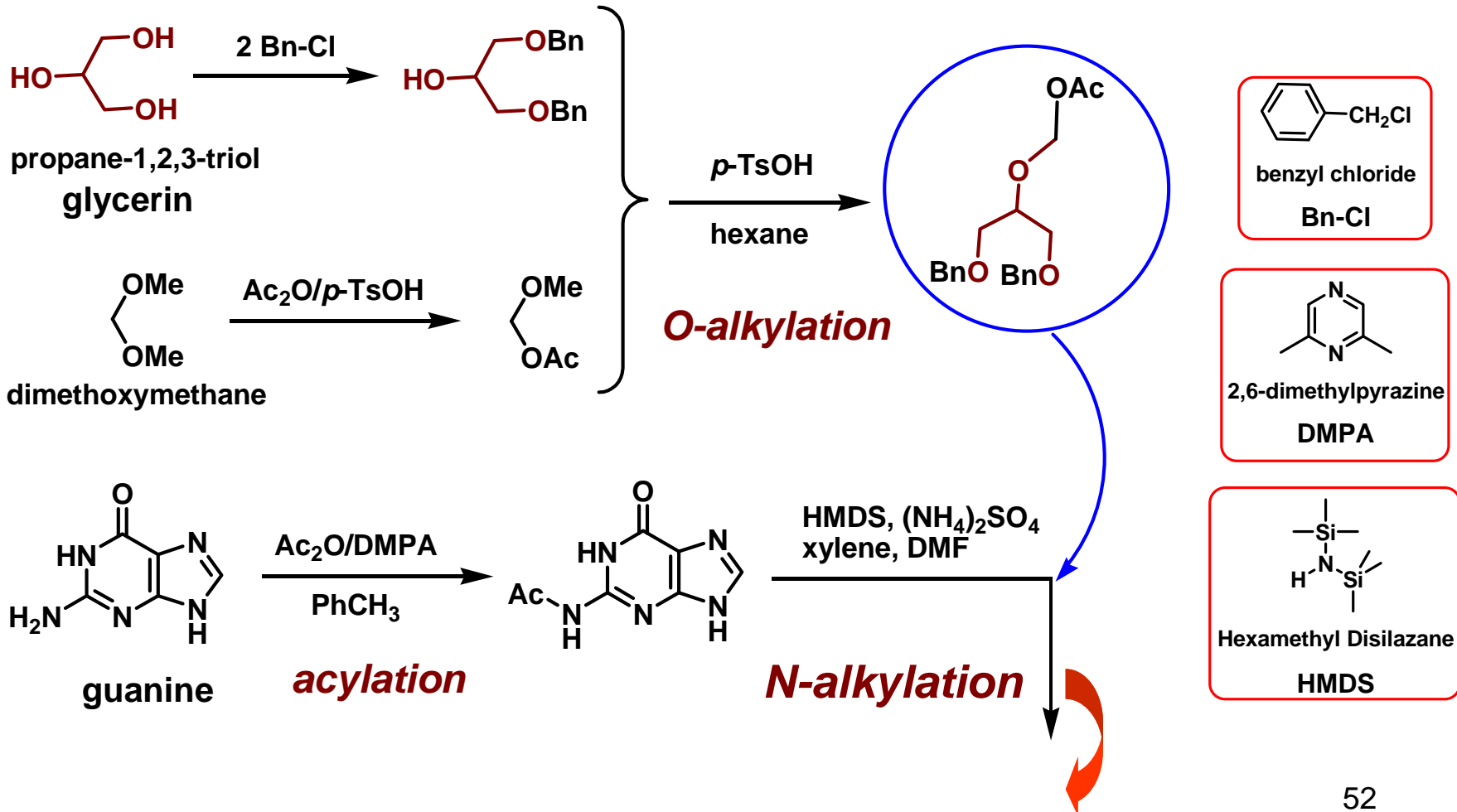
- In 1974, scientists at Wellcome discovered the potent antiviral agent acyclovir (Zovirax®) for the treatment of various viral infections including herpes viruses HSV-1 and HSV-2.
- In 1980, Dr. Kelvin Ogilvie and his research team at McGill University discovered Ganciclovir [*CAN. J. CHEM.* 1982, 60, 3005.], and developed by Verheyden and Martin at Syntex Research in 1980.
- The first commercially viable process for the manufacture of ganciclovir was developed by Roche Colorado Corporation, formerly known as Syntex Chemicals, in the early 1990s.
- The 1st generation process is known as **Persilylation Process**.

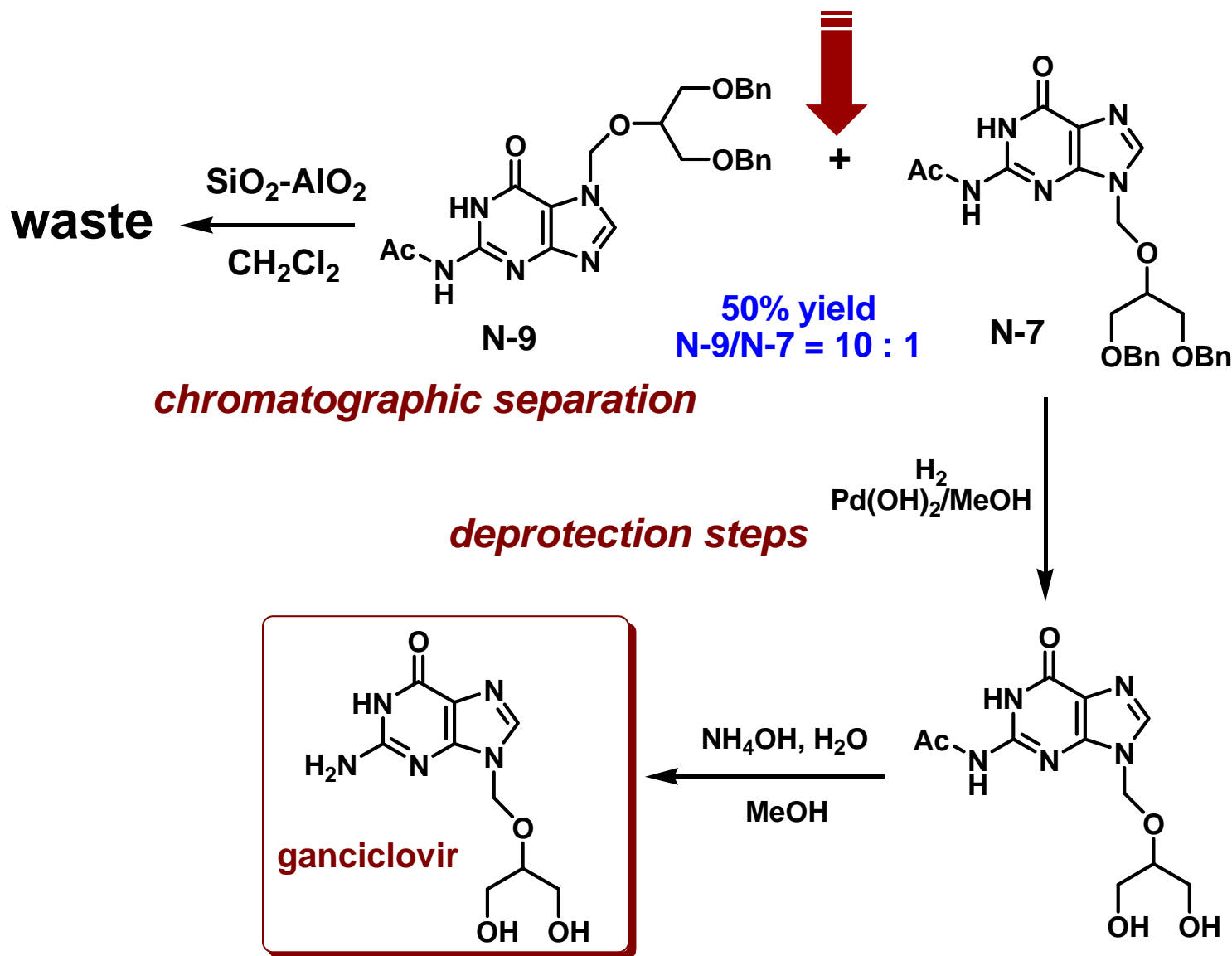


Persilylation Process --- Brown process

U.S. Patent 4, 621,140, November 4, 1986.

U.S. Patent 4,803,271, February 7, 1989.





Problems with **Persilylation Process**

- A six-step process, in which 4-steps are protection-deprotection reactions.
- Involved 28 reagents and intermediates, and required the purification and isolation of 5 discrete intermediates.
- Involved at least 8 different kinds of solvents.
- Afforded specification grade ganciclovir in 54% yield.
- Involved a potentially hazardous palladium catalyzed hydrogenation step, which is needed to remove dibenzyl ether protecting group.
- Poor selectivity of key alkylation reaction, affording the desired N-7 isomer as minor product (**N-7:N-9 = 1:10**) and requiring costly and tedious chromatographic separation.

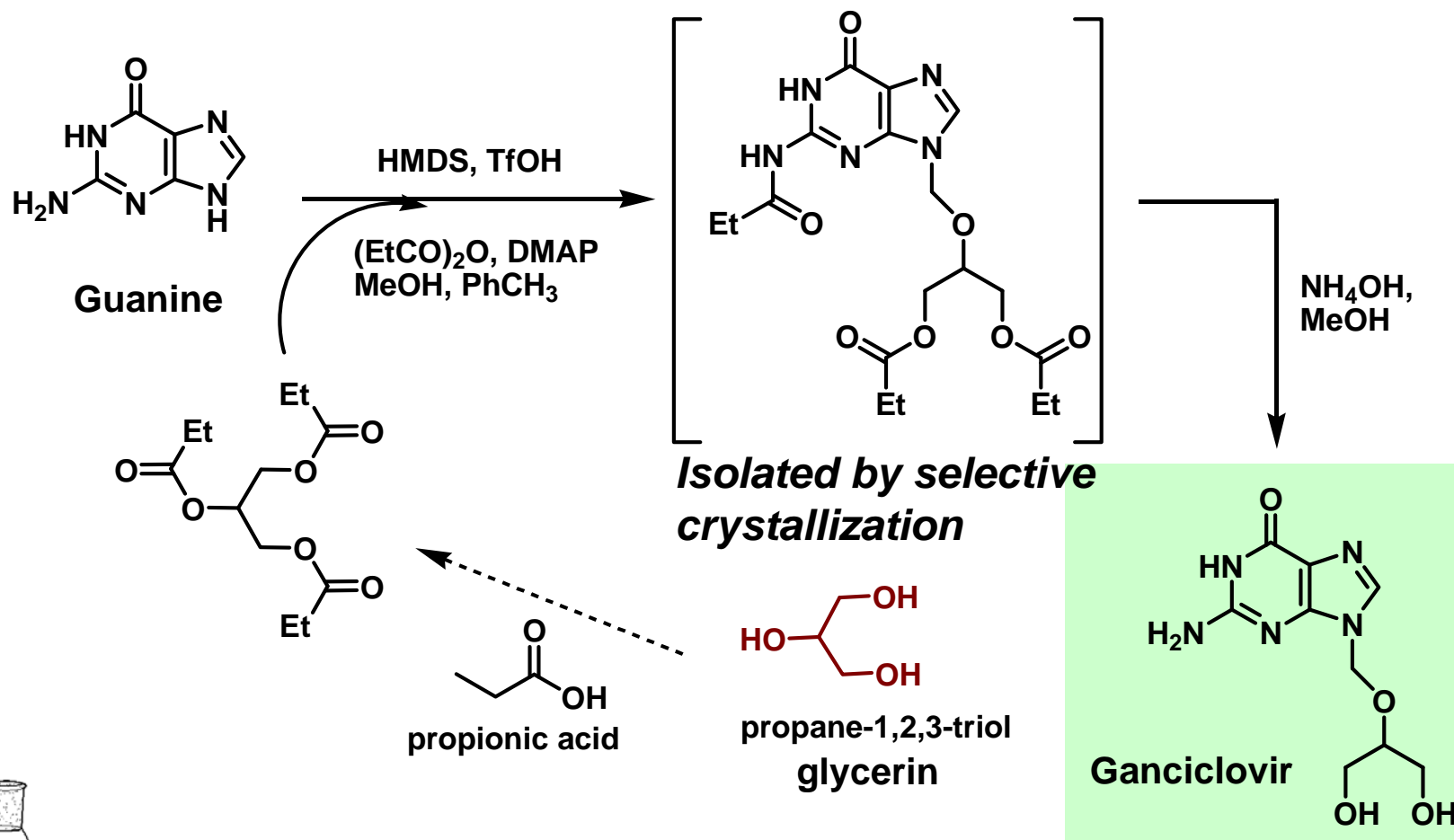


In 1993, the Boulder Technology Center of Roche Colorado Corporation completed the demonstration of a new and expedient process for the production of ganciclovir by (1) leveraging the **basic principles of molecular conservation** to minimize the creation and disposal of undesired wastes, and (2) formulating **efficient process engineering design** for streamlining process operation and the recycling of raw materials. The new (2nd generation) process is called **The Guanine TriEster (GTE) Process.**

This technology was awarded the Presidential Green Chemistry Challenge Award [**Greener Synthetic Pathways Award**] in the U.S. in 2000.



The Guanine TriEster (GTE) Process --- Green process



The “greener” features of the GTE process

- **Fewer process steps:**
 - The process demonstrates the potential for a “one step” process for the production of ganciclovir.
- **Waste quantity reduction/elimination:**
 - Reduced the number of chemical reagents and intermediates from 28 to 11.
 - Eliminated 2 hazardous solid waste streams ($\text{SiO}_2\text{-AlO}_2$ & $\text{Pd}(\text{OH})_2$).
 - Eliminated 11 different byproducts from the liquid waste streams.
 - Efficiently recycled and reused 4 of the 5 raw materials not incorporated into the final product.



[U.S. Patent 5, 565, 565, October 15, 1996.]





- Involved virtually no protection-deprotection steps, and thus eliminated a potentially hazardous palladium catalyzed hydrogenation step.
- The process thus reduced air emissions by ~66% and liquid/solid waste generation by ~89%.
- **Yield improved:**

The process provides more than a 25% increase in overall yield and a 100% increase in production throughput.
- **Greener:**

The process achieves applying the principles of

 1. Prevent Waste
 2. Increase Atom Economy
 3. Design Less Hazardous Chemical Syntheses



- The process designed and used a 4-carbon triester coupling reagent, which generated innocuous byproduct (EtCOOH) via simple hydrolysis.
- The process demonstrated the novel design of the direct silylation of guanine, that gives rise to a highly regioselective alkylation and thus less unwanted alkylated byproduct.

For a review of synthetic approaches to N-9 substituted guanines.

- F. P. Clausen and J. Juhl-Christensen, *Organic Prep. & Proced. Intl.*, 1993, 25, 375.
- V. V. N. K. V. Prasada Raju, et. al. *ARKIVOC* 2009 (xii) 296-301.
- K. Izawa* and H. Shiragami, *Pure & Appl. Chem.*, 1998, 70, 313-318.

For the study describing a possible approach to selective alkylation of guanines.

- D. Sing, M.J. Wani and A. Kumar, *J. Org. Chem.* 1999, 64, 4664.
- J. Boryski and B. Golankiewicz, *Synthesis*, 1999, 625.
- United States Patent 7078524, Issued on July 18, 2006.



References

- Development of an Environmentally Friendly, Cost Effective Process for the Production of cytovene® Antiviral Agent.
www.aspentech.com/publication_files/AICHE2000.pdf
- Biologically active acyclonucleoside analogues. 11. The synthesis of 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (BIOLF-62). K. Ogilvie, et. al., *Can. J. Chem.* **1982**, 60, 3005.
- Synthesis of acyclovir, ganciclovir and their prodrugs: A review [Review], Gao, H.; Mitra, A. K. *Synthesis*, **2000**, 2000.
- Regioselective synthesis of various prodrugs of ganciclovir, Gao, H.; Mitra, A. K. *Tetrahedron Letters*, **2000**, 41, 1131.
- A Facile Synthesis of 9-(1,3-Dihydroxy-2-propoxymethyl) guanine (Ganciclovir) from Guanosine, Boryski, et al., *Synthesis*, **1999**, 625.

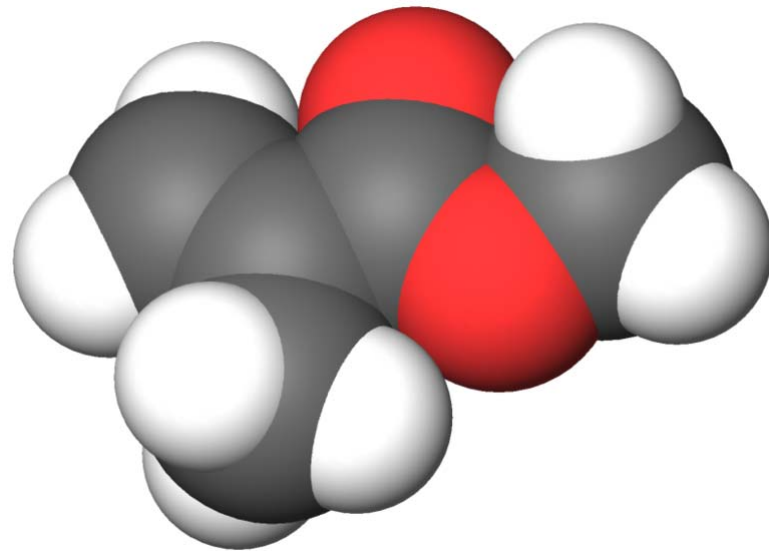


Case 4.

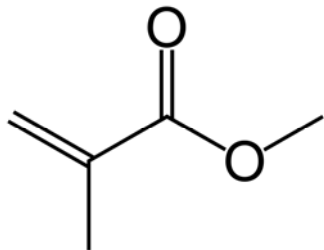
實例4

Methyl Methacrylate (MMA)

異丁烯酸酯，甲基丙烯酸酯



What is Methyl Methacrylate ?



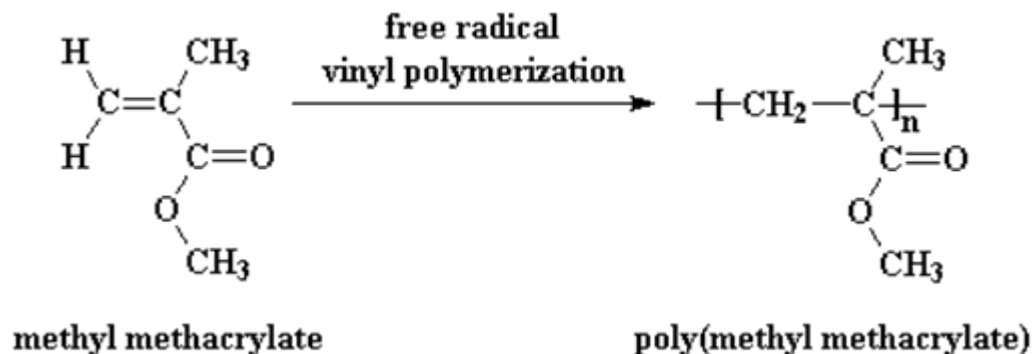
2-(methoxycarbonyl)-1-propene

Molecular formula C₅H₈O₂

Molar mass 100.12 g/mol

It is a colorless, volatile, flammable, liquid that is slightly soluble in water.

- It polymerizes readily upon heating in the presence of a free radical initiator to form polymethylmethacrylate (PMMA) resins.

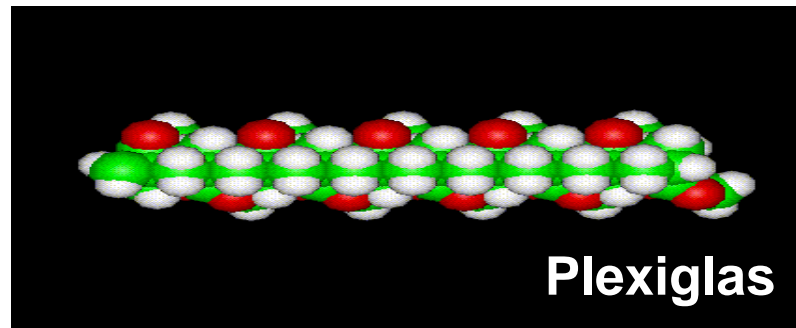


acrylates

acrylics



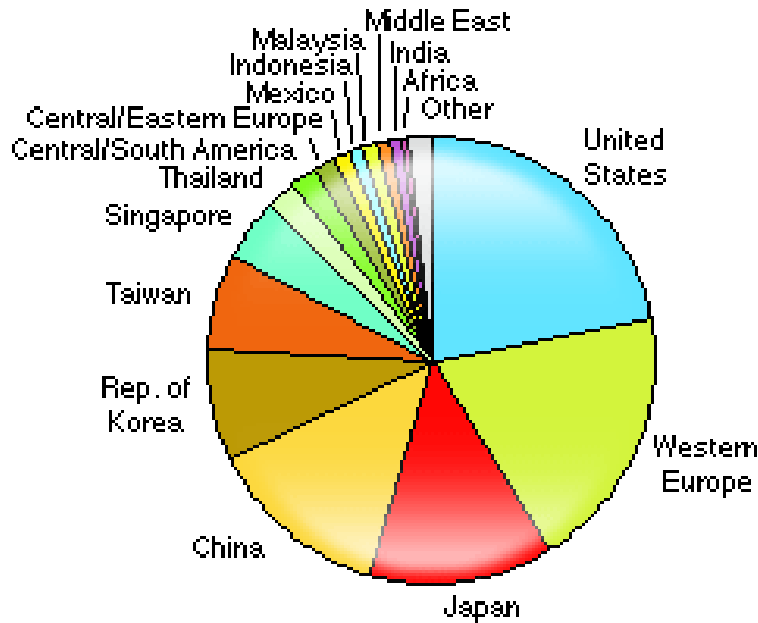
- PMMA resins is called "Plexiglass", and sold by the names "Acrylite" and "Lucite" and is commonly called Acrylic Glass.
- MMA is also copolymerized with other monomers (vinyl acetate, acrylate esters or other methacrylates)
- Construction/remodeling activity, automotive applications and original equipment manufacture account for approximately 80% of world MMA consumption.
- The biggest emerging application of acrylics has been in Liquid Crystal Displays (LCD), demanded in Japan, South Korea, China, and Taiwan.
- At least 30 MMA manufacturing plants globally (2004) with a total capacity of about 2.5 million metric tons per year.



Methyl Methacrylate



World Consumption of Methyl Methacrylate—2008



Demand for MMA is greatly influenced by general economic conditions.

World consumption of MMA grew at an average annual rate of 3.6% during 2005–2008, down from 5.0% during 2002–2005, caused by a sluggish global economy.

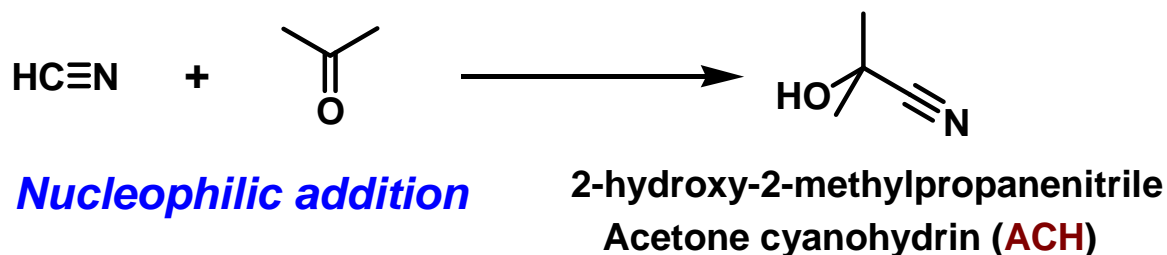
S. Bizzari, **CEH Report** : June 2009.

- Most of the world's production of MMA is based on the route, pioneered in 1933 by ICI, that begins with hydrogen cyanide and acetone to make acetone cyanohydrin, and is known as the **ACH process**.

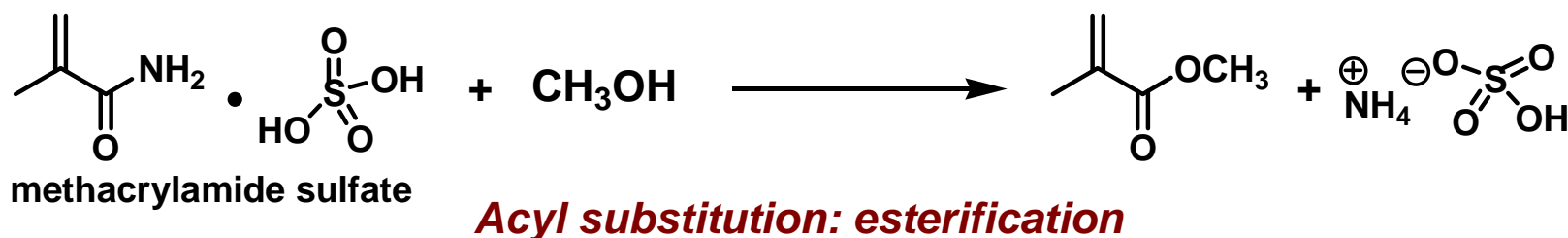
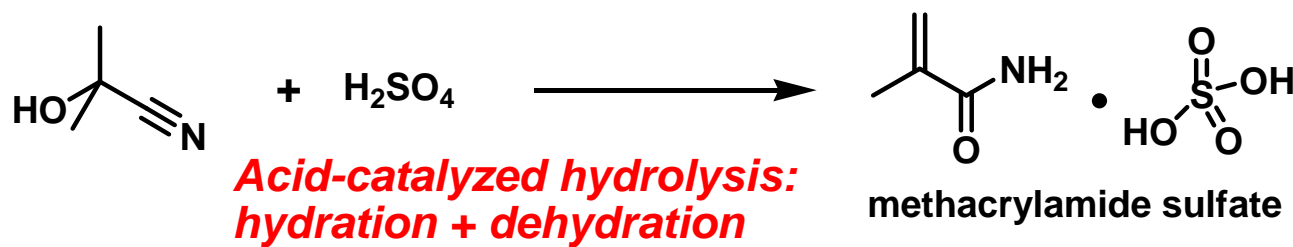


◆ synthesis

ACH Process --- brown synthesis



Most popular route in the world's production of MMA, pioneered in 1933 by ICI.

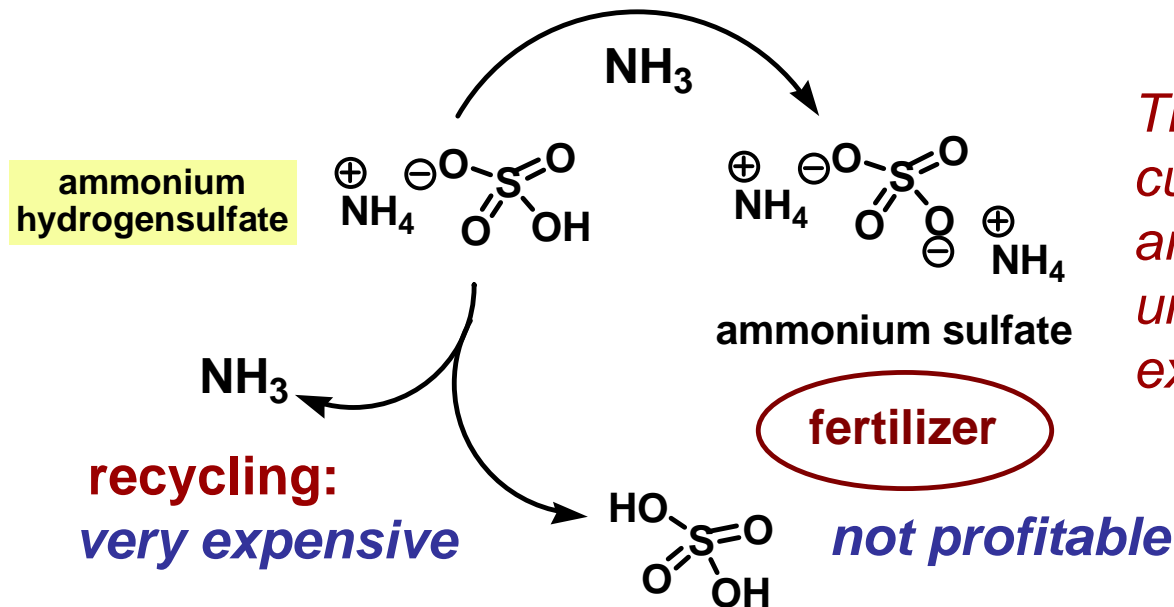


$$\% \text{ atom economy} = [100 / (27 + 58 + 32)] \times 100\% = 85.5\% (\text{NH}_3)$$



Problems with ACH Process

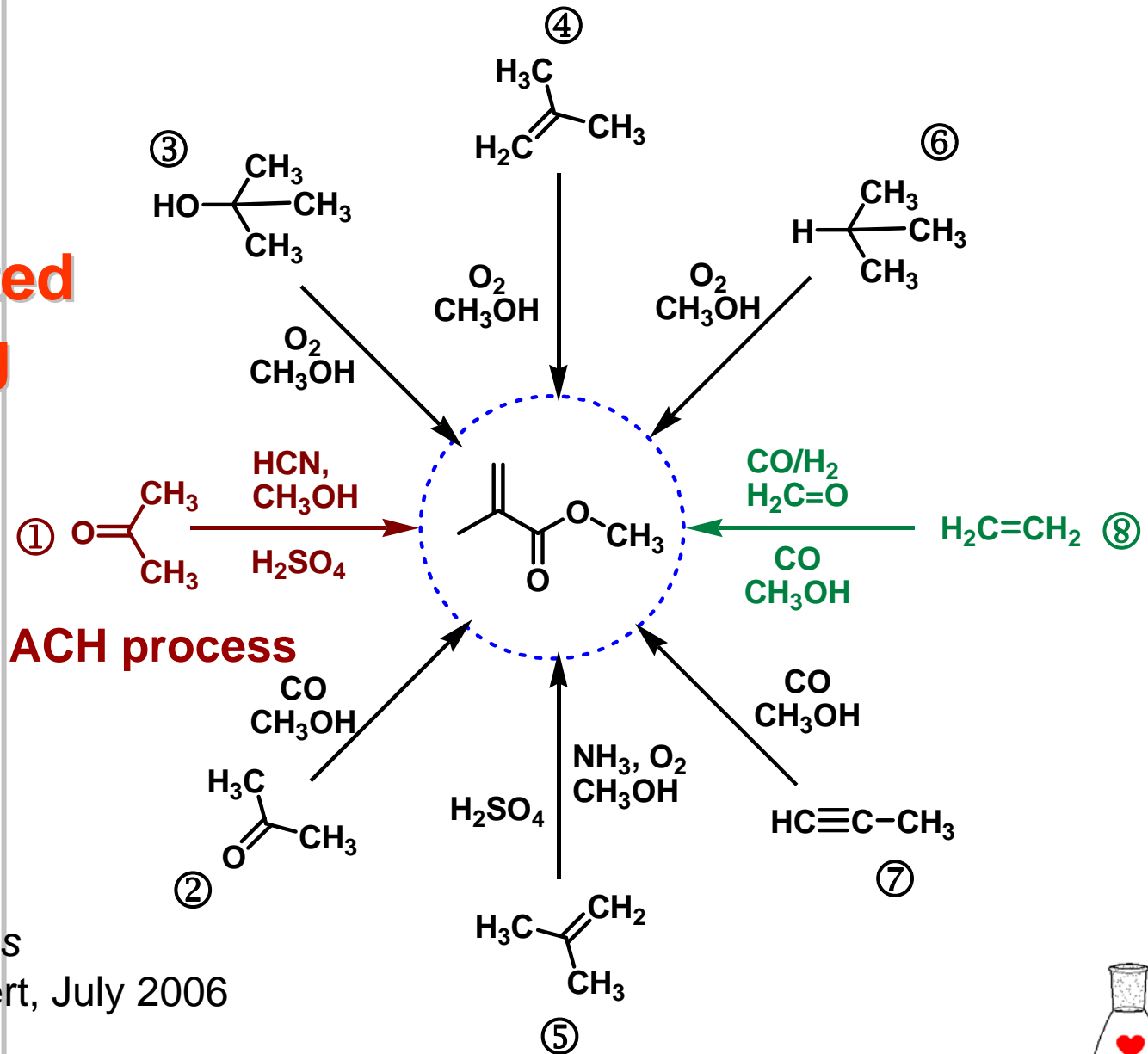
- Hydrogen cyanide (HCN): highly toxic, difficult sourcing,
- NH_3 byproduct (atom lose)
- ammonium hydrogensulfate:
 - * about 1.2 tons/ton of MMA
 - * biggest pitfall to ACH process



The ACH technology is currently environmentally and economically untenable for new expansions.



Major MMA Process Technologies Commercialized or Developing

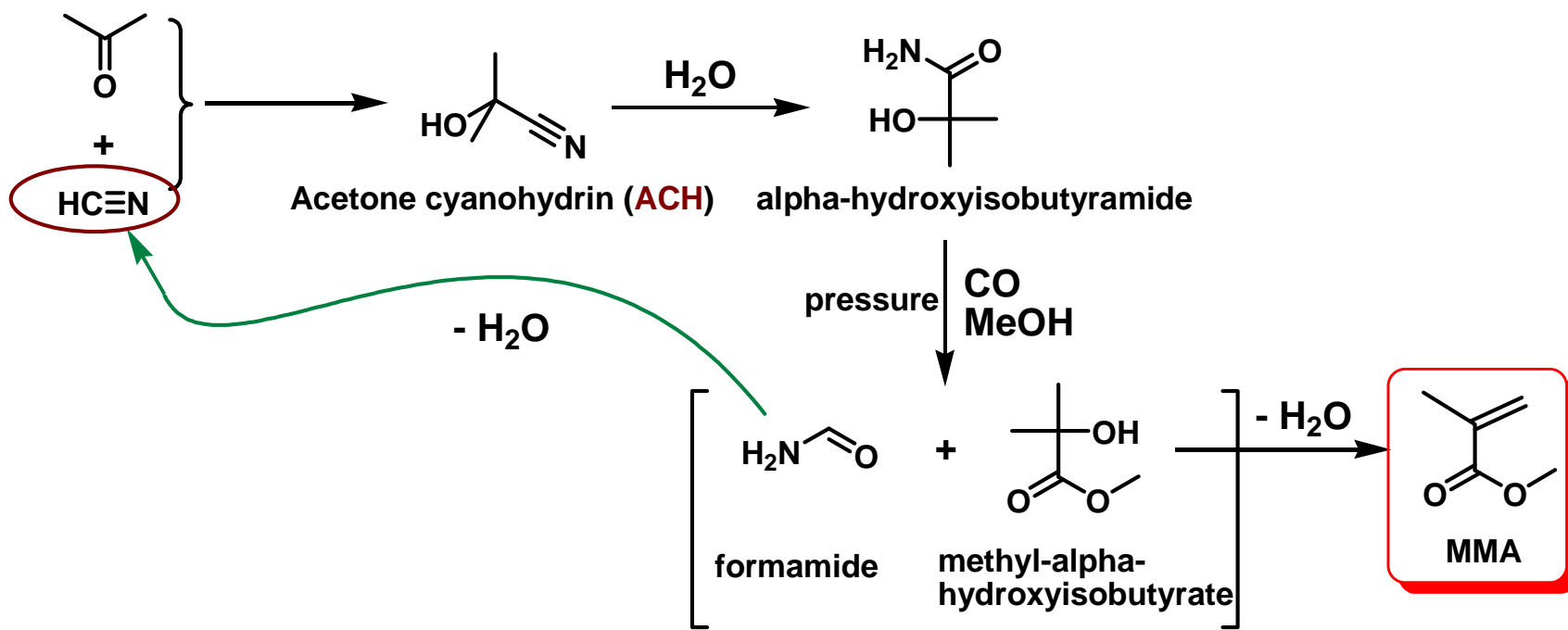


Nexant's ChemSystems
 PERP, New Report Alert, July 2006
<http://www.nexant.com>



- ① Most of the world's production of MMA is based on this route pioneered in 1933 by ICI, known as the **ACH process**. Mitsubishi Gas Chemicals developed a recycle version, in which ACH is made as usual from acetone and HCN. This process eliminates the expensive H_2SO_4 recovery plant.

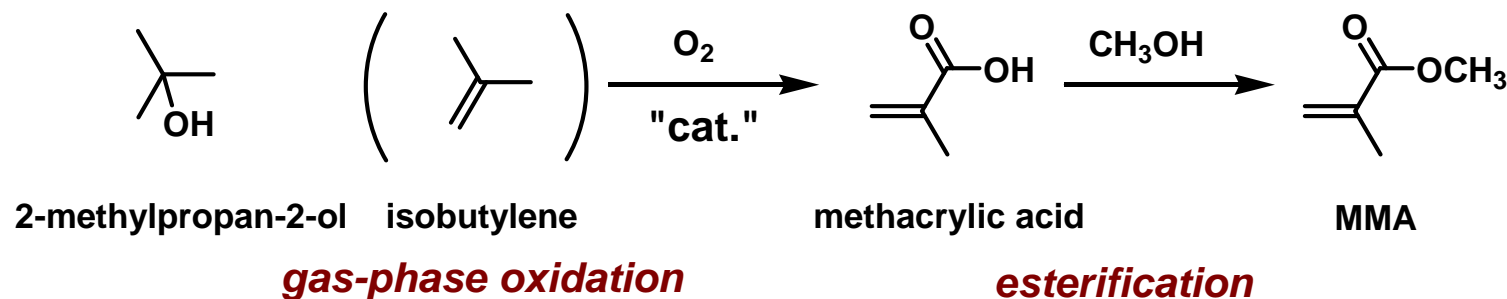
The "MGC" or Mitsubishi route:



③/④

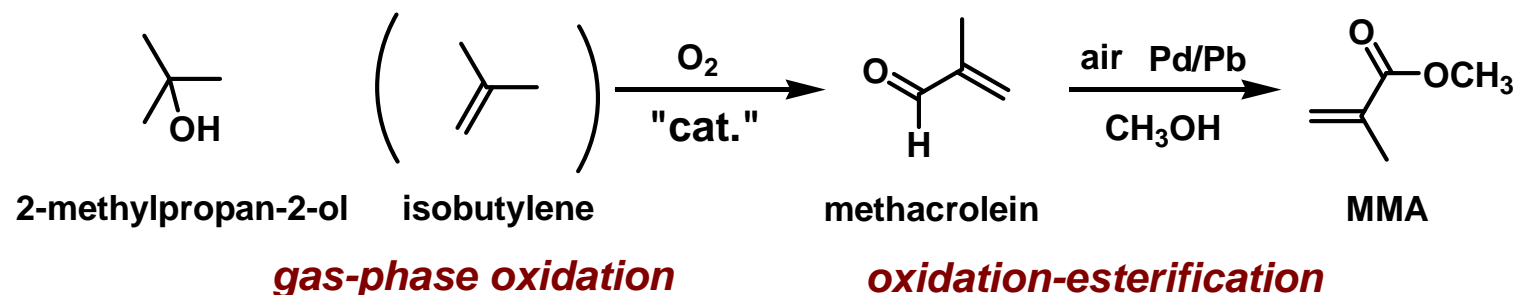
The "i-C4" Route

Two-stage gas-phase oxidation of isobutylene (or TBA) to methacrylic acid, followed by esterification.

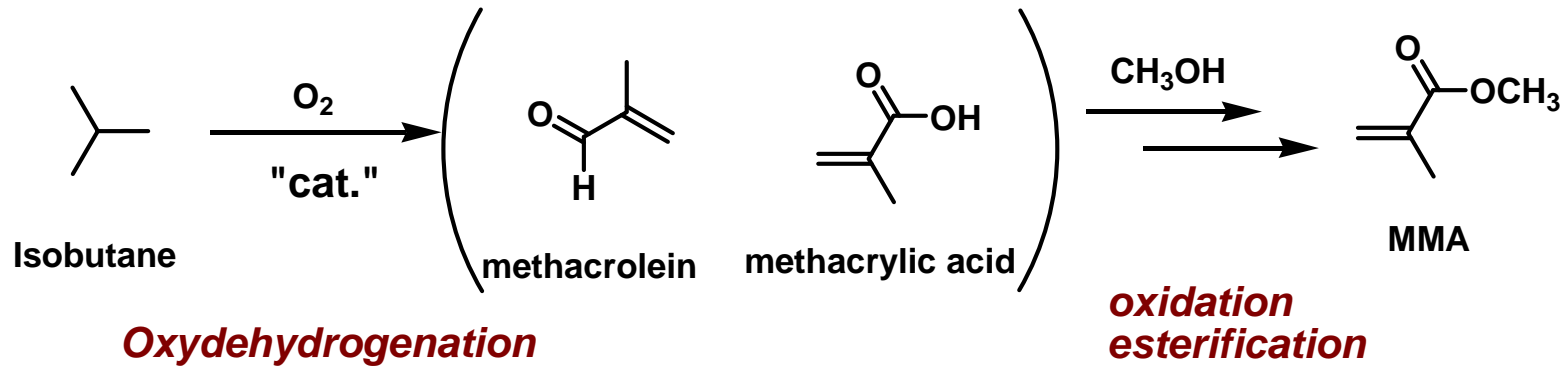


The Asahi Chemical "Direct Metha" route

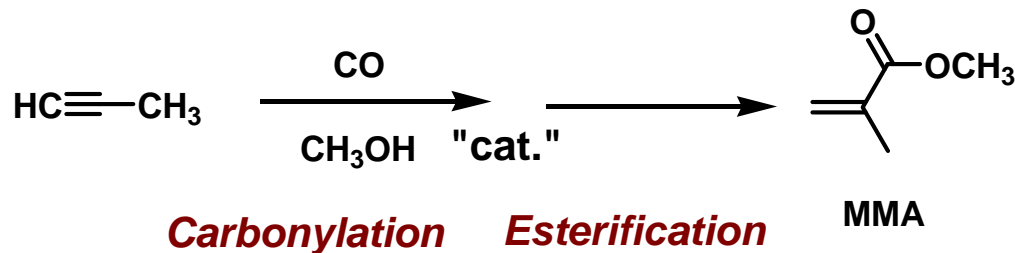
A new process in which isobutylene (or TBA) is first oxidized to methacrolein, which is then oxidized by air over a Pd/Pb catalyst with simultaneous esterification to MMA.



- ⑥ **Isobutane Oxydehydrogenation to Methacrolein/Methacrylic acid:**
An analogous process to the established isobutylene selective oxidation. The most advanced is that of Arkema and Sumitomo.
Attraction: lower cost raw materials.



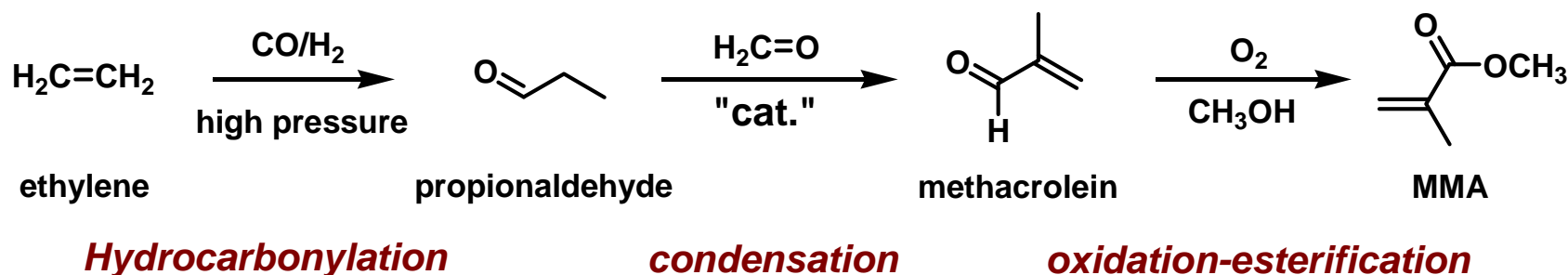
- ⑦ **Carbonylation/Esterification of Propyne Directly to MMA:**
Developed by Shell. Very simple in concept. However, the availability of raw material is restricted.



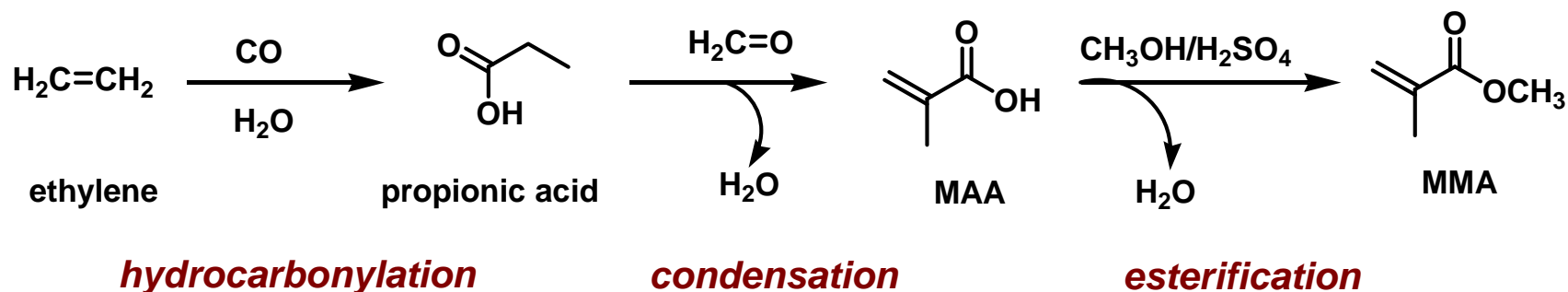
⑧

The BASF route

Hydroformylation of ethylene to propionaldehyde, condensation with formaldehyde to methacrolein, followed by oxidation and esterification.



The RTI-Eastman-Bechtel Three-Step MMA process

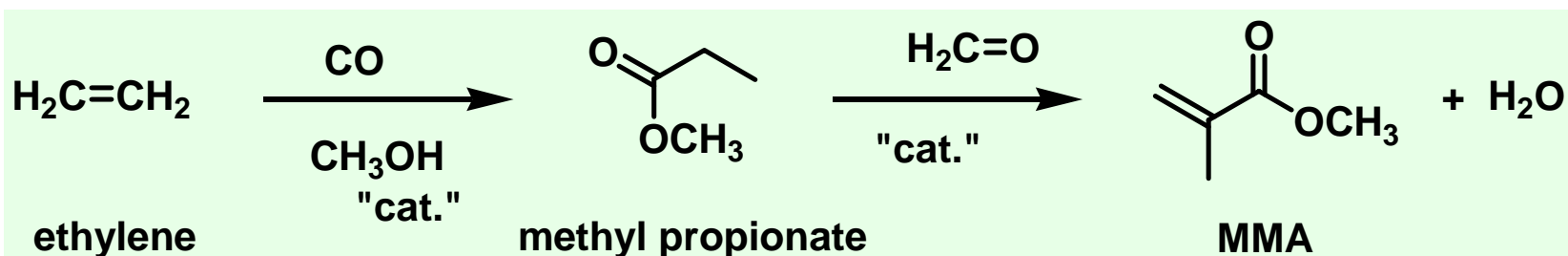


Research Triangle Institute (RTI), Eastman Chemical Company, and Bechtel

⑧

The Alpha process

Combined carbonylation and esterification of ethylene to methyl propionate, which is reacted with formaldehyde under almost anhydrous conditions to form methyl methacrylate.



Hydrocarbonylation-esterification condensation

$$\% \text{ atom economy} = [100 / (28+28+30+32)] \times 100\% = 84.7\% \text{ (H}_2\text{O)}$$

Developed by Lucite International, ICI's successor, and was acquired by Mitsubishi Rayon.

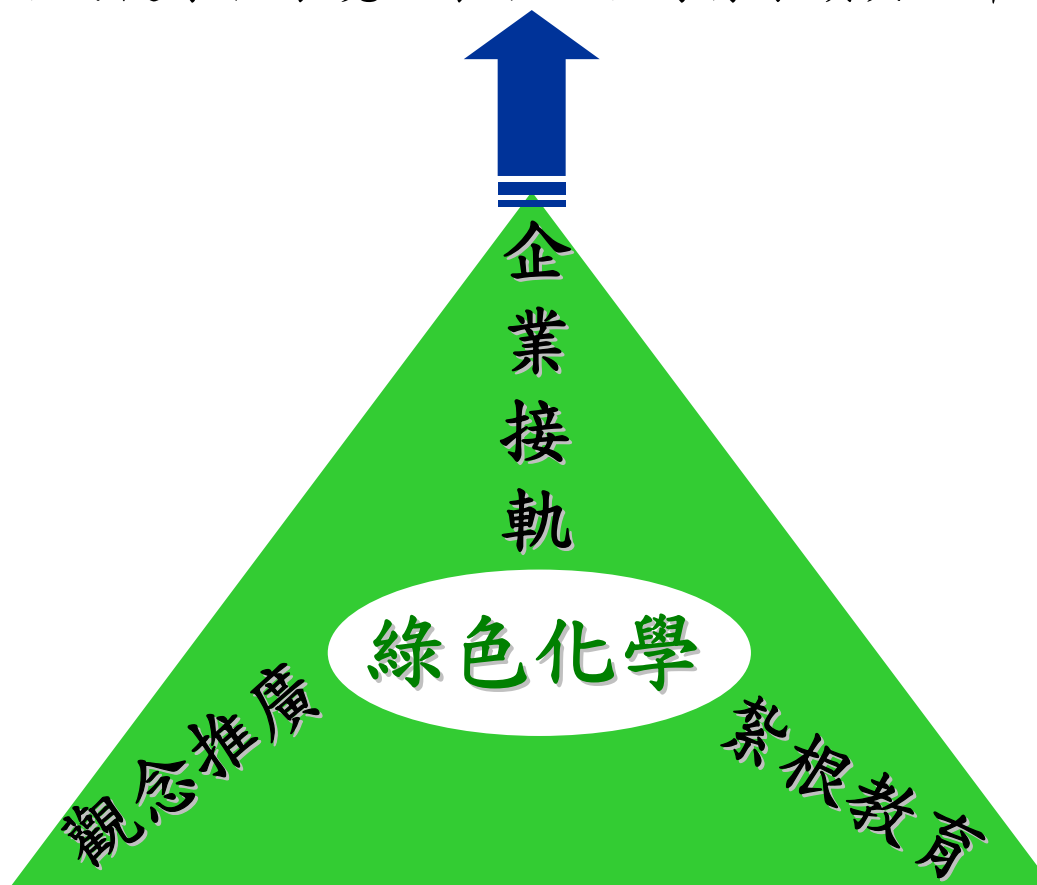
Lucite used this new technology for the first plant of 120,000 tons/year in Singapore (2008).



Sustainability

“safeguarding human health and environment to allow for future generations to maintain the necessary resources to sustain life”

[永續性：守護人類的健康和環境，讓子孫能持有永續其生命的必需資源。]



“The chemical industry plays a key role in sustaining the world economy and underpinning future technologies, yet is under unprecedented pressure from the effects of globalization and change in many of its traditional markets.”

[化學工業在永續世界經濟和奠立未來的技術上扮演著關鍵的角色，但也承受著來自全球化和很多傳統市場變化的衝擊所帶來的前所未有壓力。]

“Against this background, what will be needed for the industry to embrace efforts to make it "greener"?”

[在這種情況下，工業界致力於成為“更綠色”的努力中，會需要些什麼？]



Green Chemistry: Science and Politics of Change,
M. Poliakoff, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas,
Science, **2002**, 297, 807 – 810.



感謝您的聆聽，請指教



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