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

2011 綠色/永續化學合成工作坊
December 2, 2011, 化學會年會，台灣清華大學

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與產生，而進行化學產品和製造過程的設計、開發與執行。］

Anastas PT, Warner JC, editors.
Green Chemistry: theory and practice.
Oxford: Oxford University Press; 1998.

Anastas PT, Kirchhoff MM,
Origins, Current Status, and Future Challenges of Green Chemistry
Acc. Chem. Res. 2002, 35. 686.

The Twelve Principals of Green Chemistry

1. Prevent waste
2. Design safer chemicals and products
3. Design less hazardous chemical syntheses
4. Use renewable feedstocks
5. Use catalysts, not stoichiometric reagents
6. Avoid chemical derivatives
7. Maximize atom economy
8. Use safer solvents and reaction conditions
9. Increase energy efficiency
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

Anastas PT, Warner JC, editors. ***Green Chemistry: theory and practice.*** **Oxford: Oxford University Press; 1998.**

John C. Warner

Research chemist at Polaroid (1988)
Professor at the UMass, Boston (1996),
-- established first doctoral program in green chemistry
Professor at UMass, Lowell (2004)
-- founded Center for Green Chemistry

Chief technology officer and chairman of the board of Warner Babcock Institute for Green Chemistry (2007)

"Green chemistry is the mechanics of doing sustainable chemistry,"

Warner:
"By focusing on green chemistry, it puts us in a different innovative space. It is a science that presents industries with an incredible **opportunity for continuous growth** and **competitive advantage**."

Chemical & Engineering News, 88(40), October 04, **2010**

Paul T. Anastas

Professor of chemistry for the environment at Yale University,
Director of Yale's Center for Green Chemistry & Green Engineering,
Widely regarded as one of the fathers of "green chemistry,“
The Environmental Protection Agency assistant administrator for the Office of R&D,

"Why did you become a chemist?"

Some are excited by the **intellectual challenges of chemistry**. Others want to use chemistry and chemical engineering to solve problems and **make the world a better place**.

Anastas:

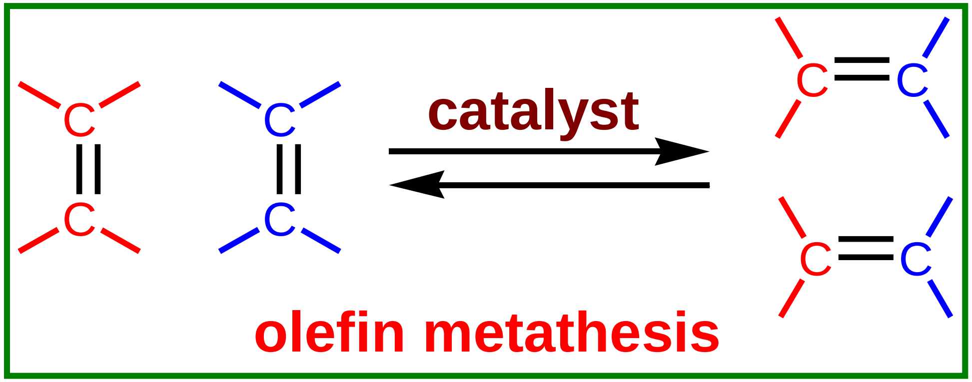
"The world needs both. Building a sustainable world is the most taxing intellectual exercise we have ever engaged in. It is also the most important for the future of the world."



Robert H. Grubbs, 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 mankind, society, and the environment,……"



永續化學

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.

綠色化學

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.

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.

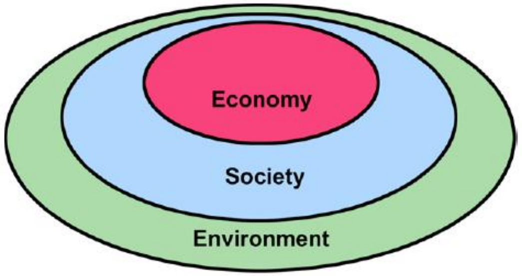


Fig. 1. A sustainable community [3].

"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.**

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

綠色化學的終極目的是縮減或淘汰對人類健康和環境具有危害性的物質的使用與產生，因此任何化學產品及其相關活動—製造過程的設計、開發、與實行，當然包含化學合成，都要秉持此認知而思考。

Anastas and Warner:

"In virtually every aspect in society,
it has long been acknowledged that preventing a problem
is superior to trying to solve it once it has been created."

green chemistry

seeks to reduce and prevent pollution at its source.

在源頭減低與防止污染

源頭在哪裡？

綠色永續合成

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，它必須要應付人類面臨的許多種種挑戰。]

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

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 (COG).

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

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 by 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**

關照 COG　必也能關照我們的環境

Case 1. **Disodium iminodiacetate (DSIDA)**

A key intermediate in the production of Roundup® herbicide

Case 2. **Aprepitant**

The Active Ingredient in Emend®:

A New Therapy for Chemotherapy-Induced Emesis

Case 3. **Ibuprofen**

One of core non-steroidal anti-inflammatory medicines

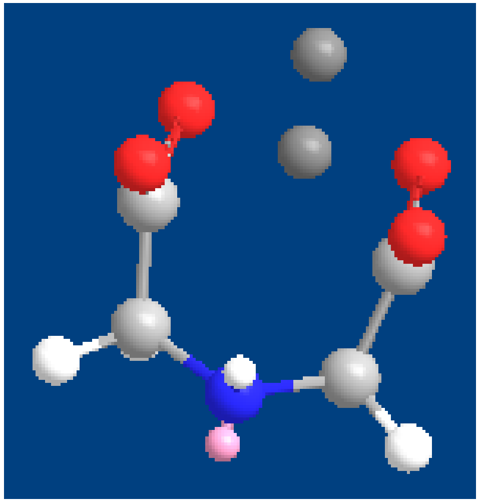
Case 4. **Polyaspartate**

Biodegradable Alternative to Polyacrylate

Case 1.

實例1

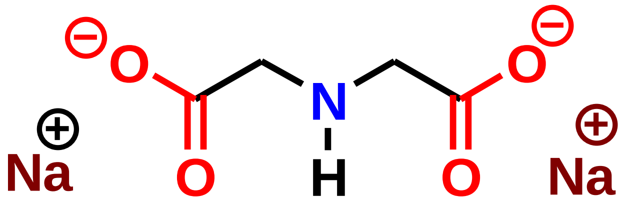
Disodium iminodiacetate (DSIDA)



US Presidential Green Chemistry Challenge Awards:

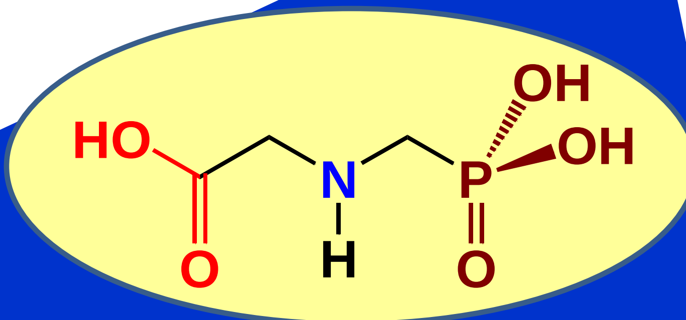
Greener Synthetic Pathways Award **1996**

What is Disodium iminodiacetate (DSIDA)?



sodium 2,2'-azanediyldiacetate
disodium 2-[(2-oxido-2-xoethyl)amino]acetate

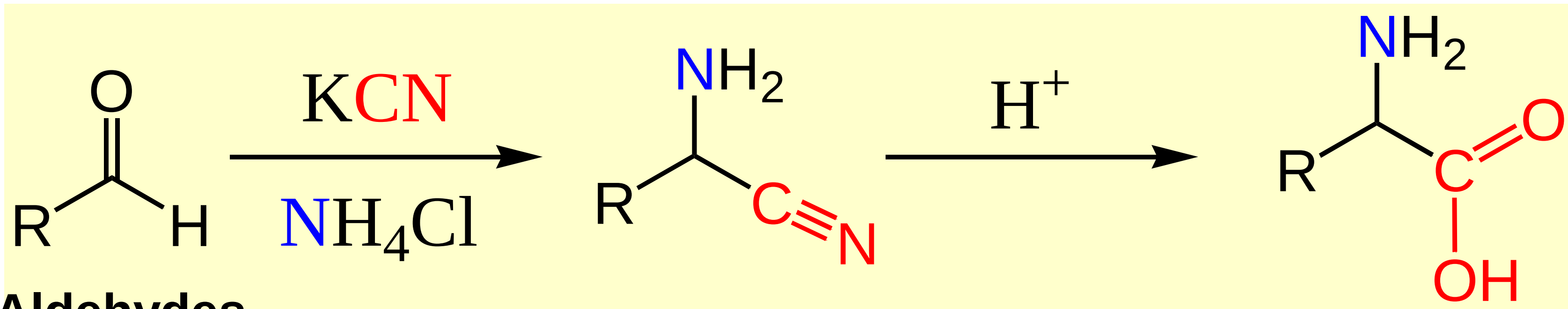
a key intermediate in the production of Monsanto's Roundup® herbicide



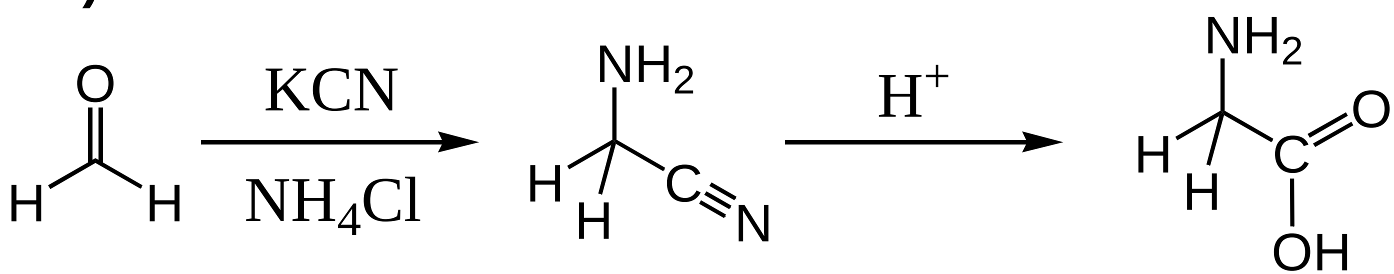
Glyphosate: *N*-(phosphonomethyl)glycine in the form of its isopropylamine salt (41%)

Roundup® agricultural herbicides are the flagship of Monsanto's agricultural chemicals business.

Strecker amino acid synthesis



Aldehydes (or Ketones)

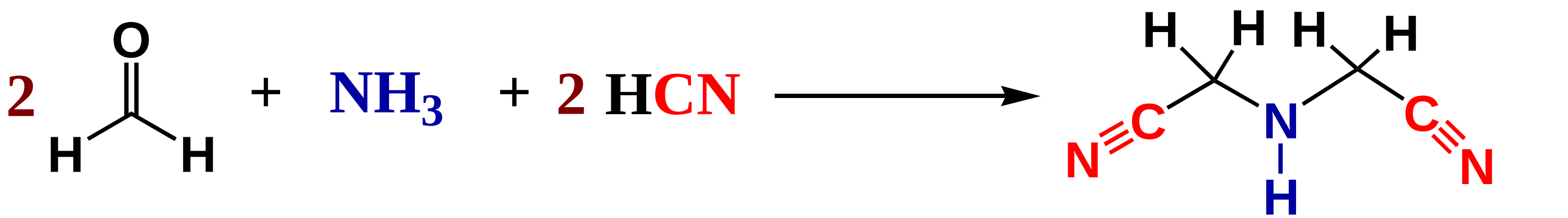


glycine

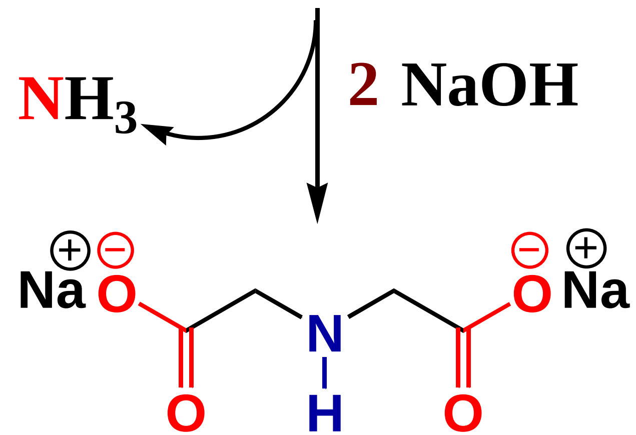
2-aminoacetic acid

Traditionally, the Strecker process has been used to manufacture DSIDA. It requires formaldehyde, ammonia, hydrogen cyanide, and hydrochloric acid.

The Strecker process for synthesizing DSIDA



hydrogen cyanide:
extremely toxic;
requires special handling



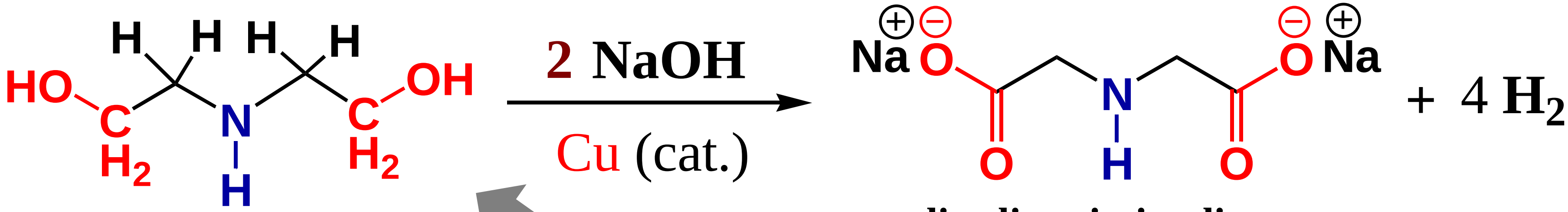
disodium iminodiacetate

exothermic reaction
generating potentially unstable intermediates.

waste: *1 kg for every 7 kg of product.*

Green process for synthesizing DSIDA

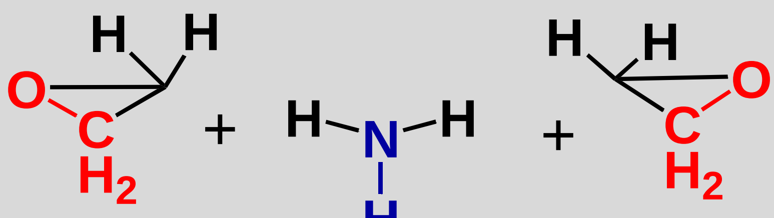
copper-catalyzed dehydrogenation of diethanolamine



diethanolamine

2,2'-azanediyldiethanol

disodium iminodiacetate



oxirane

ethylene oxide

Greener Synthetic Pathways Award

1996

- ***the dehydrogenation reaction is endothermic;***
  avoid the use of cyanide and formaldehyde;
- ***fewer process steps, higher overall yield;***
  no purification or waste cut is necessary;
- ***recover catalyst by filtration, ready for subsequent use in the manufacture of* Roundup*;***
- ***This catalysis technology is applicable in the production of other amino acids and***
- ***becomes a general method for conversion of primary alcohols to carboxylic acid salts.***

1. Prevent Waste
2. Increase Atom Economy
3. Design Less Hazardous Chemical Syntheses
4. Design Safer Chemicals
9. Use Catalysts

Case 2. **實例2**

Aprepitant

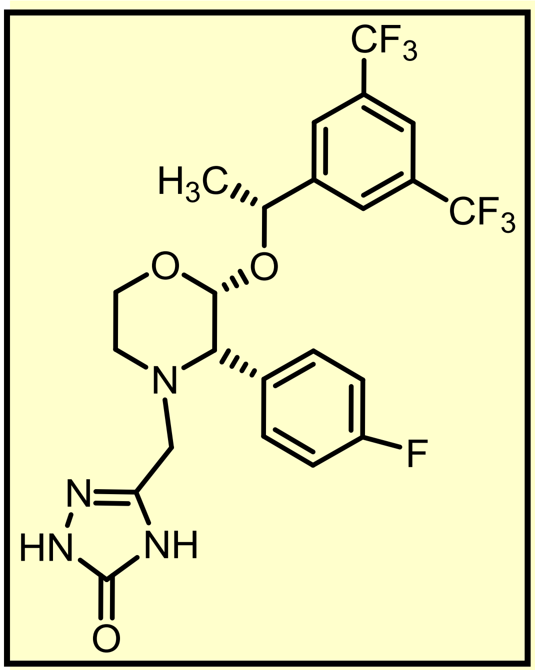
The Active Ingredient in Emend®:
A New Therapy for Chemotherapy-Induced Emesis

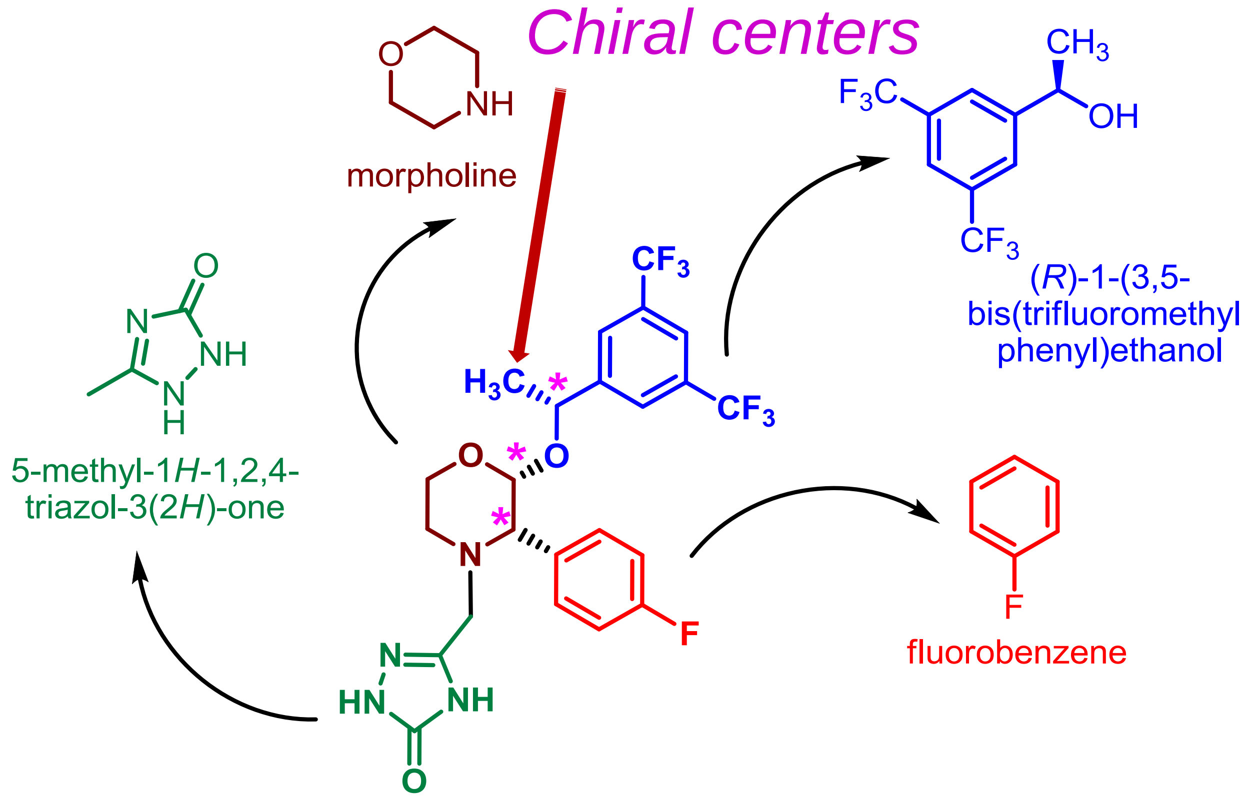
US Presidential Green Chemistry Challenge Awards:
Greener Synthetic Pathways Award **2005**

What is Aprepitant [Emend]?

- An antiemetic chemical compound that belongs to a class of drugs called substance P antagonists (SPA). It mediates its effect by blocking the neurokinin 1 (NK_1) receptor.
- Trials showed that >90% occupancy of the substance P receptor was achieved at all doses.
- Originally labeled for oral treatment of **chemotherapy-induced nausea and vomiting (emesis 嘔吐)**, depression, and pain.
- In 1999, Merck confirmed that evaluation of dental pain model was no longer under investigation. Pain intensity was not significantly different than acetaminophen or placebo.
- Phase III trials for depression were discontinued in November of 2003 due to lack of efficacy.
- Launched in April 2003 by Merck & Co. in United States under the brand name **Emend**.

What is the Structure of Emend?



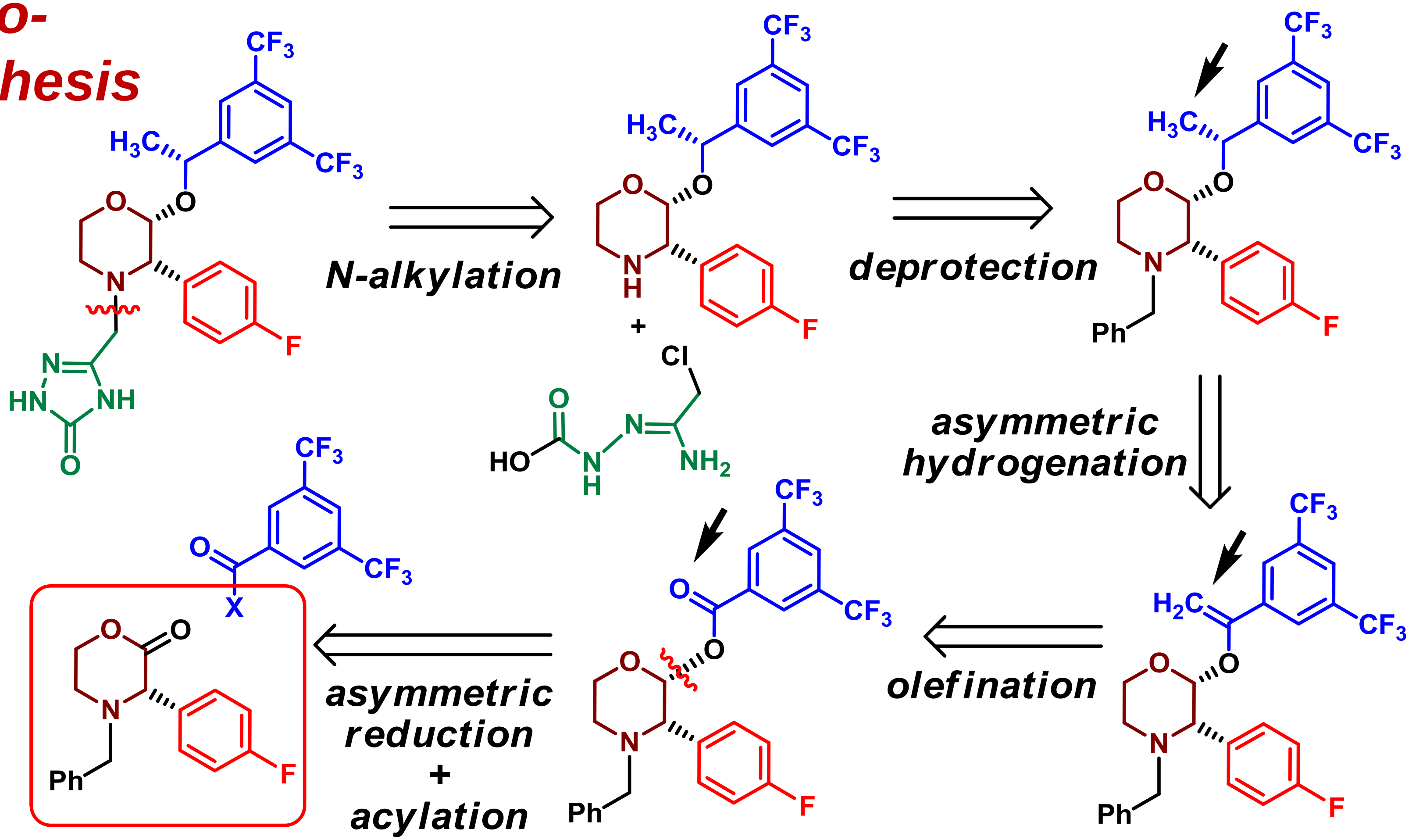


It is an off-white crystalline solid.
It has a very limited solubility in water, but a reasonable high solubility in non-polar molecules, such as oils.
Despite having polar components, it is a non-polar substance.

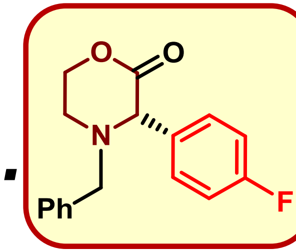
synthesis

Merck's first-generation commercial synthesis was based on the discovery synthesis. --- *J. Med. Chem.* **1998**, *41*, 4607.

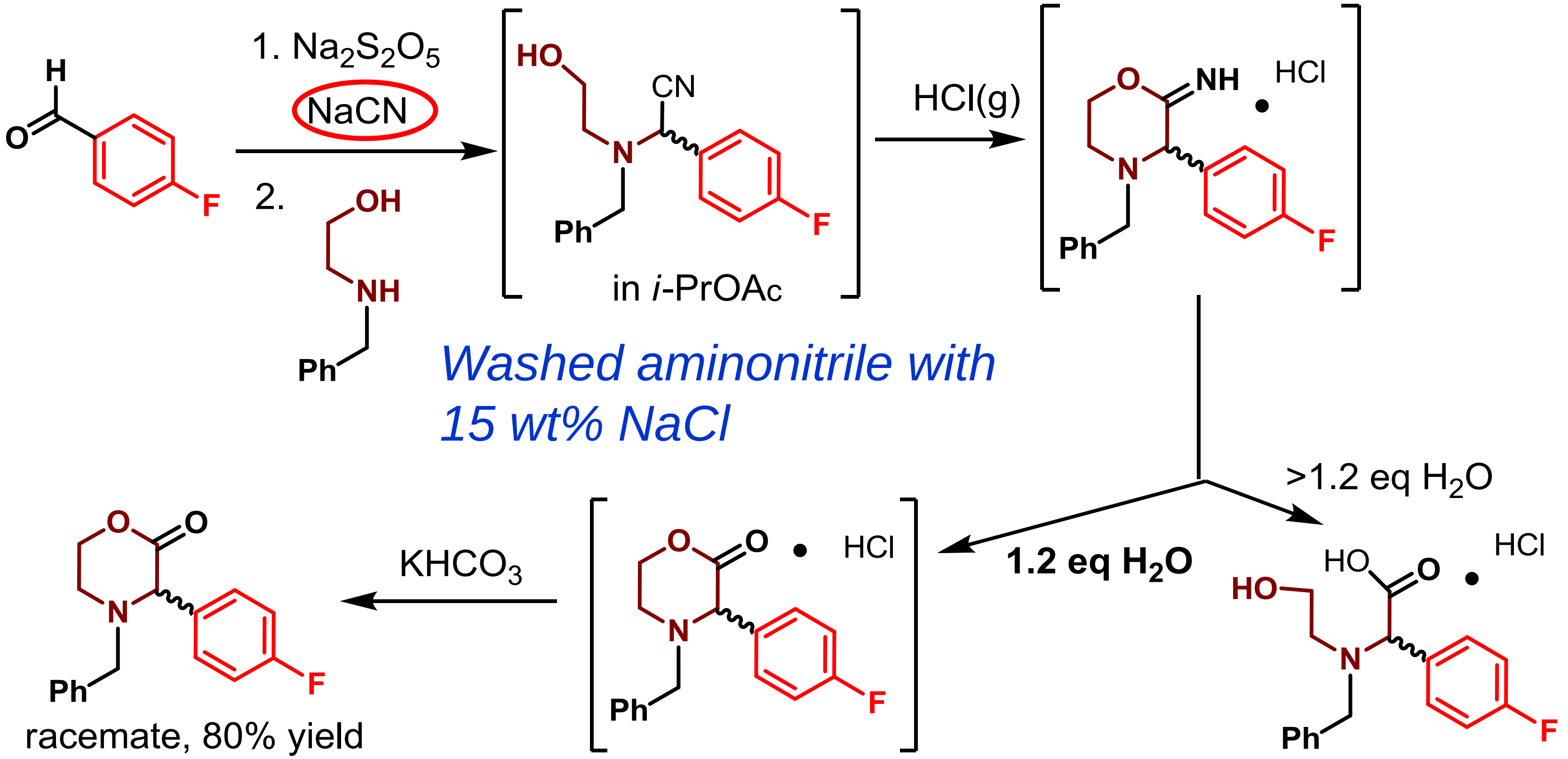
Retro-synthesis



Emend Synthesis: Synthesis of (S)-4-benzyl-3-(4-fluorophenyl)morpholin-2-one .

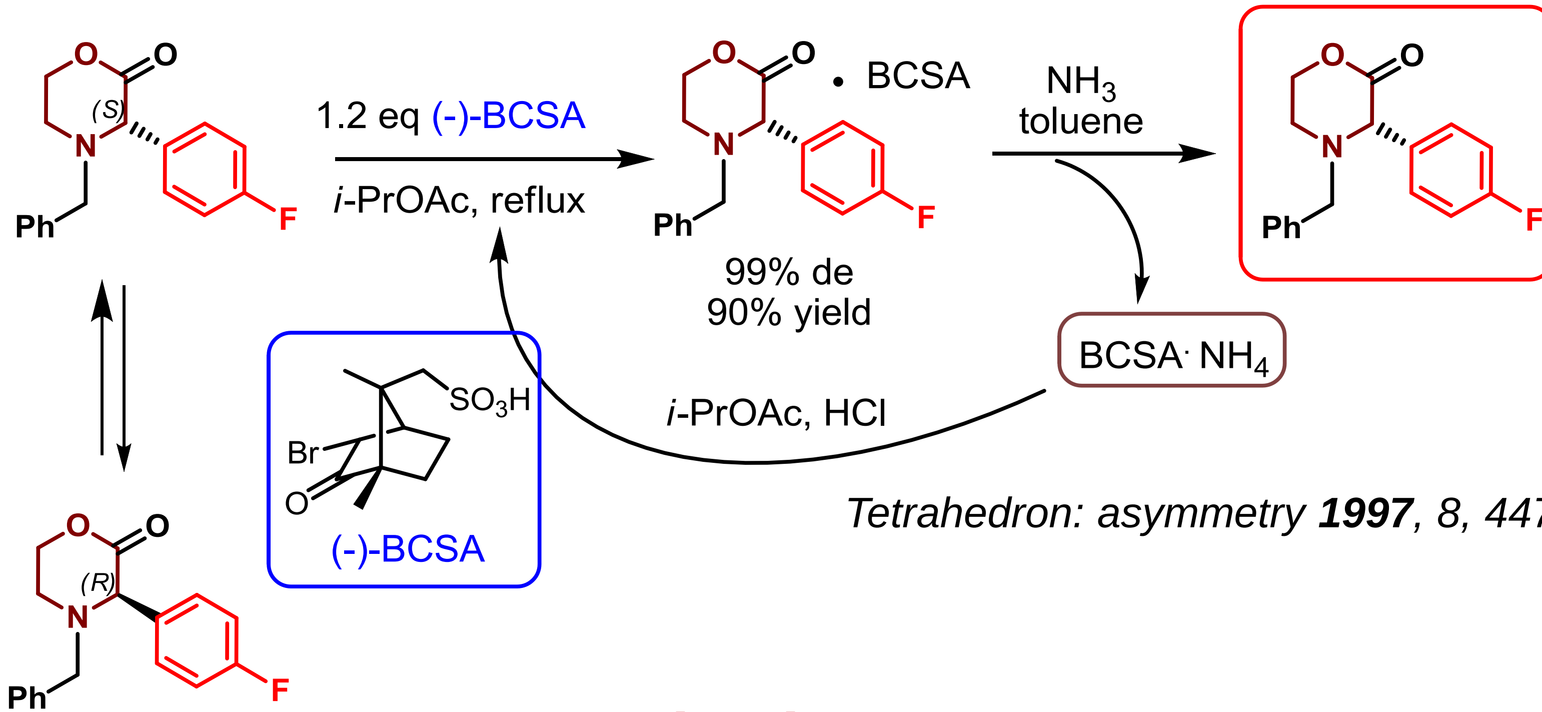


(A) One-Pot Synthesis of Racemic Morpholin-2-ones



*European Patent 1112259, **2001***

(B) *Dynamic Resolution of Racemic Morpholin-2-ones*

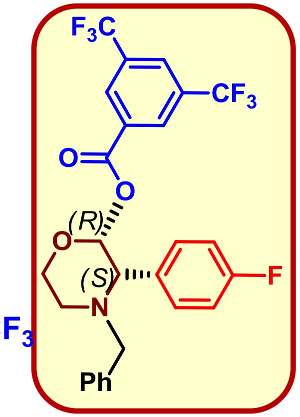


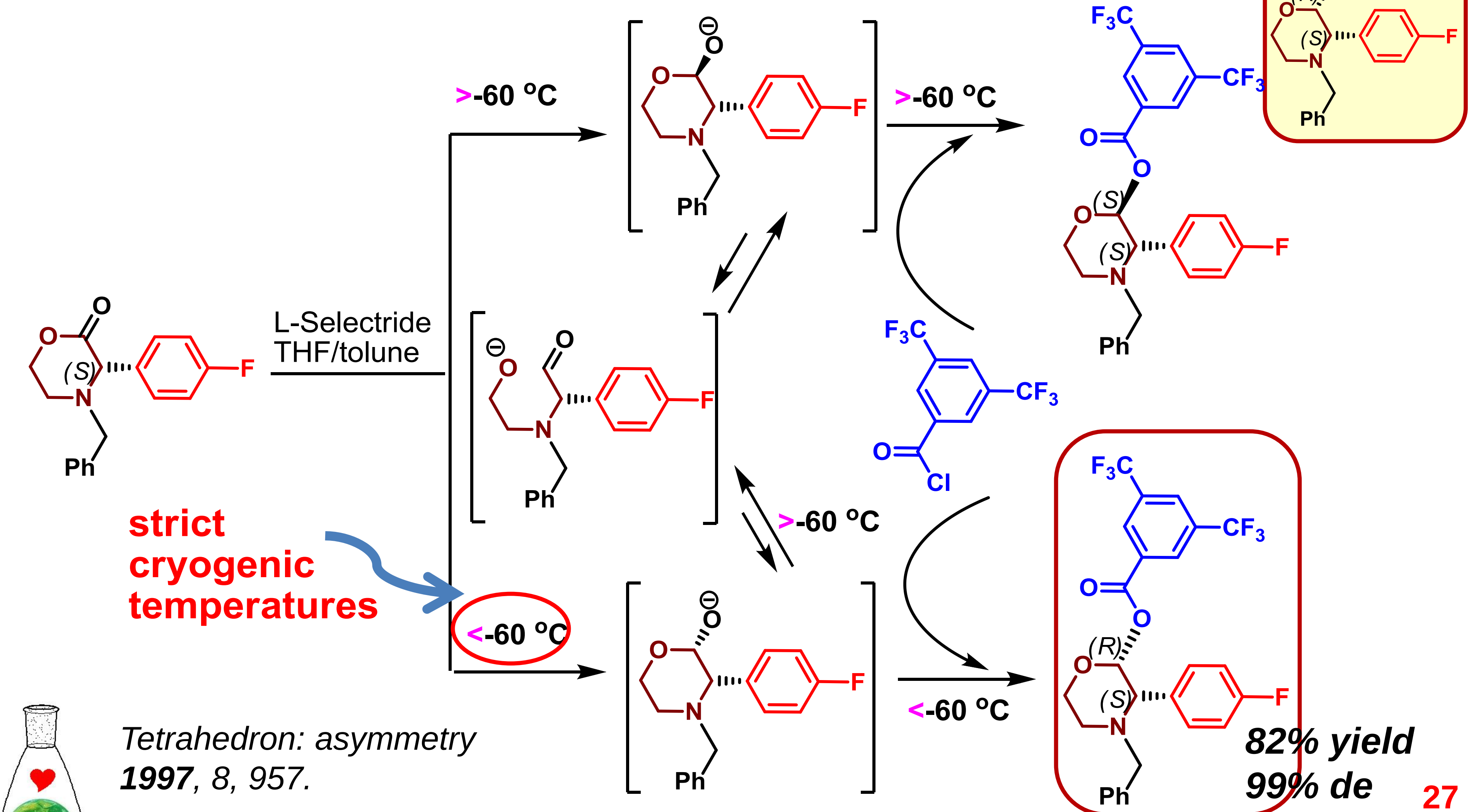
Tetrahedron: asymmetry ***1997****, 8, 447.*

Drawbacks:

Use of toxic NaCN
Expensive resolving agent (BCSA)
Lack of racemization/recycle

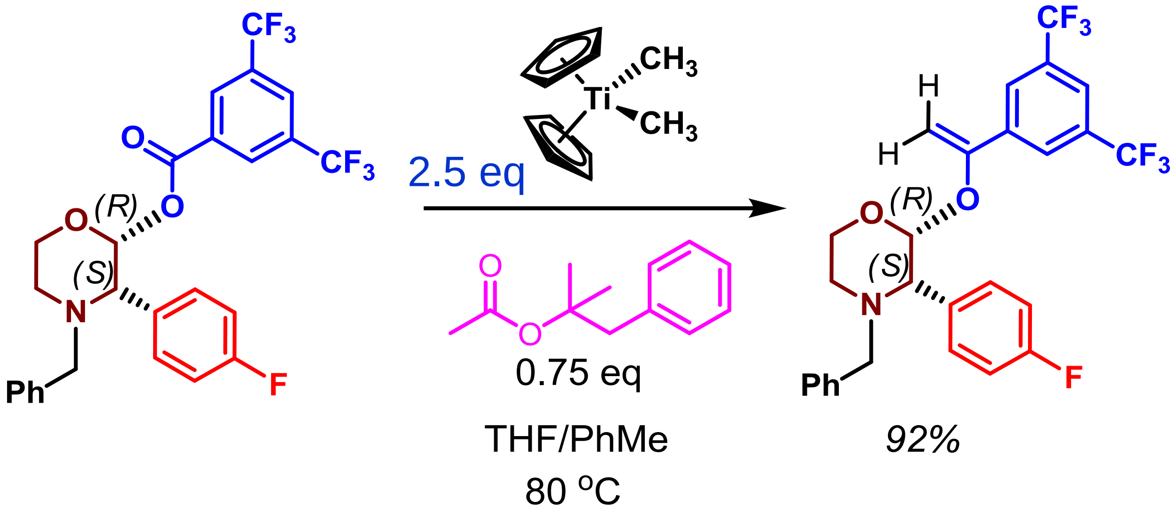
Emend Synthesis: Acyl Acetal Formation (Fragment Coupling)



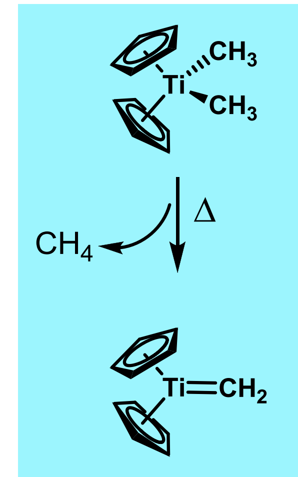


Tetrahedron: asymmetry ***1997***, *8*, *957*.

Emend Synthesis: *Olefination (C=O → $C=CH_2$)*



Petasis Reagent



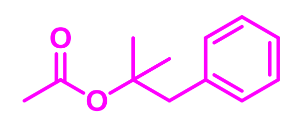
reactive and unstable

Organometallics ***1996****, 15, 663.*

2-methyl-1-phenylpropan-2-yl acetate is a sacrificial (祭祀) ester, which is less reactive towards Petasis reagent than morpholine ester.

Drawbacks:

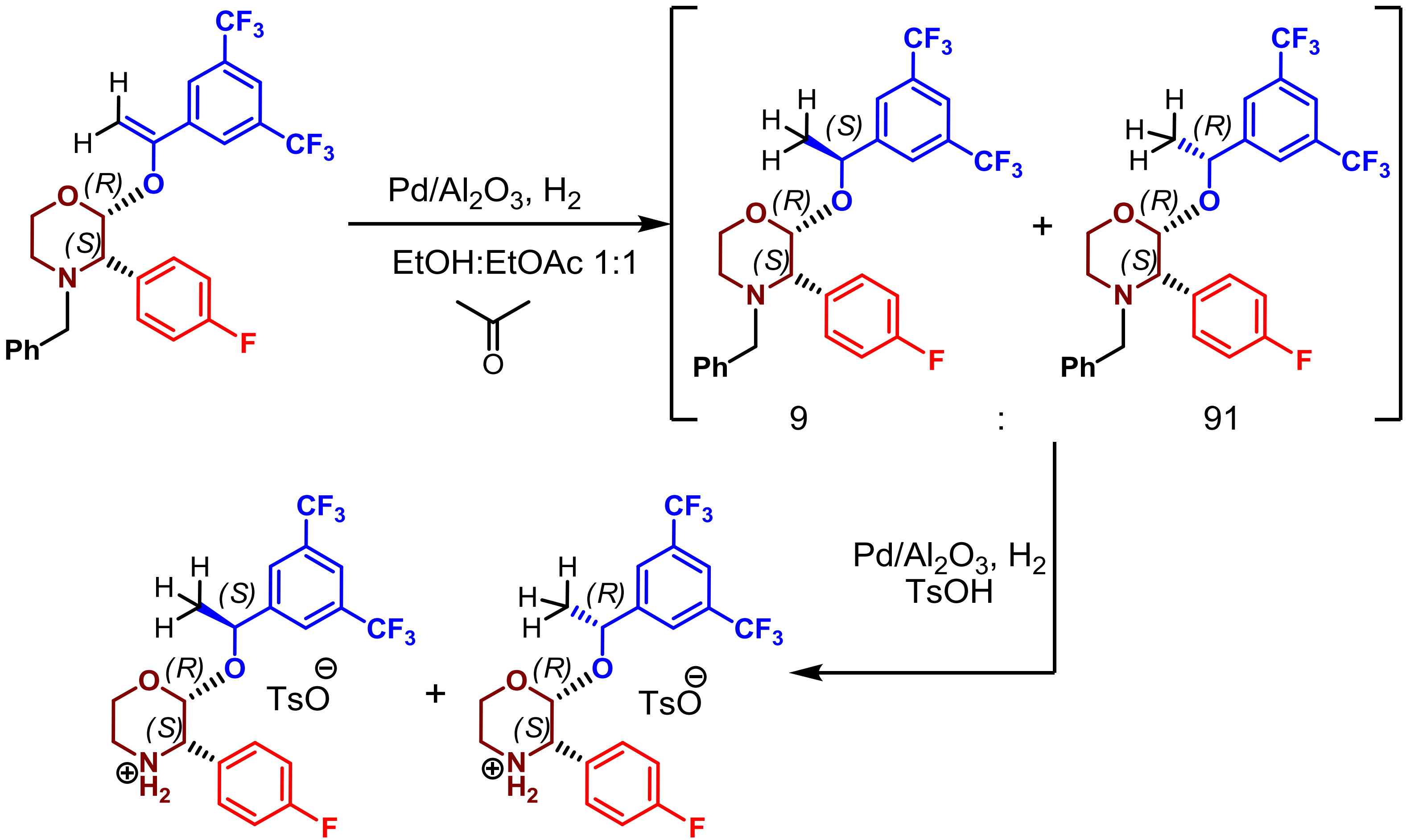
Petasis reagent (>2 eq is necessary) is very expensive and potentially hazardous → Recycling imperative → → huge capital investment



"sacrificial ester"

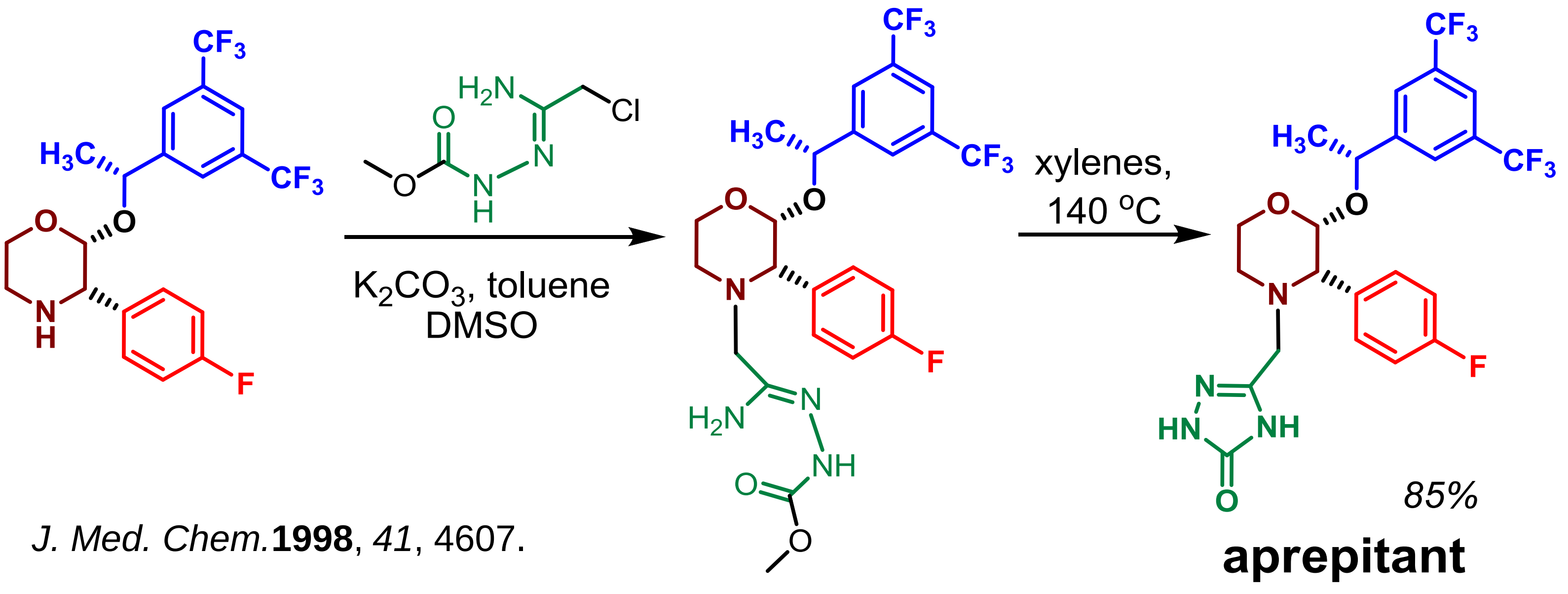
Org. Proc. Res. Develop. ***2004****, 8, 256.*

Emend Synthesis: Hydrogenation & Deprotection



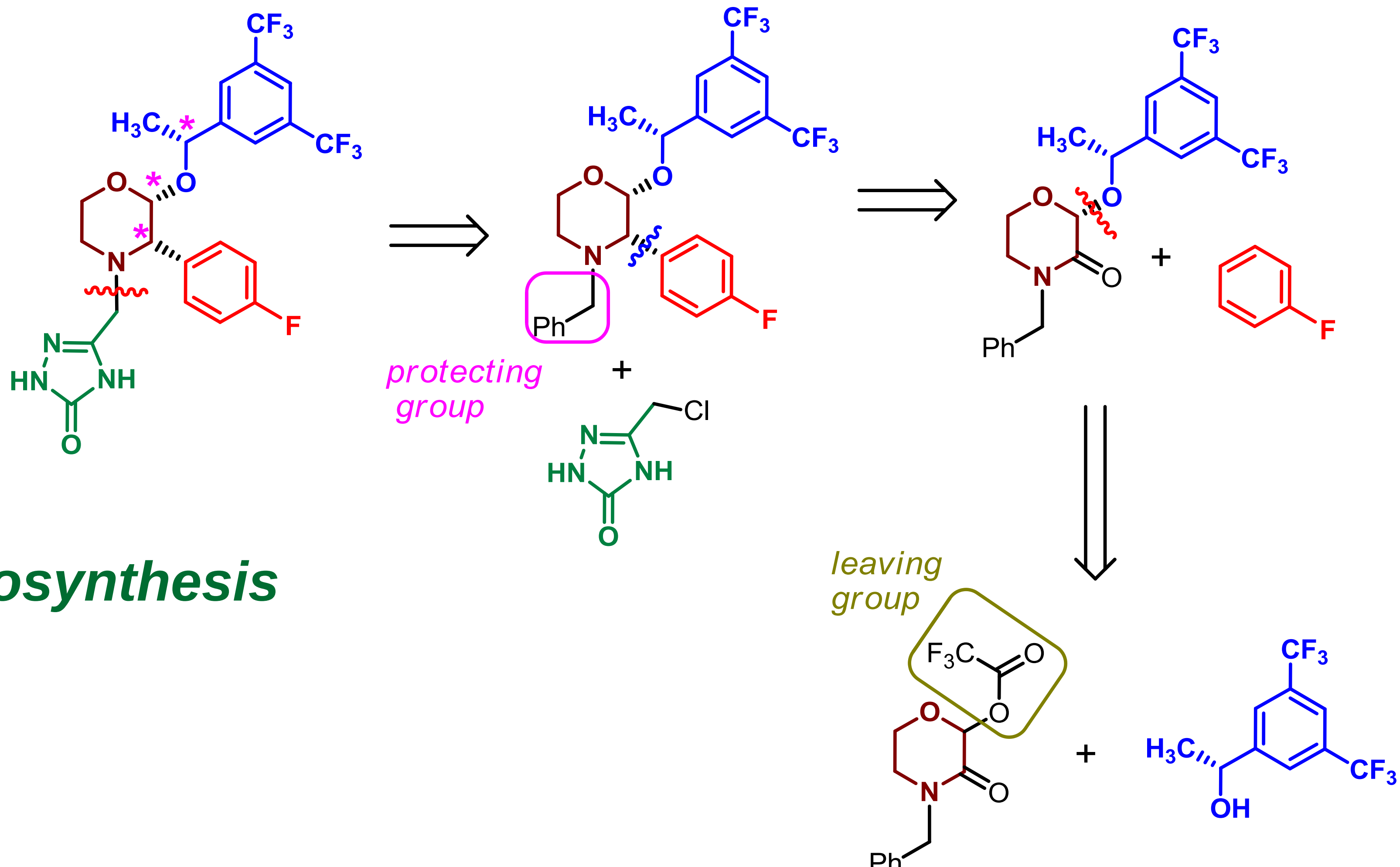
88% isolated yield
>99% de

Emend Synthesis: Completion --- Attachment of Triazolinone Ring



J. Med. Chem. **1998**, *41*, 4607.

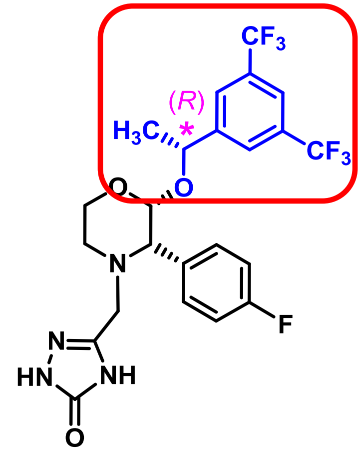
Merck's 2005 Presidential Award commercial synthesis --- *Greener Synthetic Pathways*



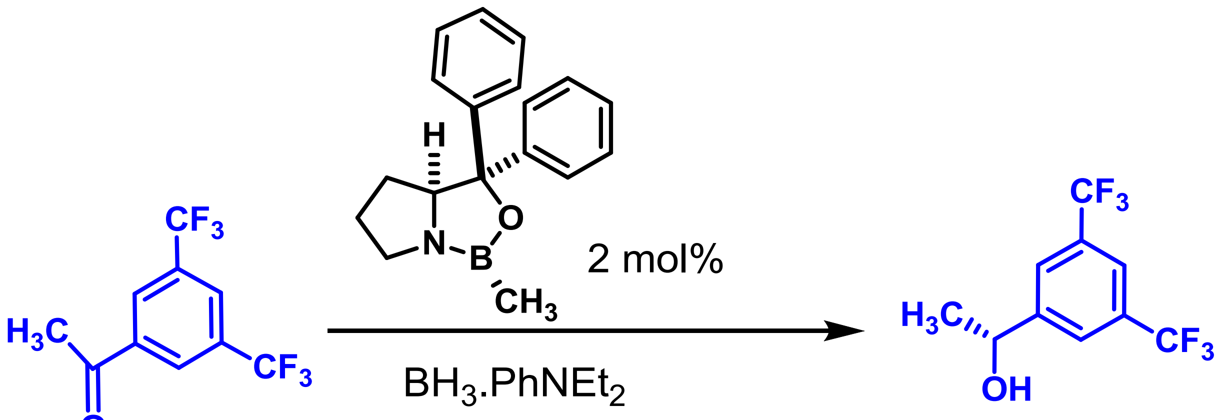
Retrosynthesis

J. Am. Chem. Soc. **2003**, *126*, 2129.

Emend Synthesis: Benzylic Stereogenic Center



Corey-Bakshi-Shibata (CBS) Reduction:

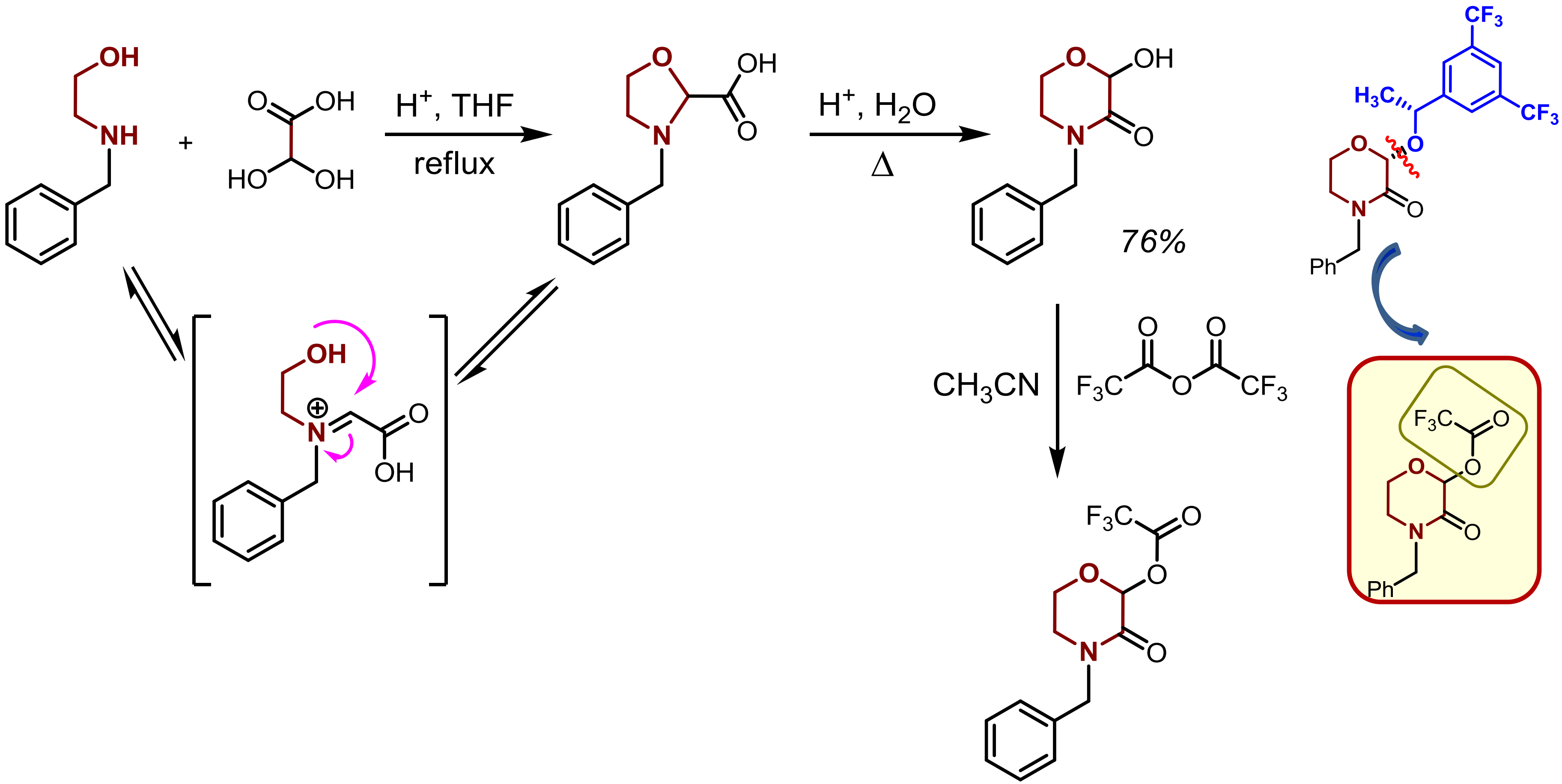


97% yield, 99% ee

>99% ee after recrystallization

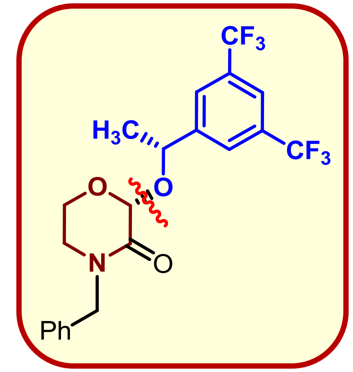
(*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol

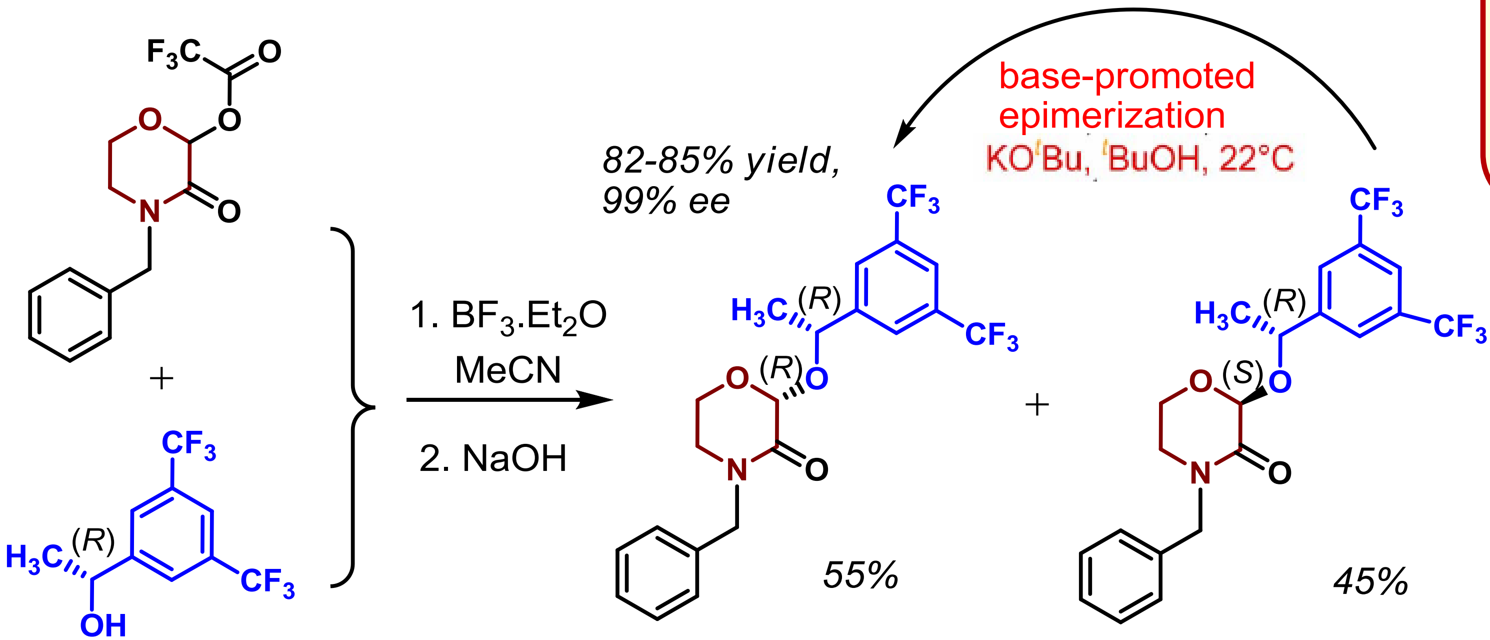
Emend Synthesis: Construction of the Lactam



J. Am. Chem. Soc. **2003**, *126*, 2129.

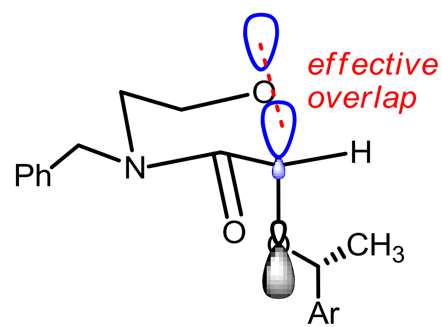
Emend Synthesis: Fragment Coupling



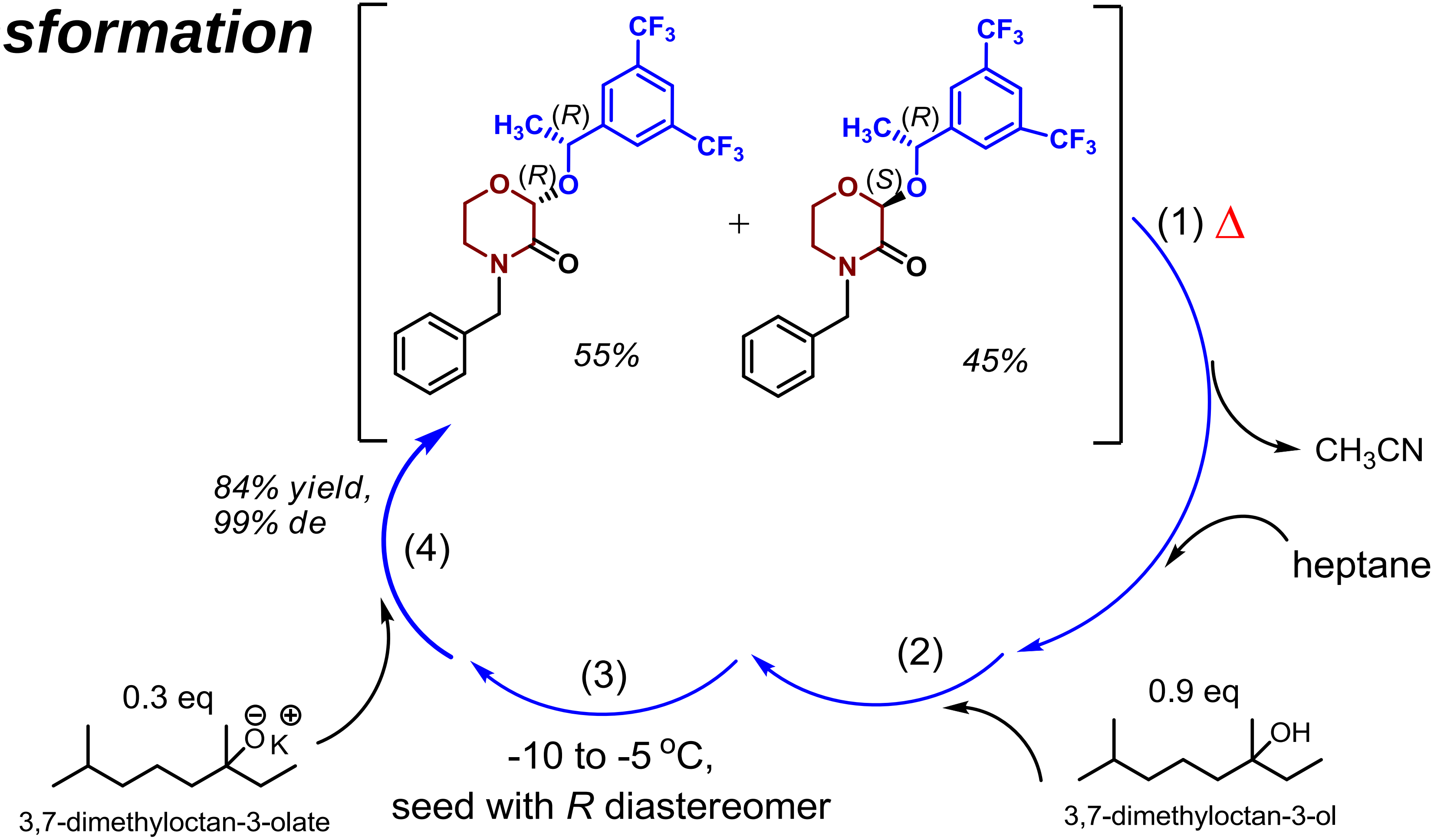


J. Am. Chem. Soc. **2003**, *126*, 2129.

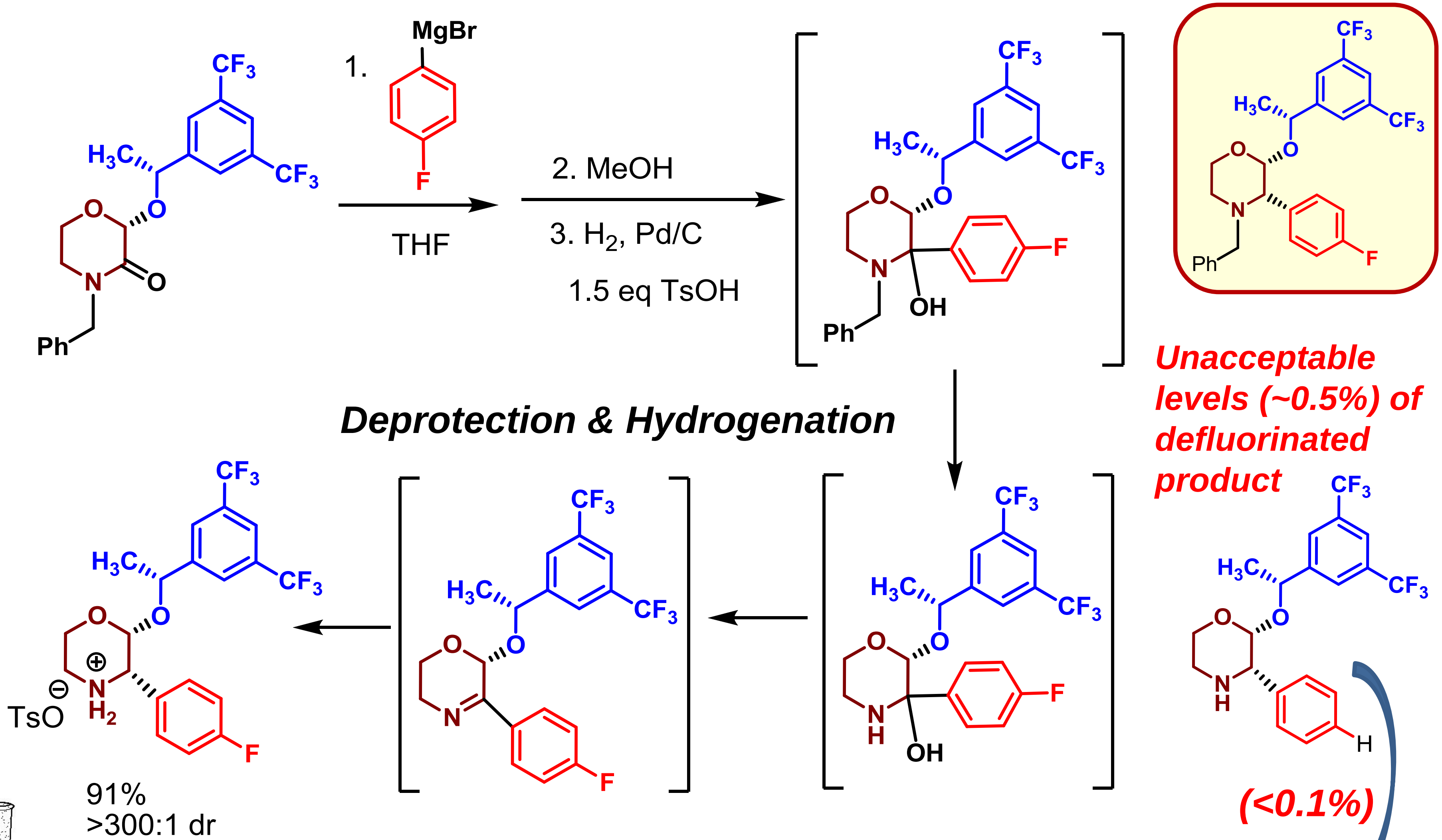
More stable conformer has axial orientation (Anomeric effect)



Crystallization-Induced Asymmetric Transformation



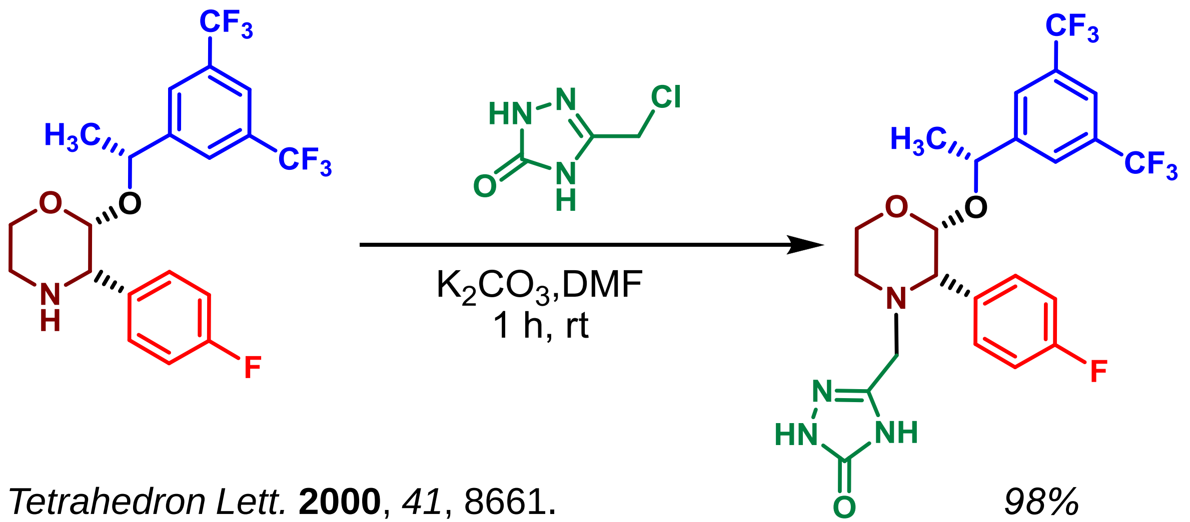
Emend Synthesis: Conversion to the Morpholine



J. Am. Chem. Soc. **2003**, *126*, 2129.

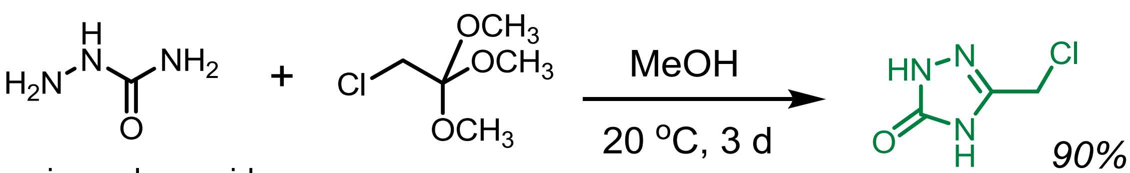
Org. Proc. Res. Develop. **2006**, *10*, 109.

Emend Synthesis: ***Completion***



Tetrahedron Lett. **2000**, *41*, 8661.

aprepitant

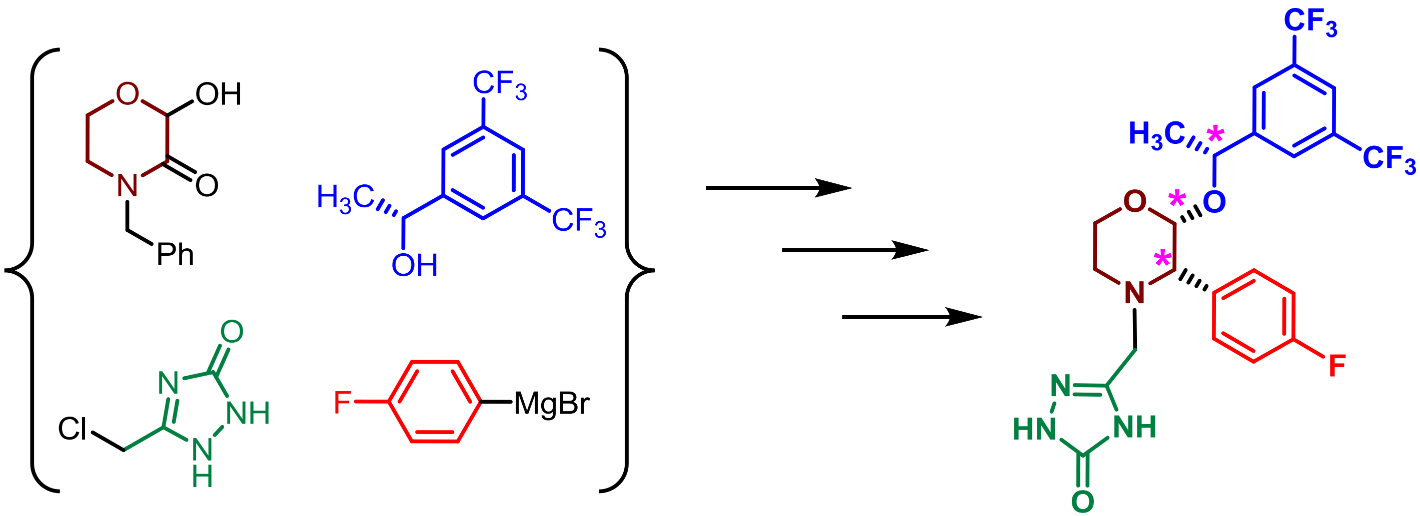


hydrazinecarboxamide (semicarbazide)

ortho-ester

3-(chloromethyl)-1*H*-1,2,4-triazol-5(4*H*)-one (triazolinone)

The greener commercial synthesis of Emend



- **Convergent synthesis**

  Use four compounds of similar size and complexity.

  Oyield 55%. 6 steps (increased yield from 12%).
- **Use less raw materials** (20% as original synthesis).
- **Avoid expensive reagents.**

  (chiral acid – BCSA, L-Selectride, Dimethyl titanocene)

- **Avoid special reaction condition.**
  (stric cryogenic temperature).
- **Eliminate toxic or hazardous chemicals.**
  (NaCN, Dimethyl titanocene, gaseous NH_3 and CH_4)
- **Reduce waste** (by 85% --- 340,000L/metric ton aprepitant)

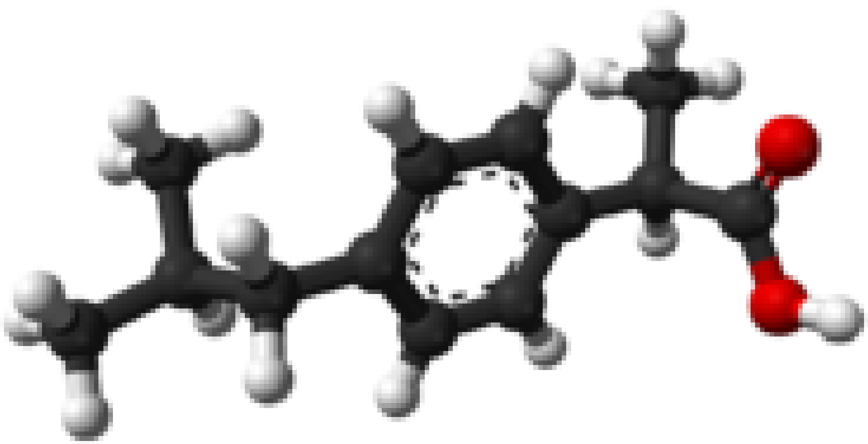
Process chemistry is more than just scale-up

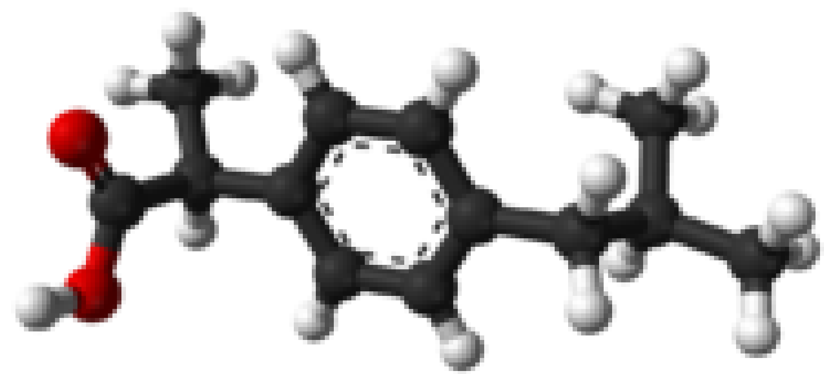
製程化學並非僅止於量產規模

- ***Safe*** 安全
- ***Cost effective*** 成本效率
- ***Enviromentally friendly*** 環境友善
- ***Timely development*** 適時發展

Case 3. 實例3

Ibuprofen

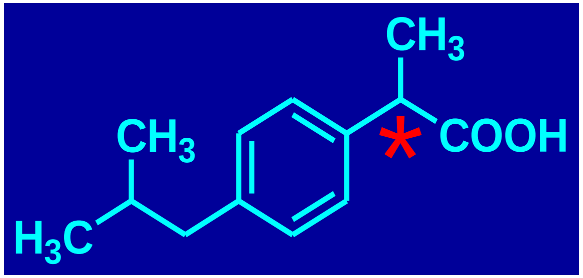


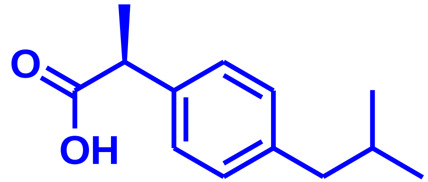


US Presidential Green Chemistry Challenge Awards:

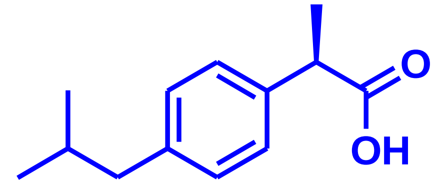
Greener Synthetic Pathways Award **1997**

What is ibuprofen?





(S)-ibuprofen



(R)-ibuprofen

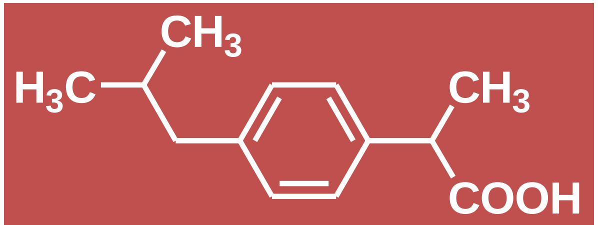
(S)-2-(4-isobutylphenyl)propanoic acid, (S)-ibuprofen, is active form both *in vitro* and *in vivo*.

(S)-ibuprofen **(R)-ibuprofen**

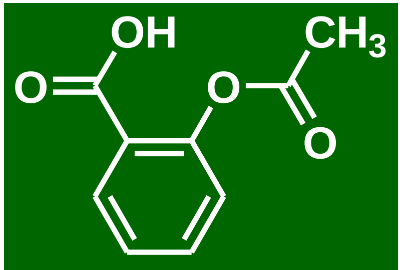
2-arylpropionyl-CoA epimerase (isomerase)

marketed as racemic mixtures.

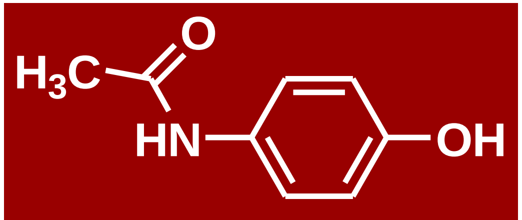
- One of core non-steroidal anti-inflammatory medicines (非類固醇消炎藥) in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system ---- *Over-the-Counter (不需處方可出售的) medicine.* [others: aspirin, paracetamol (acetaminophen)]



ibuprofen



aspirin



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）.

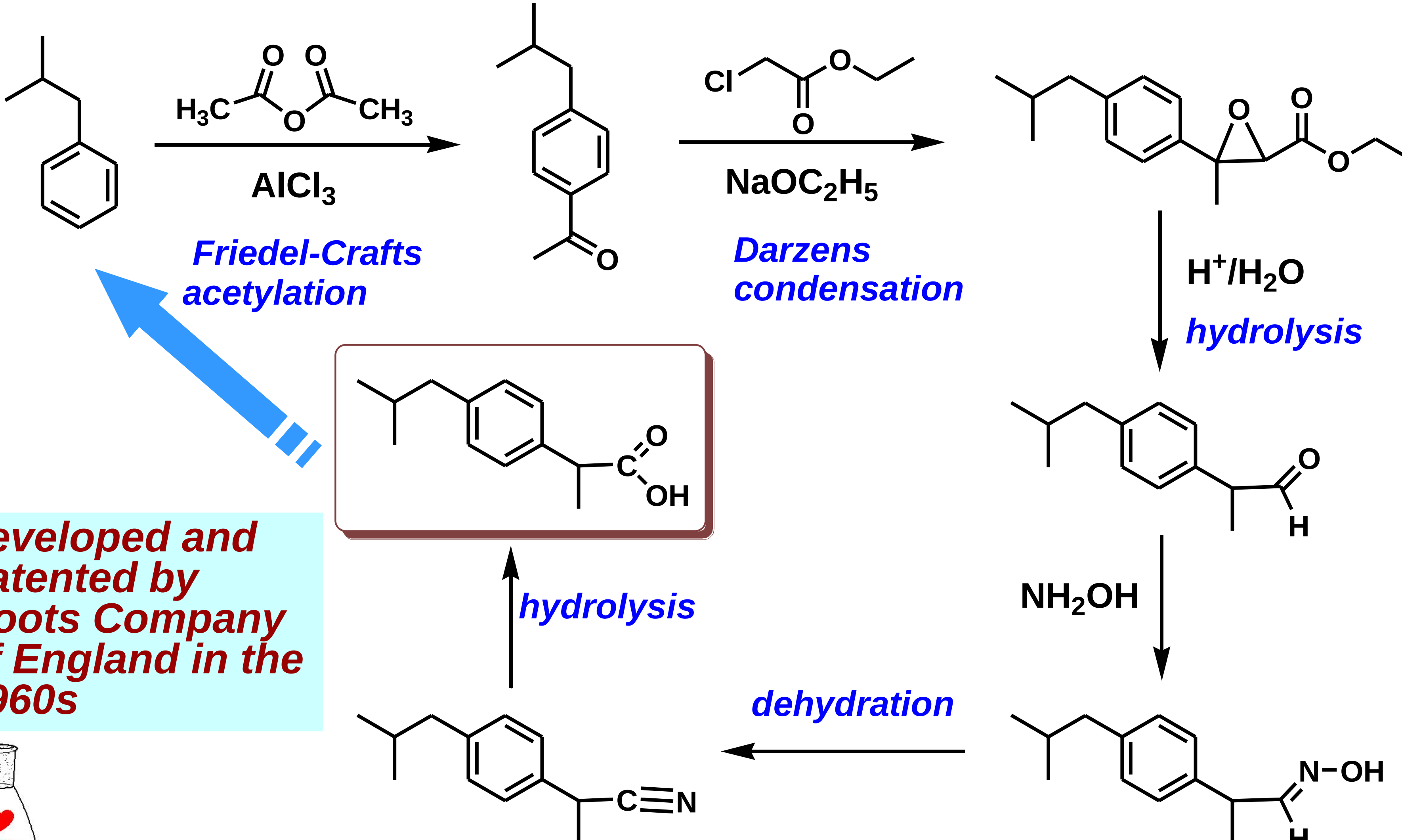
- It was launched in 1969 as a medication for the treatment of rheumatoid arthritis [風濕性關節炎] in the UK and in 1974 in the USA.
- The Boots Group was awarded ***Queen's Award for Technical Achievement*** for the development of ibuprofen in 1987.
- 具解熱、消炎和鎮痛的作用，可治療發燒、疼痛和發炎。
- 減輕關節炎(arthritis) ，原發型痛經(primary 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 = Boots + Hoechst Celanese

Boots synthesis of ibuprofen
--- brown synthesis



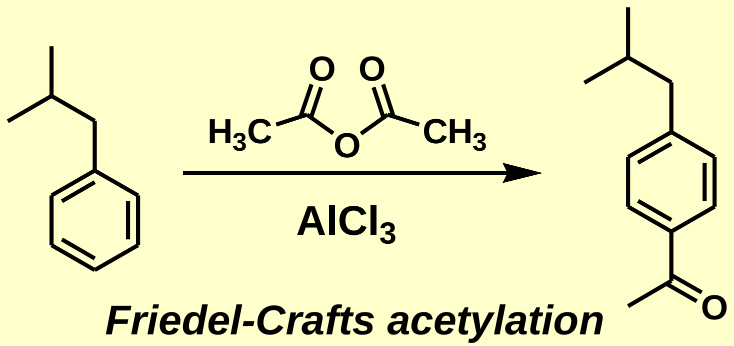
developed and patented by Boots Company of England in the 1960s

	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) x 100 = **40%**

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

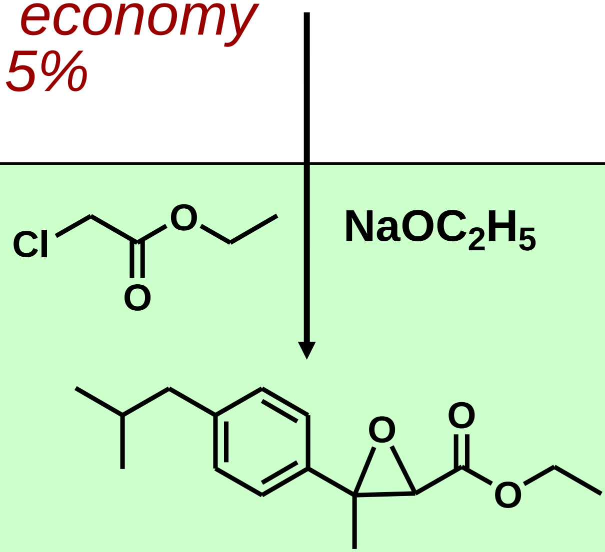
Problems with Boots synthesis of ibuprofen



atom economy = 74.5%

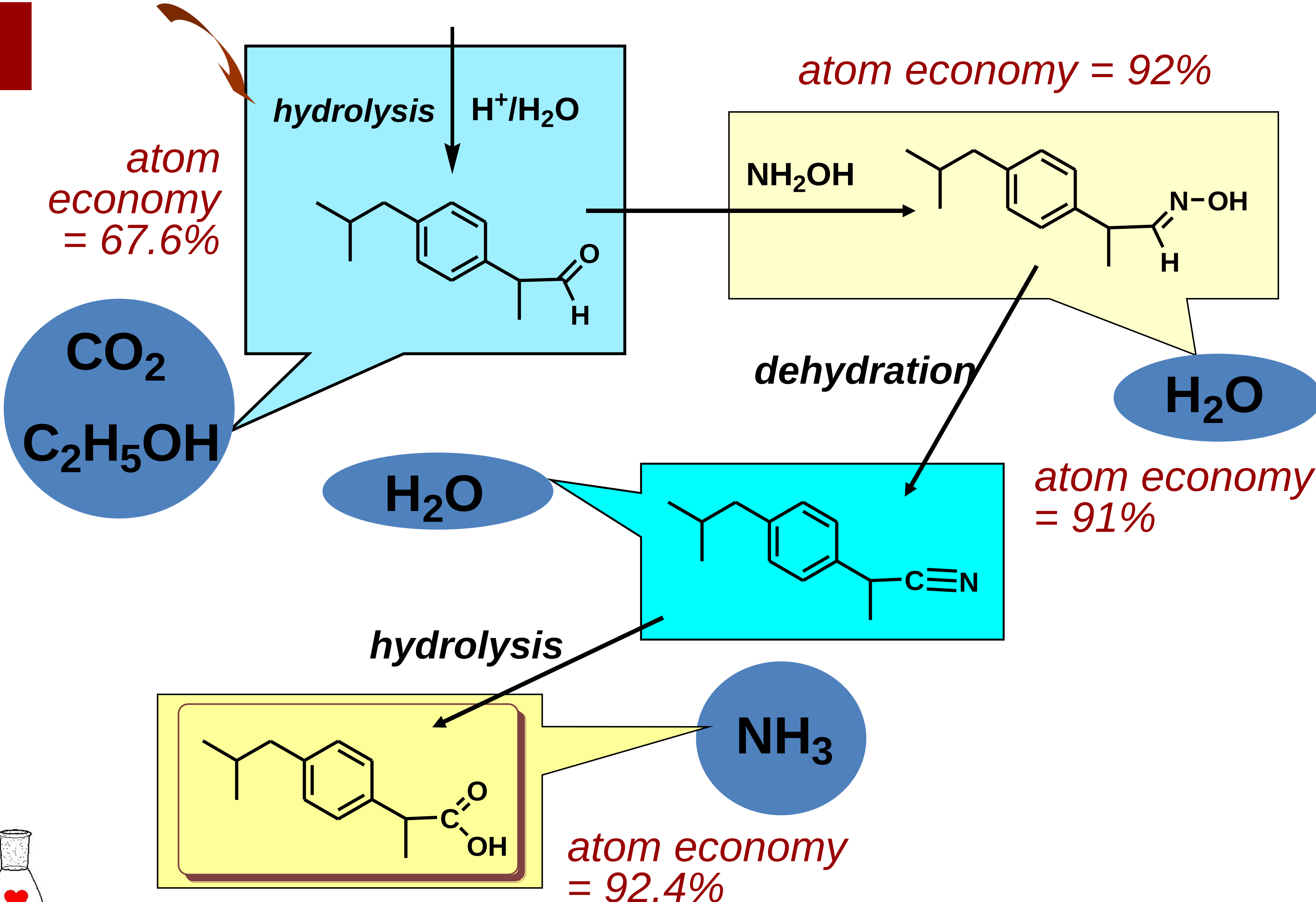
HCl AcOH Al

aluminium trichloride, **$AlCl_3$**, is not a true catalyst. it is changed into a hydrated form, $Al(OH)_3/H_2O$, that has to be disposed of – usually in landfill sites.



NaCl C_2H_5OH

atom economy = 71.6%


hydrolysis
H+/H2O
atom economy = 67.6%
CO2
C2H5OH
atom economy = 92%
NH2OH
N−OH
H
O
H
dehydration
H2O
atom economy = 91%
H2O
C≡N
hydrolysis
NH3
O
C
OH
atom economy = 92.4%

- **6 steps!**

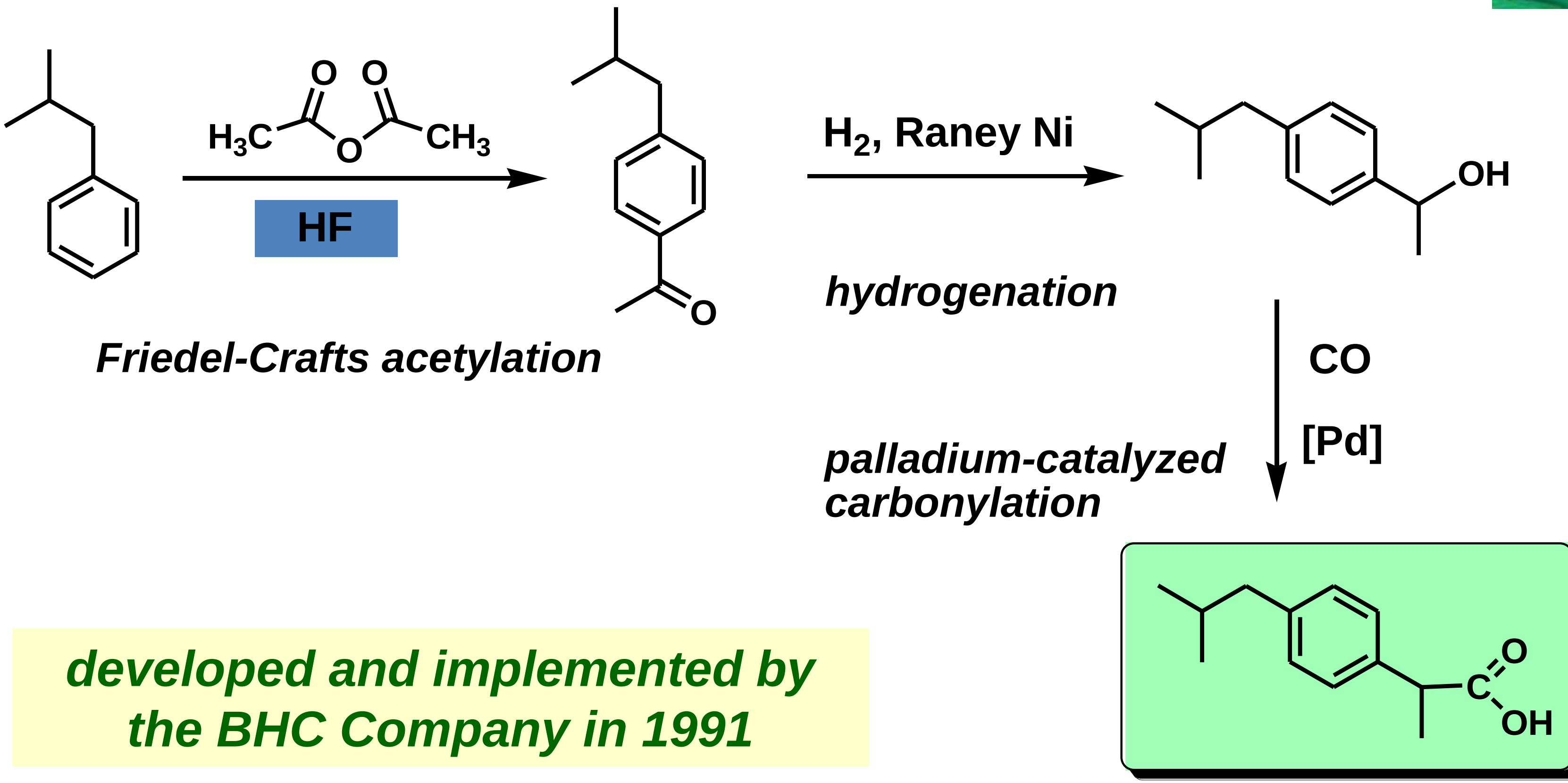
  If 90% yield for each step, then overall yield is 53%.
- **atom economy is 40%!**

  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 x 10^{10}) tablets are produced.*

World population on November 2010 is estimated by the United States Census Bureau to be 6.884 billion (6,884,000,000).

BHC synthesis of ibuprofen
--- green synthesis

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



developed and implemented by the BHC Company in 1991

	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) x 100 = **77.4%**						

Table 2. Atom economy in the BHC synthesis of ibuprofen

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.

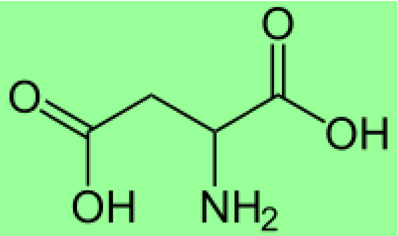
Case 4. 實例4

Polyaspartate

Biodegradable Alternative to Polyacrylate

US Presidential Green Chemistry Challenge Awards:

***Award in the small business category* 1996**



Aspartic acid
天冬氨酸

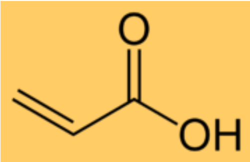
2-Aminobutanedioic acid

2-氨基丁酸

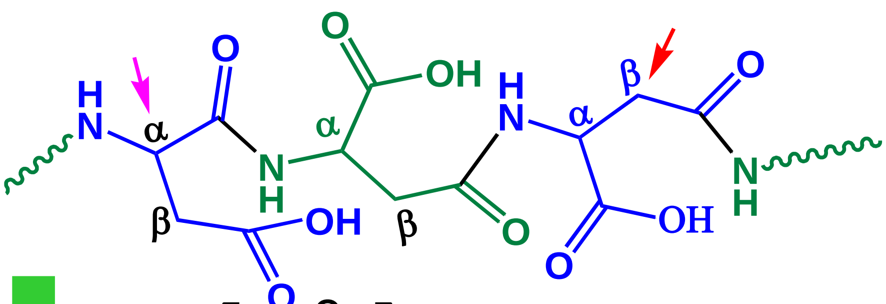
Acrylic acid
壓克力酸

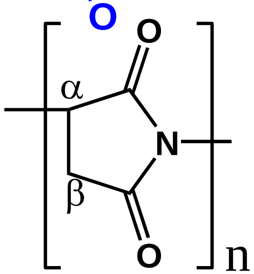
propenoic acid

丙烯酸



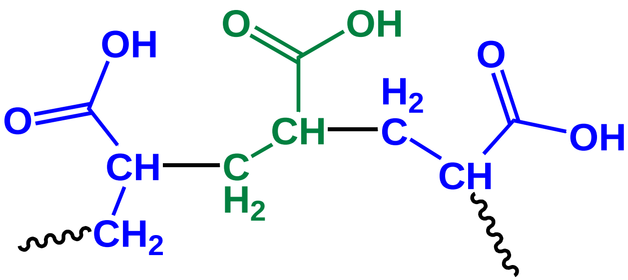
Polyaspartic acid
聚天冬氨酸



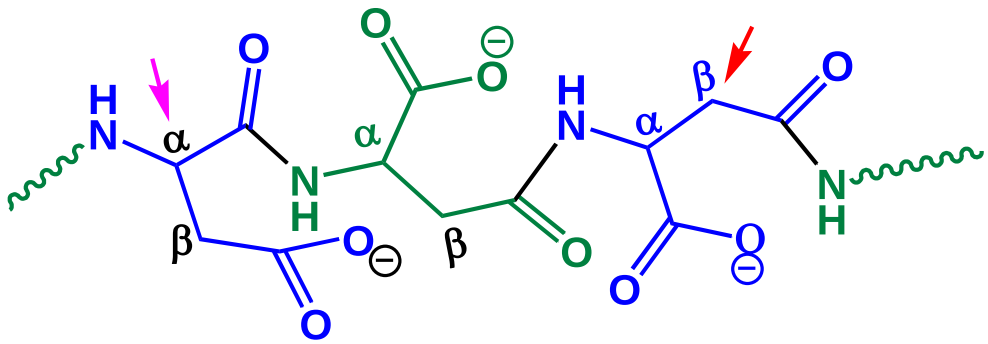


poly(succinimide)

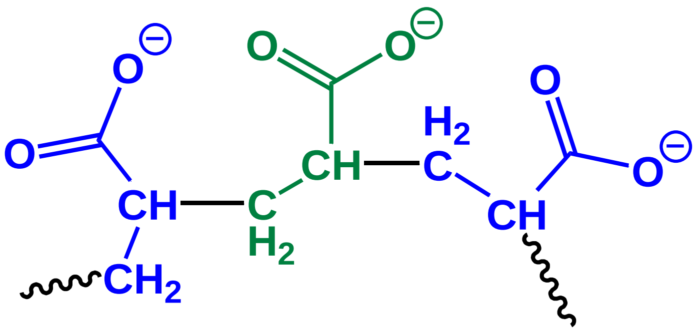
Polyacrylic acid
聚丙烯酸



Polyaspartate
聚天冬氨酸鹽

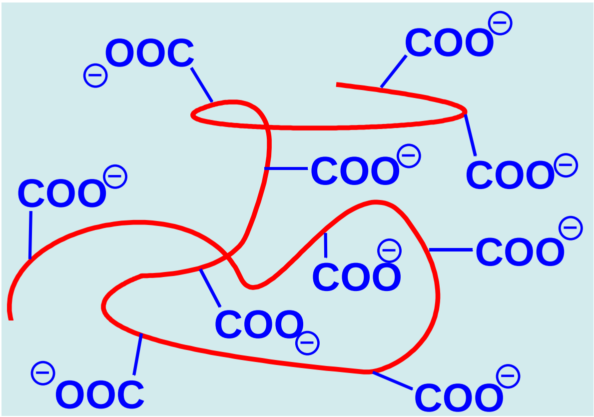


Polyacrylate
聚丙烯酸鹽



What are polyaspartate and polyacrylate in common?

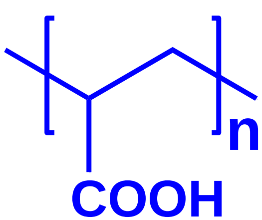
Polyanion, Hydrophilic, Water soluble



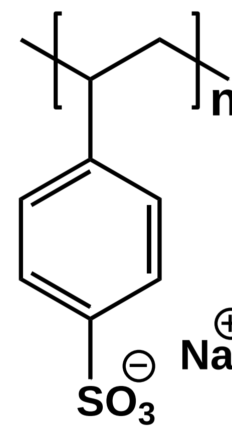
Polyelectrolytes

- polymers whose repeating units bear an electrolyte group, dissociating in aqueous solution (water) to generate positive or negative charge.
- also called macroions or polyions or polysalts.
- can be polyanions or polycations.
- generally water soluble polymers if their structure is linear.
- the polymer will be highly expanded in aqueous solution.
- can be modified to function as antiscalant（抗垢劑）and dispersant（分散劑）.

Examples

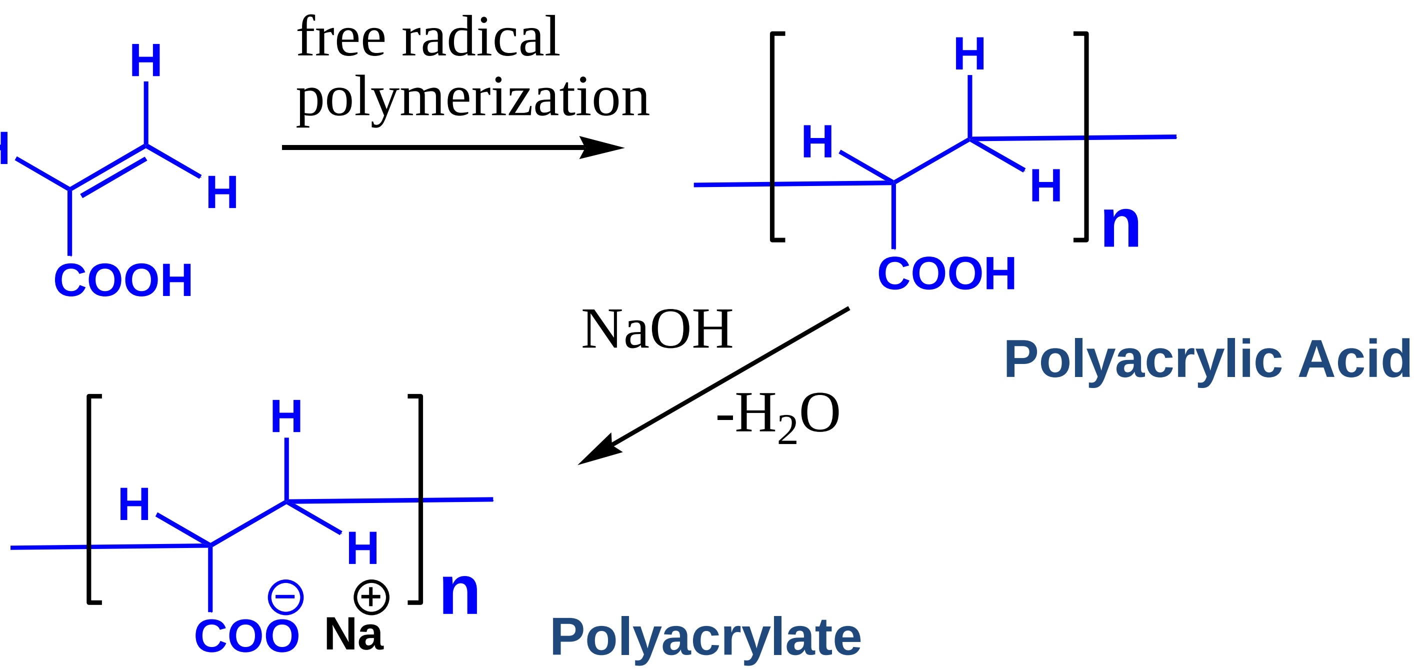


polypeptides (proteins), DNA, poly(sodium styrene sulfonate, PSS), polyacrylic acid (PAA).



Polyacrylate (PAC)

Synthesis



PAC can function as both an antiscalant（抗垢劑 ）and a dispersant（分散劑）.

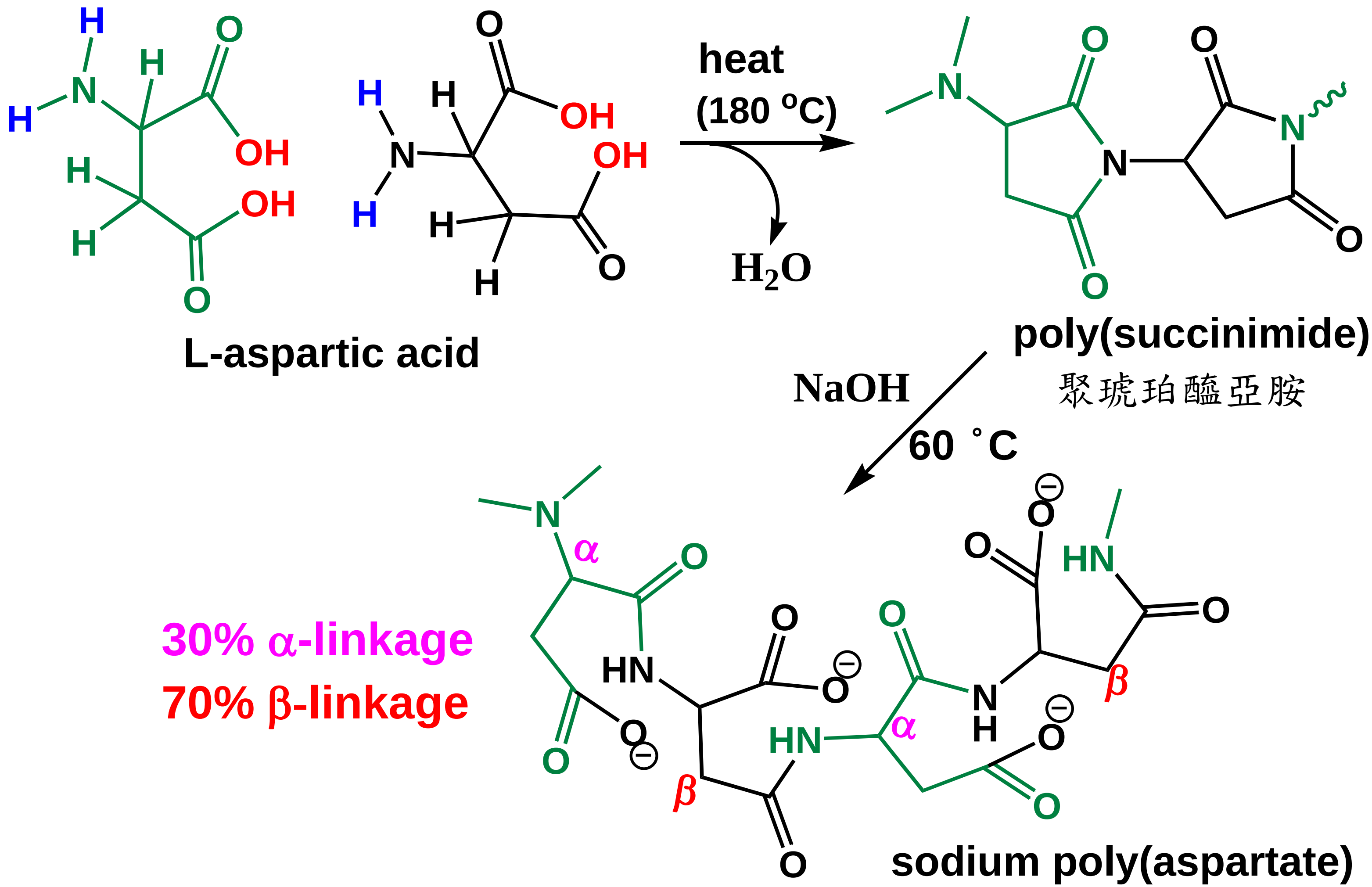
PAC and the Environment

- PAC is nontoxic and environmentally benign, **but it is not biodegradable.**
- Because it is widely used for many applications, it poses an environmental problem from a landfill perspective.
- When PAC is used as an antiscalant or a dispersant, it becomes part of wastewater.
- PAC is nonvolatile and not biodegradable, so the only way to remove it from the water is to precipitate it as an insoluble sludge.
- The sludge must then be landfilled.
- Feedstocks are made from fossil fuels.

Polyaspartate

- Polyaspartate has similar properties to the polyacrylates and so it can be used as a dispersant, or an antiscalant, or a superabsorber.
- Polyaspartate is **nontoxic**, **biodegradeable** (可生物分解的), and environmentally safe.
- Biodegradation results in decomposition of TPA to environmentally benign products such as carbon dioxide and water.
- The Donlar Corporation developed an economic way to produce “thermal polyaspartate (TPA)” in high yield (~97%), that eliminates use of organic solvents, cuts waste, and uses less energy.
- Polyaspartate is a biopolymer synthesized from L-aspartic acid, a natural amino acid.

Synthesis of thermal polyaspartate (TPA)



Green Chemistry *in ACTION*

- In April 1997, Donlar opened the world's largest manufacturing facility for biodegradable polyaspartates, in Peru, Illinois, with a production capacity of more than 30 million pounds a year.
- The opening of this facility resulted in commercial availability of TPA.
- TPA is marketed and sold as a corrosion and scale inhibitor, a dispersing agent, a waste water additive, a superabsorber, and also as an agricultural polymer.
- As an agricultural polymer, TPA is used to enhance fertilizer uptake by plants. Less fertilizer is added to the soil and the environmental impact from fertilizer run-off is reduced.

- British Petroleum Exploration and others have achieved success with a TPA additive that helps to sustain the flow of crude from oil wells in North Sea offshore oil fields.

TPA is a green alternative to Polyacrylate and other currently used water soluble polymers!

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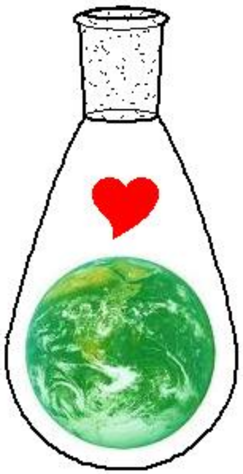

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