# Green Chemistry:
## Our Future Challenges in Chemical Synthesis

***Great Lakes Pollution-Prevention Roundtable***
**May 17, 2006**

**CJ Li**
***Department of Chemistry***
***McGill University***
***Canada***

McGill

# Great Human Achievements

## on the Macroscale and Microscale

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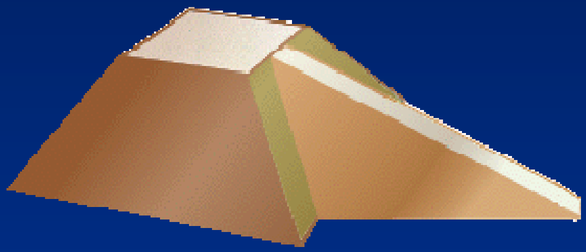
# >2000 years ago, The Great Pyramid





# Hong Kong, Dec. 2004

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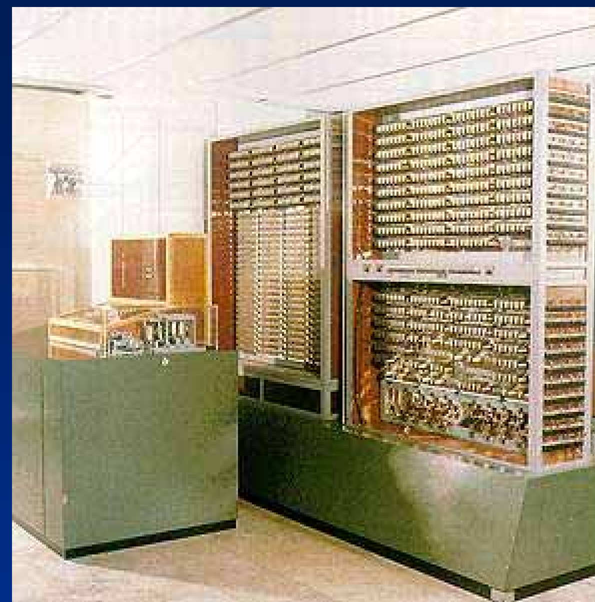
# On the nanoscale

**Z3 Computer (1941)**



**22 bites (1961) (based on vacuum-tubes)**
**Weight: 1000 Kg**
**Length: 5 meter**

**http://irb.cs.tu-berlin.de/~zuse/Konrad_Zuse/en/Rechner_Z3.html**

**Samsung Cell Phone**

**4,000,000,000 bites (2004) (based on silicon chips)**
**Weight: 0.099 Kg**
**Length: 0.05 meter**

**power/weight**

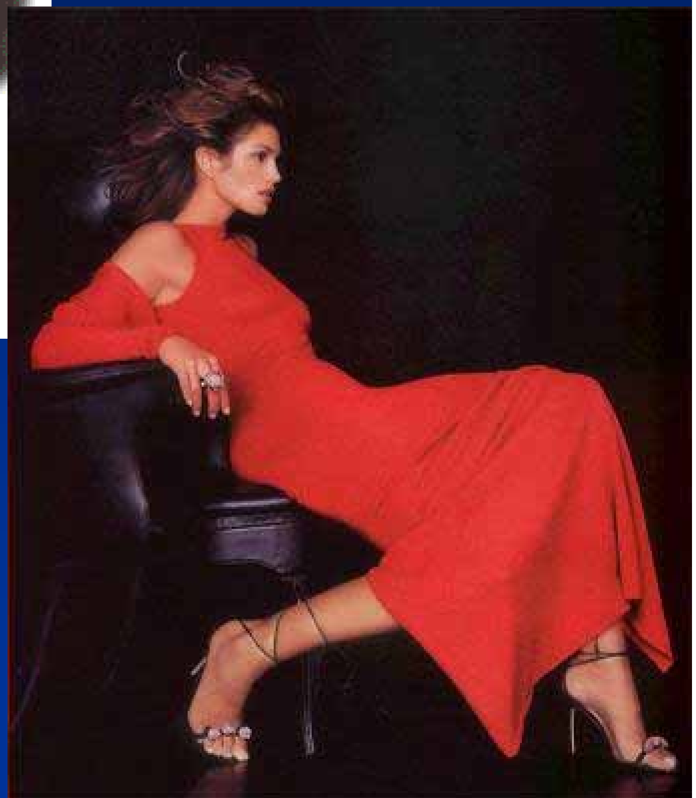
**$10^{13}$**

**http://cellphones.about.com/od/samsungreviews/**

# On the molecular scale

-The production and use of chemical products (also include nano-scale materials)

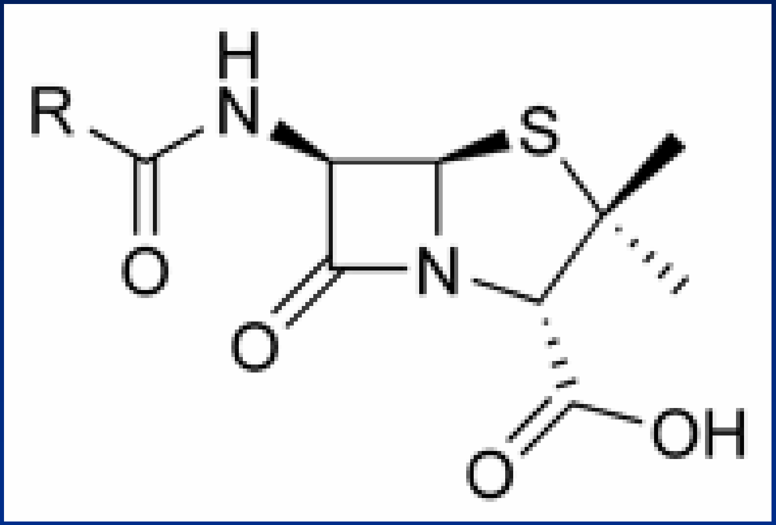

# Polyester



www.supermodels.com


posted to farmphoto.com

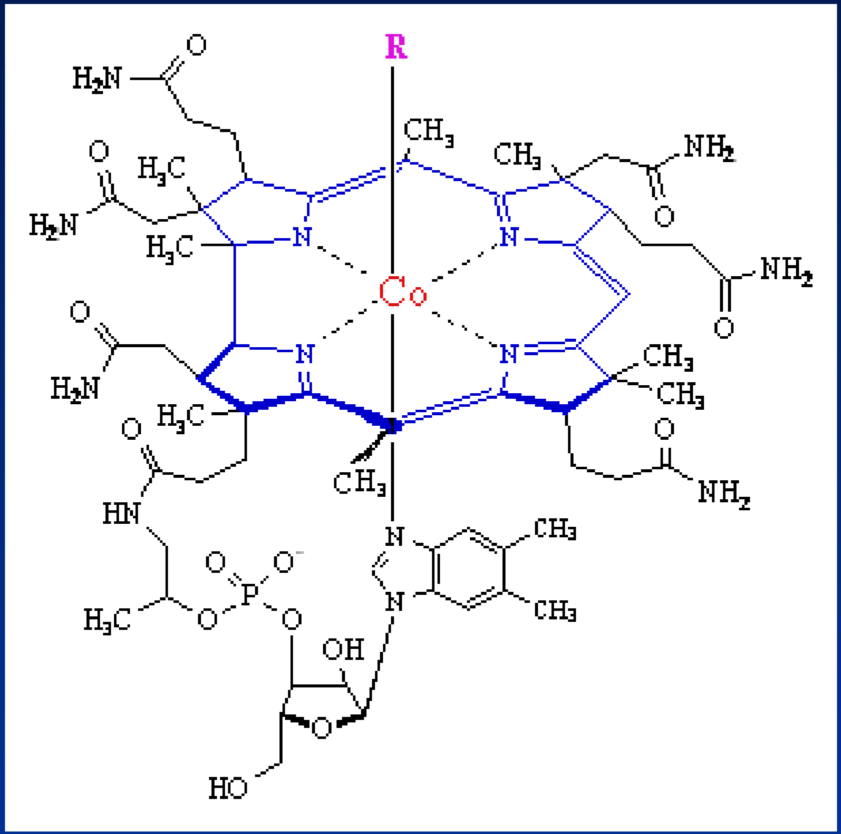

www.familycar.com




http://www.pbs.org/

# Vitamin B12

## On the molecular scale

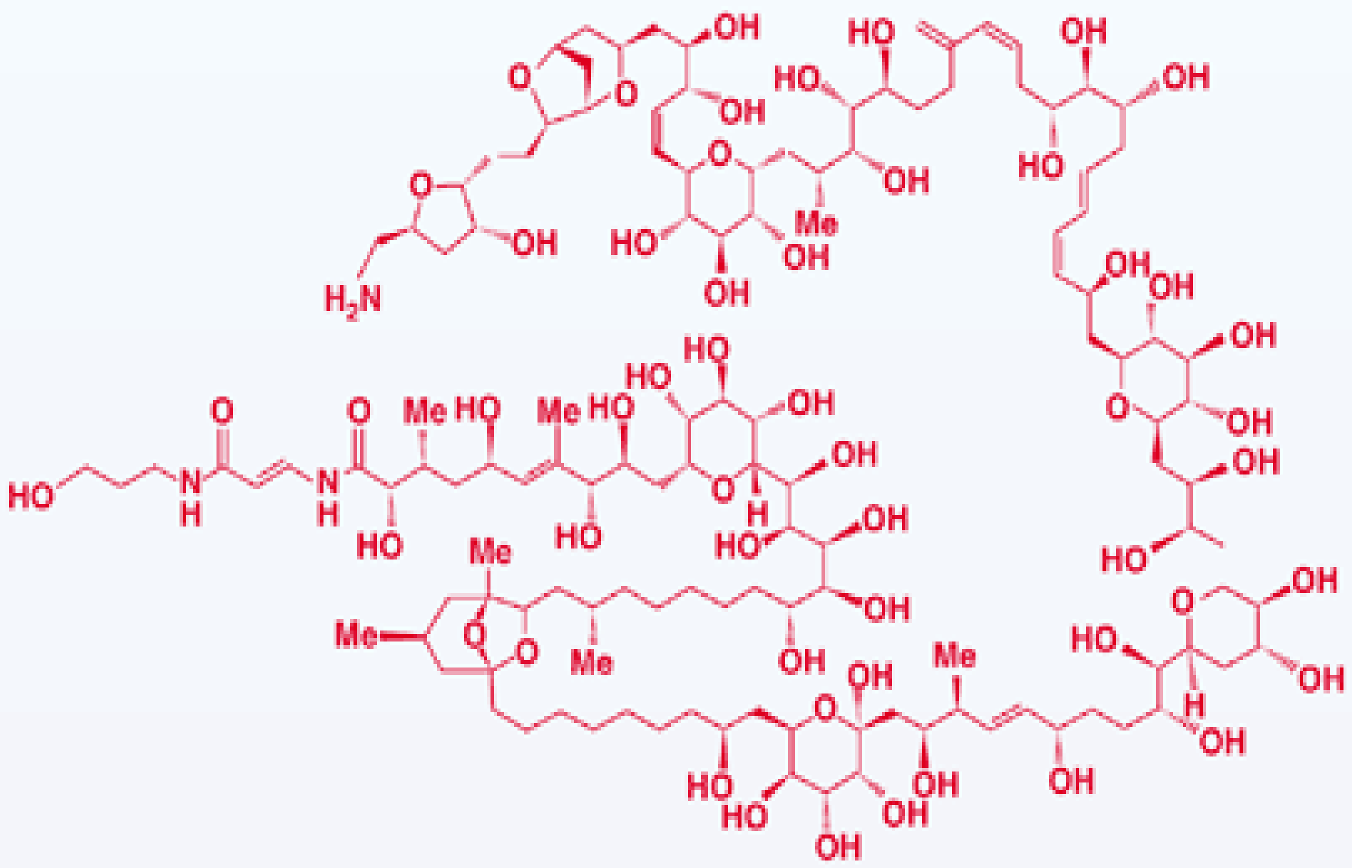



R. B. Woodward (Nobel Prize 1965)

http://www.britannica.com/nobel/micro/644_32.html

# Palytoxin

Isolated in 1981



Synthesis, 1990,
Y. Kishi (Harvard)

**http://www-chem.harvard.edu/faculty/kishi.html**

71 stereochemical elements (64 stereogenic centres, 7 geometrical)
Therefore there are $2^{71}$ possible stereoisomers ie:
$2.3 \times 10^{21}$ = 2300000000000000000000 isomers !!!

Starting material → Vitamin B12

ca. 45 steps

Starting material → Palytoxin

ca. 65 steps

**What is the challenge?**

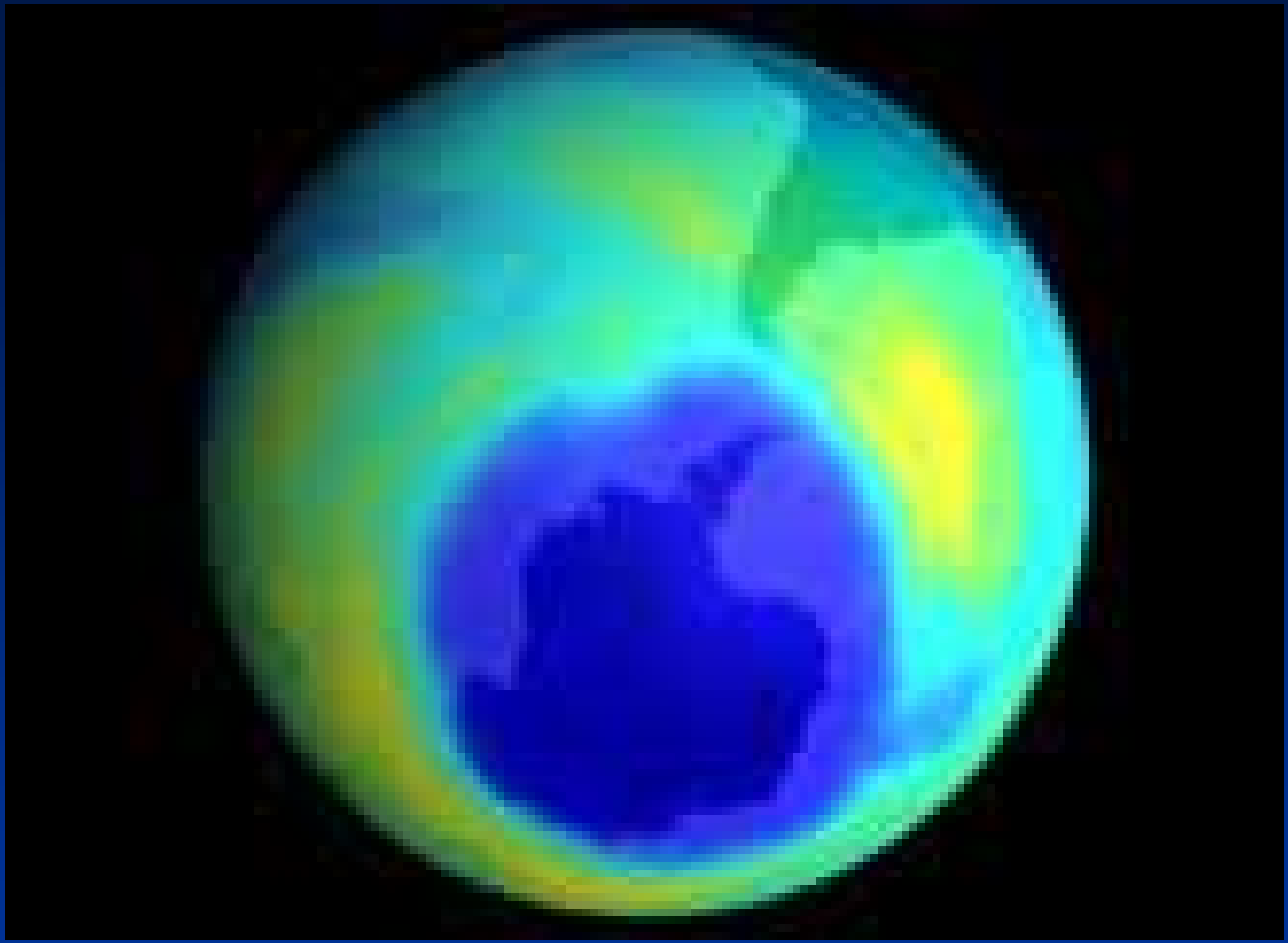
# A Sustainable Situation?

- Only 10% of the resources removed from the Earth end up in the goods manufactured
- 90% End up as waste
  - Double economic penalty
  - Resource depleting rapidly
  - The waste becomes huge environmental problems
- Source: WRI 2001

**(from Buzz Cue)**

www.nbmg.unr.edu/ slides/oil/1.htm

Slide provided by Prof. D. N. Harpp of McGill University

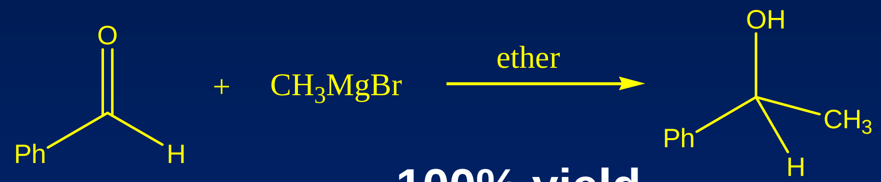


http://www.coolantarctica.com

http://www.panda.org/news_facts/education


Wesley Bocxe

# The Generation of Waste




**100% yield**

A typical 1 mmol scale reaction (630 mg product)

-from solvent (20,200 mg)
-from reaction (765 mg)
-from product separation (89,100 mg)

Total: (110,000 mg)
Solvent for washing flask, column, testtubes (water, acetone) 200mL (200,000mg)

Material efficiency $\frac{630}{310{,}000} = 0.2\%$

Excluding energy cost and cooling water

Waste=99.8%

# The Material Utilization

For a two step synthesis:

Material efficiency = 0.2% x 0.2 % =0.0004%

Waste = 99.9996%

For a 20 step synthesis: (roughly)

Material efficiency = 0.000000000000000000000000000
00000000000001%

Waste= 99.99999999999999999999999999
9999999999999%

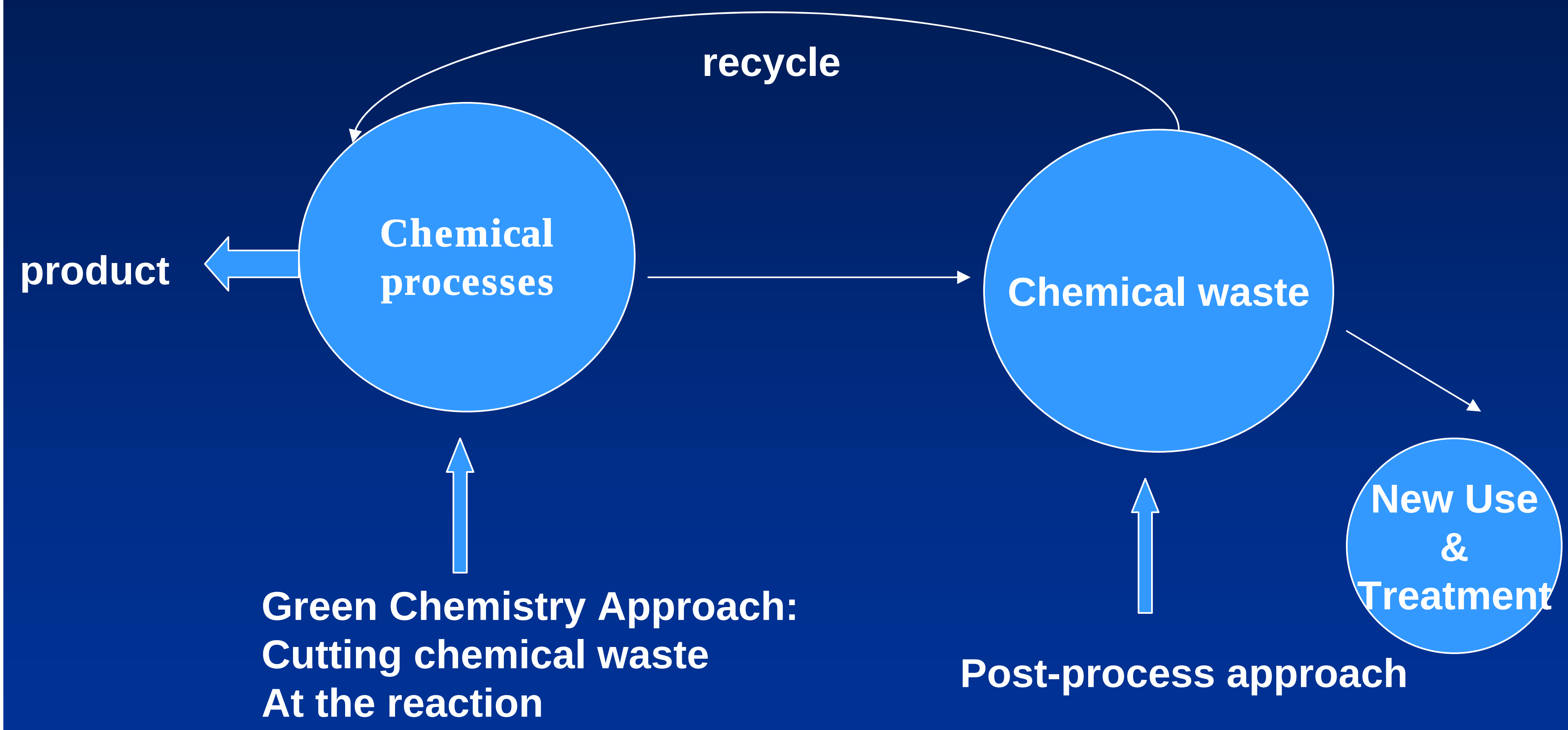
**It is still the Stone Age of synthesis!**

# 12 Principles of Green Chemistry

1. **Prevention:**
2. **Atom Economy:**
3. **Less Hazardous Chemical Syntheses:**
4. **Designing Safer Chemicals:**
5. **Safer Solvents and Auxiliaries:**
6. **Design for Energy Efficiency:**
7. **Use of Renewable Feedstocks:**
8. **Reduce Derivatives:**
9. **Catalysis:**
10. **Design for Degradation:**
11. **Real-time analysis for Pollution Prevention:**
12. **Inherently Safer Chemistry for Accident Prevention:**

***Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998***

# LONG-TERM
# Goal of Green Chemical Productions



## Synthesis in Lab

Starting material → Vitamin B12

ca. 60 steps

Starting material → Palytoxin

ca. 65 steps

## Synthesis in Nature

Starting material → (one pot; catalysis/air/water) Vitamin B12, Palytoxin

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# •The E-Factor:

**•(Roger Sheldon)**

| Industry segment | Product tonnage | ratio<br>kg byproduct/kg product |
|---|---|---|
| Oil refining | $10^6$-$10^8$ | ca. 0.1 |
| Bulk chemicals | $10^4$-$10^6$ | <1-5 |
| Fine Chemicals | $10^2$-$10^4$ | 5-50 |
| Pharmaceuticals | $10^1$-$10^3$ | 25-100+ |

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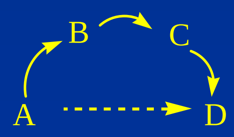
# Key Elements in Chemical Syntheses

**Media- the solvent-** (traditional: organic solvents)
**Greener alternatives: water, CO2, ionic liquids, flourous.**

**Separation-** (traditional: distillation/crystallization/chromatography)
**Greener alternatives: self-separation, membrane separation etc.**

**Raw Materials-** (traditional: fossil based)
**Greener: renewable materials, e.g. biomass.**

**The Reactions:** (traditional: incremental optimize yields)
**Greener: change the fundamental reaction to produce products more directly and with high atom efficiency.**



# •The E-Factor:

•(Roger Sheldon)

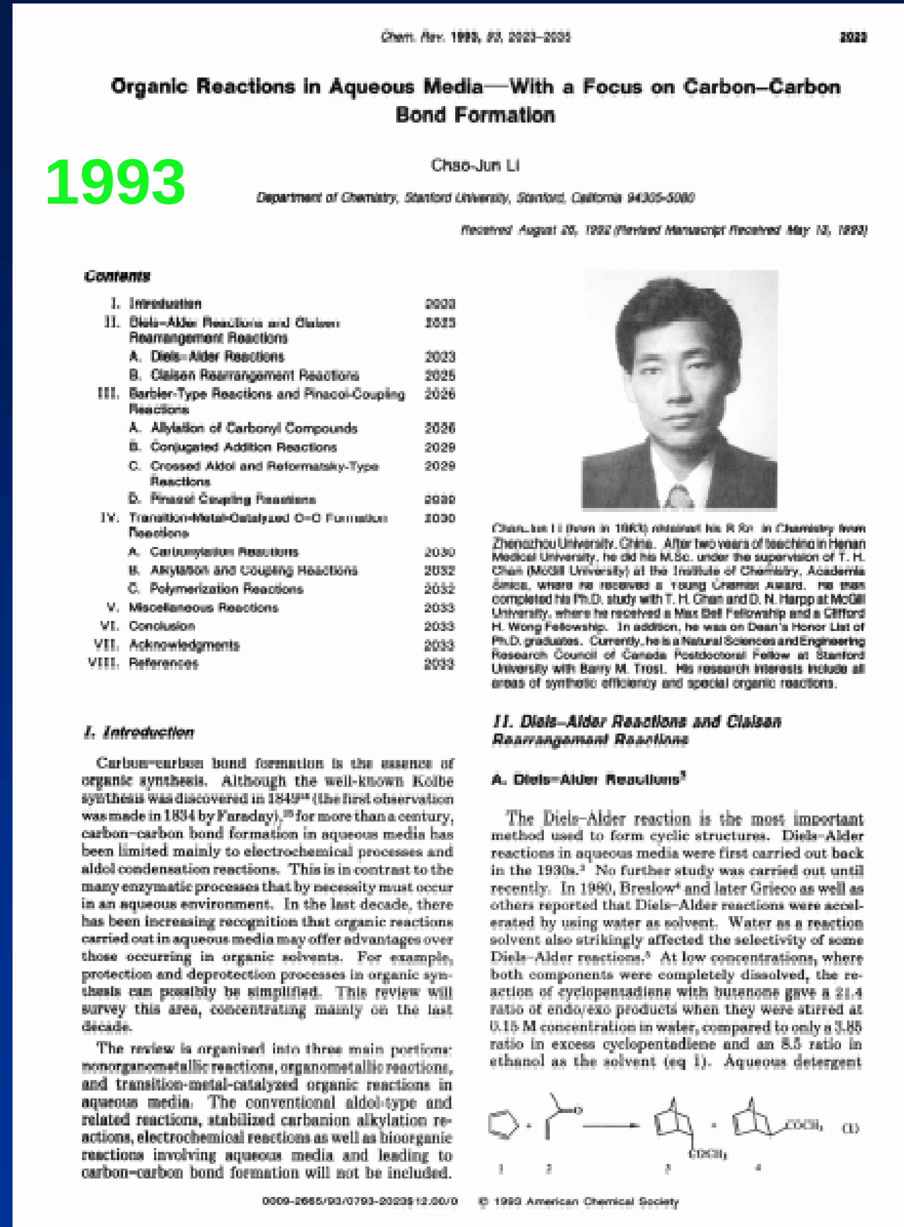
# •The E-Factor Extension:

• (C.-J. Li)

| Industry segment | Product tonnage | ratio kg byproduct/kg product | # of steps n | $\text{ratio}/10^{n-1}$ |
|---|---|---|---|---|
| Oil refining | $10^6$-$10^8$ | ca. 0.1 | 1 | 0.1 |
| Bulk chemicals | $10^4$-$10^6$ | <1-5 | 2 | 0.1-0.5 |
| Fine Chemicals | $10^2$-$10^4$ | 5-50 | 3 | 0.05-0.5 |
| Pharmaceuticals | $10^1$-$10^3$ | 25-100+ | 4+ | 0.025-0.1 |

**Increasing each step will increase the amount of byproduct about 10 times!**


1993



Chem. Rev. 1993, 93, 2023–2035 

# Organic Reactions in Aqueous Media—With a Focus on Carbon–Carbon Bond Formation

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*Received August 26, 1992 (Revised Manuscript Received May 13, 1993)*

**Contents**



Chao-Jun Li (born in 1963) obtained his B.Sc. in Chemistry from Zhengzhou University, China. After two years of teaching in Henan Medical University, he did his M.Sc. under the supervision of T. H. Chan (McGill University) at the Institute of Chemistry, Academia Sinica, where he received a Young Chemist Award. He then completed his Ph.D. study with T. H. Chan and D. N. Harpp at McGill University, where he received a Max Bell Fellowship and a Clifford H. Wong Fellowship. In addition, he was on Dean's Honor List of Ph.D. graduates. Currently, he is a Natural Sciences and Engineering Research Council of Canada Postdoctoral Fellow at Stanford University with Barry M. Trost. His research interests include all areas of synthetic efficiency and special organic reactions.

## *I. Introduction*

Carbon–carbon bond formation is the essence of organic synthesis. Although the well-known Kolbe synthesis was discovered in 1849[1a] (the first observation was made in 1834 by Faraday),[1b] for more than a century, carbon–carbon bond formation in aqueous media has been limited mainly to electrochemical processes and aldol condensation reactions. This is in contrast to the many enzymatic processes that by necessity must occur in an aqueous environment. In the last decade, there has been increasing recognition that organic reactions carried out in aqueous media may offer advantages over those occurring in organic solvents. For example, protection and deprotection processes in organic synthesis can possibly be simplified. This review will survey this area, concentrating mainly on the last decade.

The review is organized into three main portions: nonorganometallic reactions, organometallic reactions, and transition-metal-catalyzed organic reactions in aqueous media. The conventional aldol-type and related reactions, stabilized carbanion alkylation reactions, electrochemical reactions as well as bioorganic reactions involving aqueous media and leading to carbon–carbon bond formation will not be included.

## *II. Diels–Alder Reactions and Claisen Rearrangement Reactions*

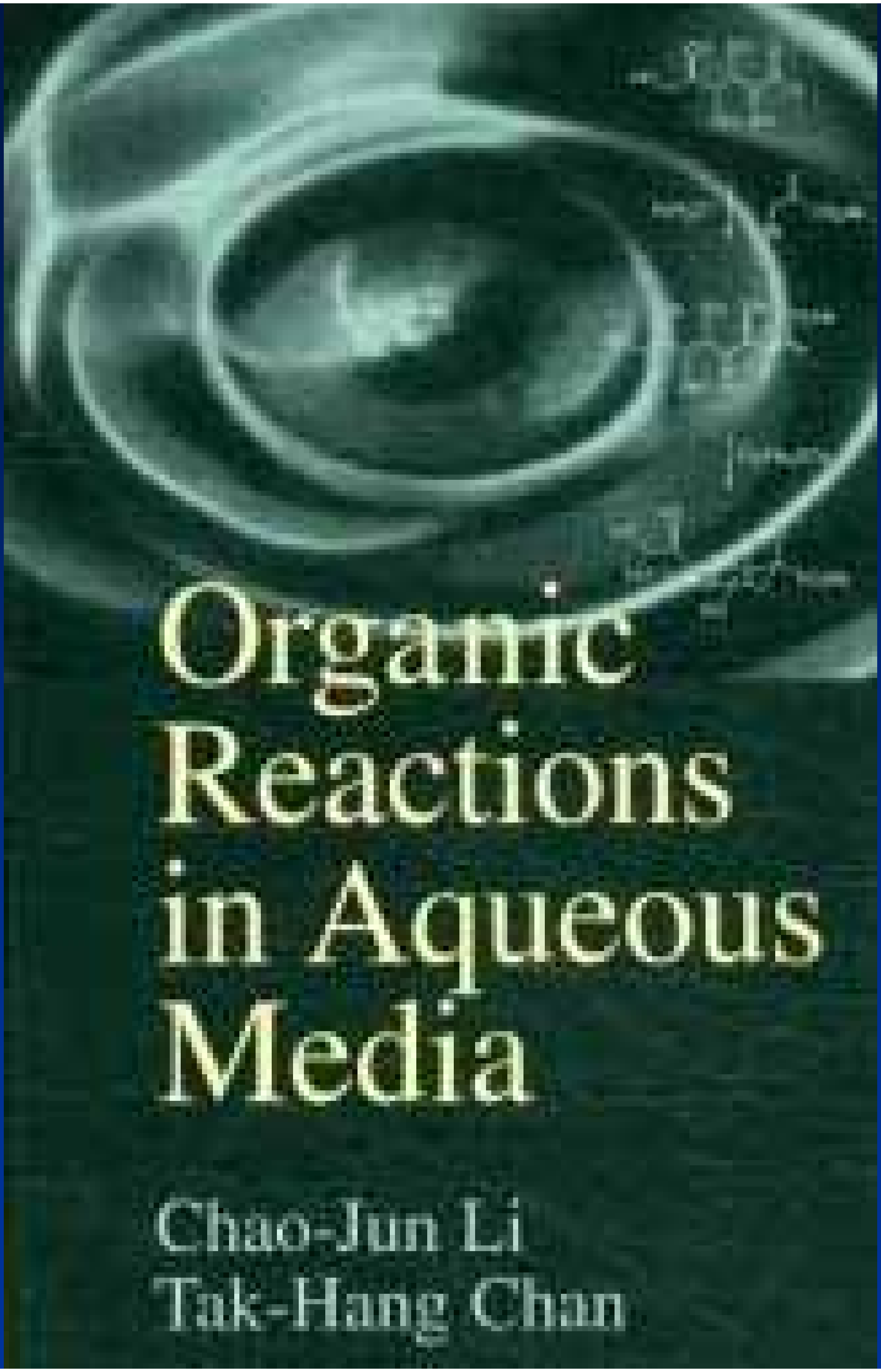
### A. Diels–Alder Reactions[2]

The Diels–Alder reaction is the most important method used to form cyclic structures. Diels–Alder reactions in aqueous media were first carried out back in the 1930s.[3] No further study was carried out until recently. In 1980, Breslow[4] and later Grieco as well as others reported that Diels–Alder reactions were accelerated by using water as solvent. Water as a reaction solvent also strikingly affected the selectivity of some Diels–Alder reactions.[5] At low concentrations, where both components were completely dissolved, the reaction of cyclopentadiene with butenone gave a 21.4 ratio of endo/exo products when they were stirred at 0.15 M concentration in water, compared to only a 3.85 ratio in excess cyclopentadiene and an 8.5 ratio in ethanol as the solvent (eq 1). Aqueous detergent

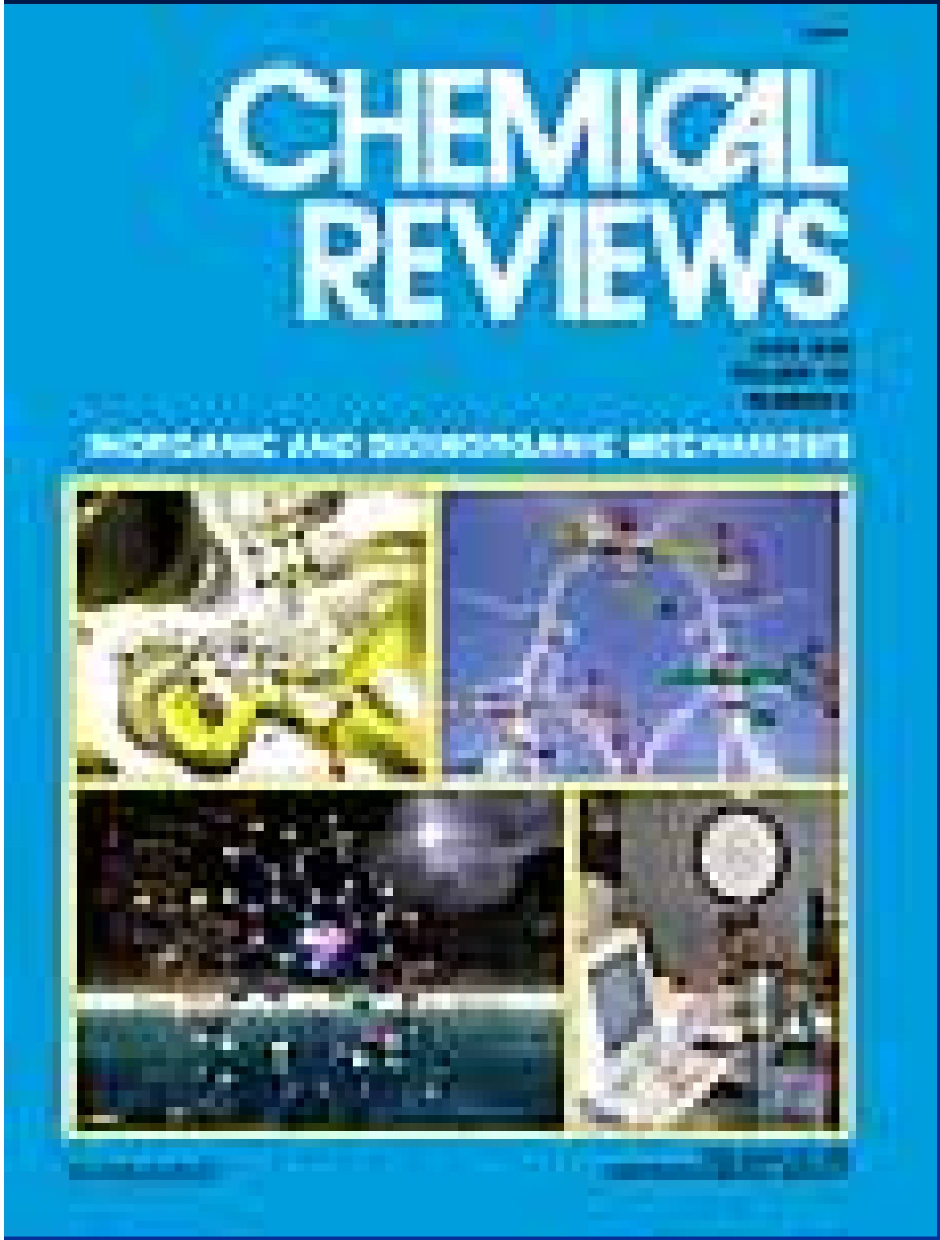

1 2 3 4 (1)

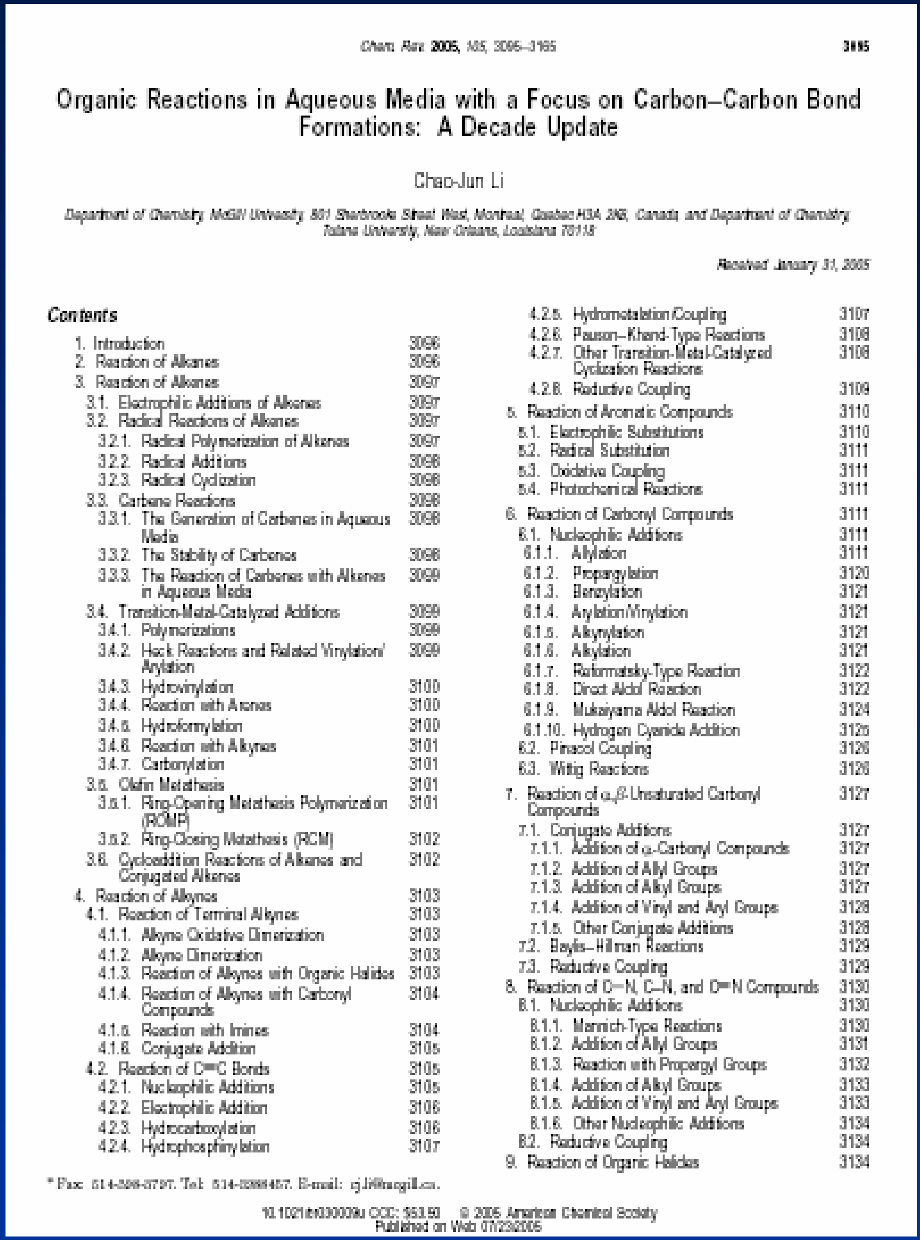
0009-2665/93/0793-2023$12.00/0 

1997


Organic Reactions in Aqueous Media
Chao-Jun Li
Tak-Hang Chan

# 2005




## Organic Reactions in Aqueous Media with a Focus on Carbon–Carbon Bond Formations: A Decade Update

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*Received January 31, 2005*

**Contents**



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10.1021/cr030009u CCC: $53.50 
Published on Web 07/23/2005

# Research Interests of the Li's Group

Hydrocarbons
$CO_2$, CO
$H_2O$
$N_2$, $NH_3$
Biomass (carbohydrates, lignins)
$O_2$

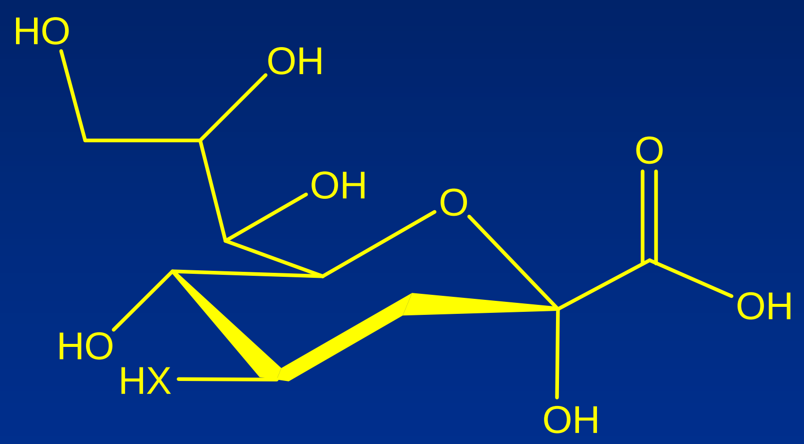
Cat. → Chemical Products

Water, ionic liquid, or $CO_2$

The environmental, social, economical impact is enormous!

# SIALIC ACIDS SYNTHESIS: An Example

Sialic acids




X=O, NH

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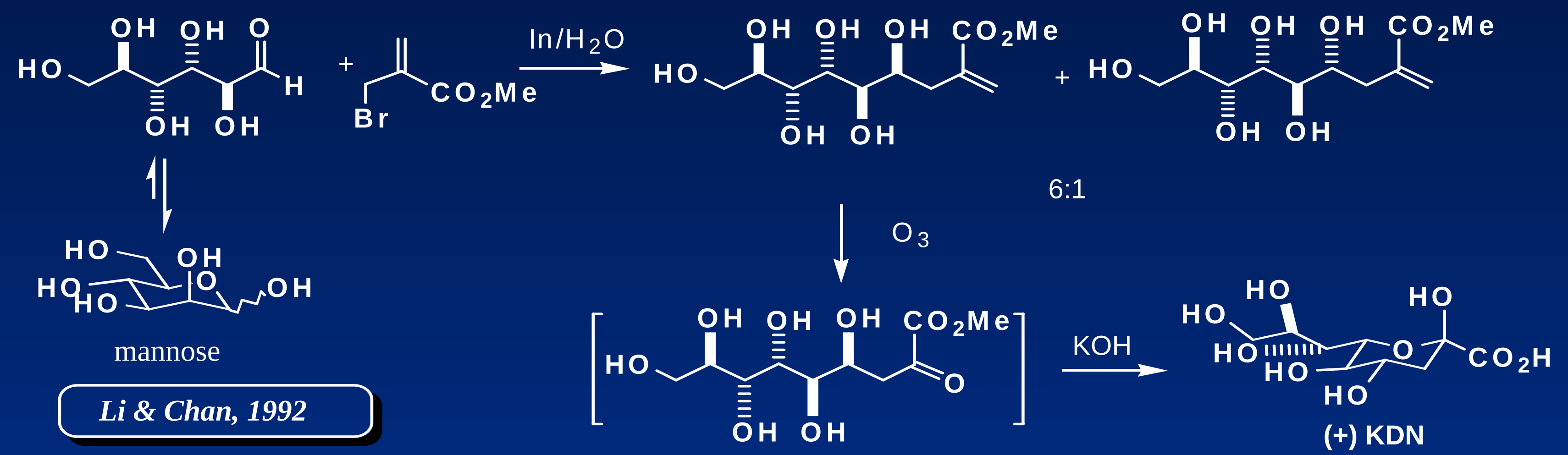
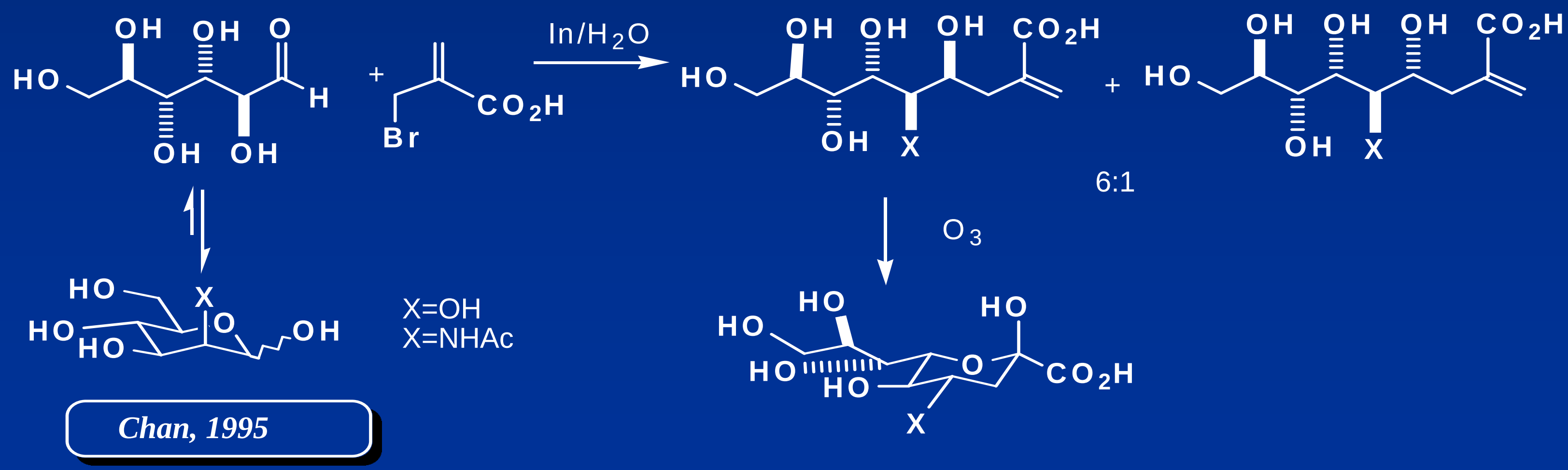
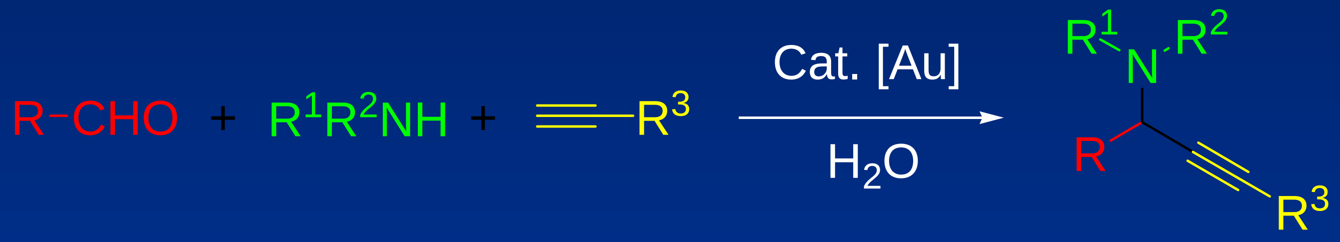
# SIALIC ACIDS SYNTHESIS: An Example



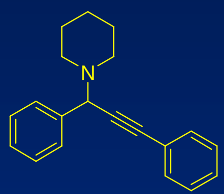



# Three-Component Couping of Aldehyde Alkyne and Amine ($A^3$-Coupling) by Gold Catalyst in Water




Wei, C. M.; Li, C. J. *J. Am. Chem. Soc*. **2003**, *125*, 9584-9585.

# Coupling of Aldehyde, Alkyne and Amine Catalyzed by $AuBr_3$ in Water

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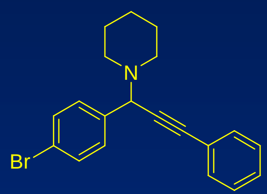


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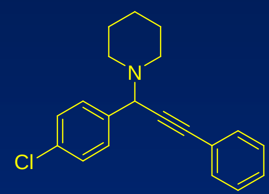


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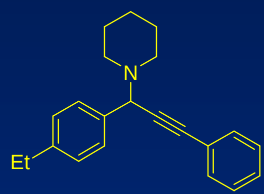
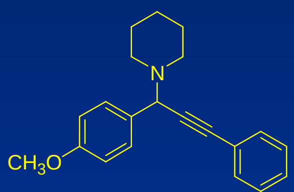
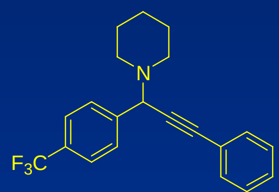


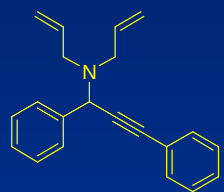

95%



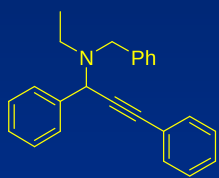

91%




98% [b]




95%

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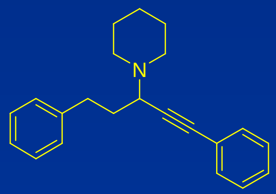
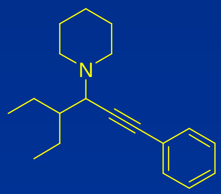
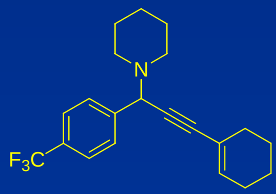


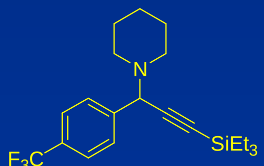

75%




96%



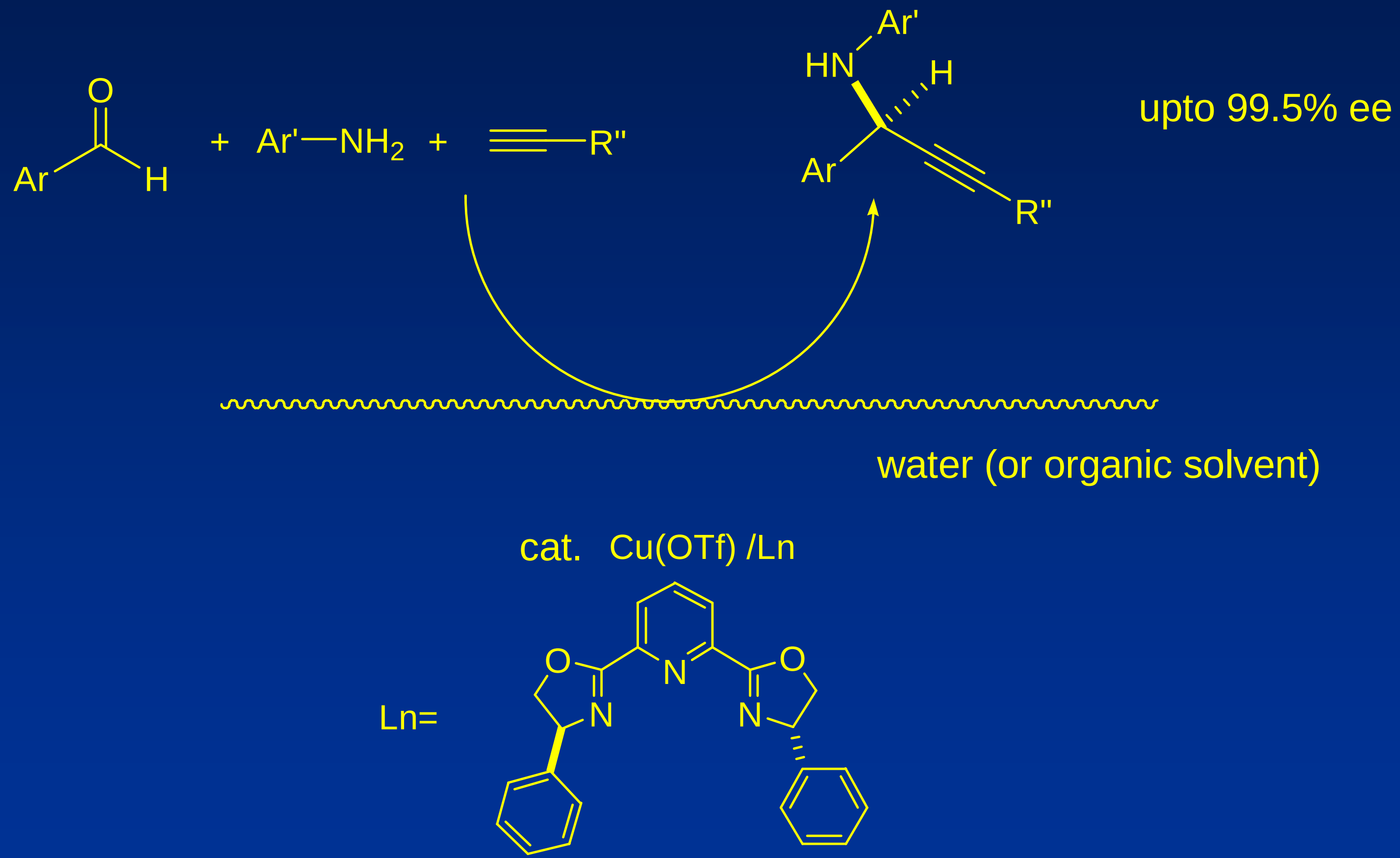

>99% [b]




>99% [b]

[b] Reaction temperature was 70$^{o}$C.

# $AA^3$-Coupling (Asymmetric Aldehyde-Alkyne-Amine Coupling)




Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638;
Wei, C. J.; Mague, J. T. Li, C. J. *Proc. Nat. Acad. Sc. (USA)*, **2004**, *101*, 5749.
Account: Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472.

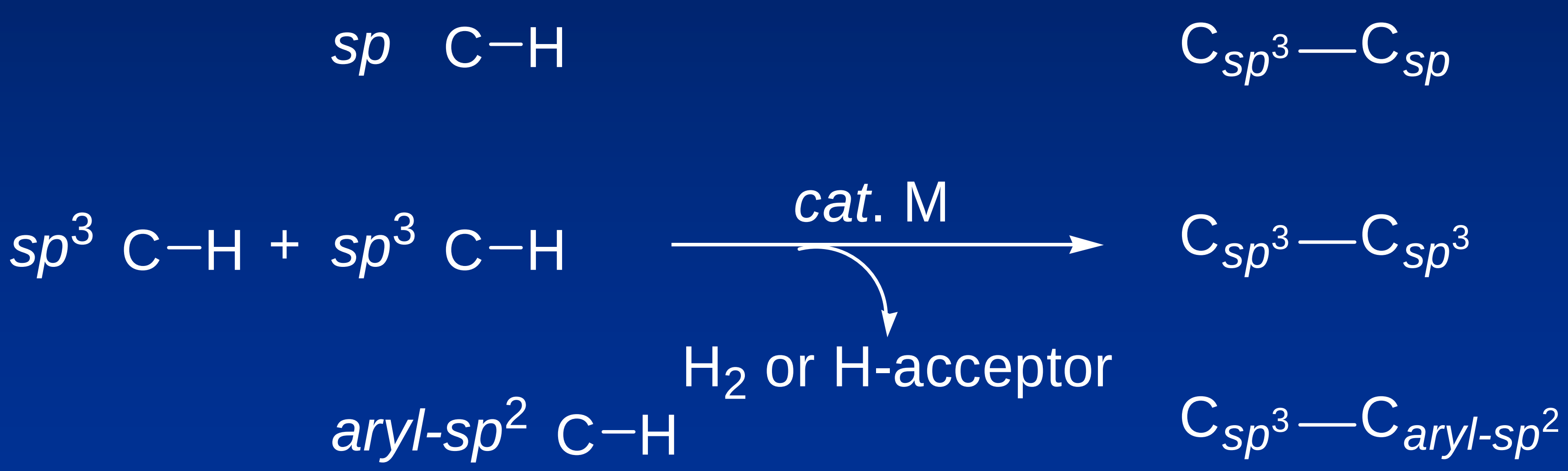
# Beyond Functional Group Chemistry?

$$\text{C-H} + \text{C-H} \longrightarrow \text{C-C}$$

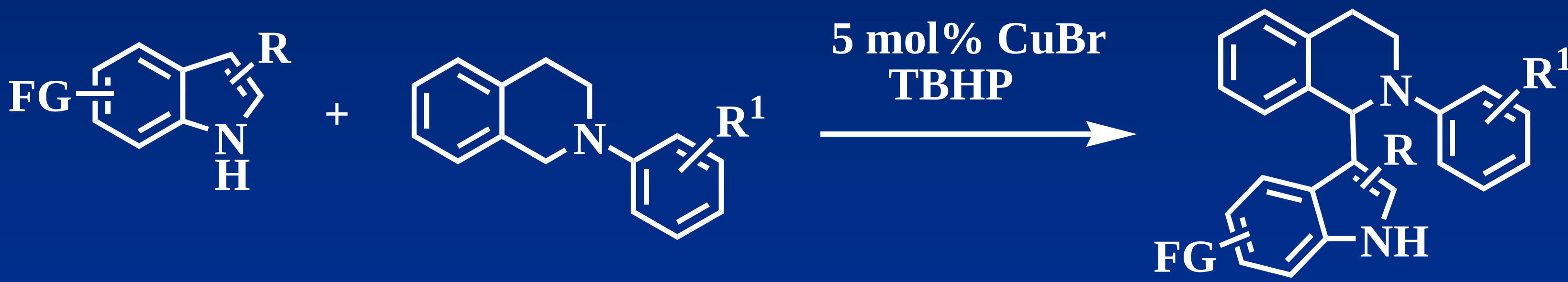
**Cross-Dehydrogenative-Coupling (CDC)**

# Beyond Functional Group Chemistry

***Scheme 1.*** Cross-Dehydrogenative-Coupling (CDC) for the Formation of C-C Bonds



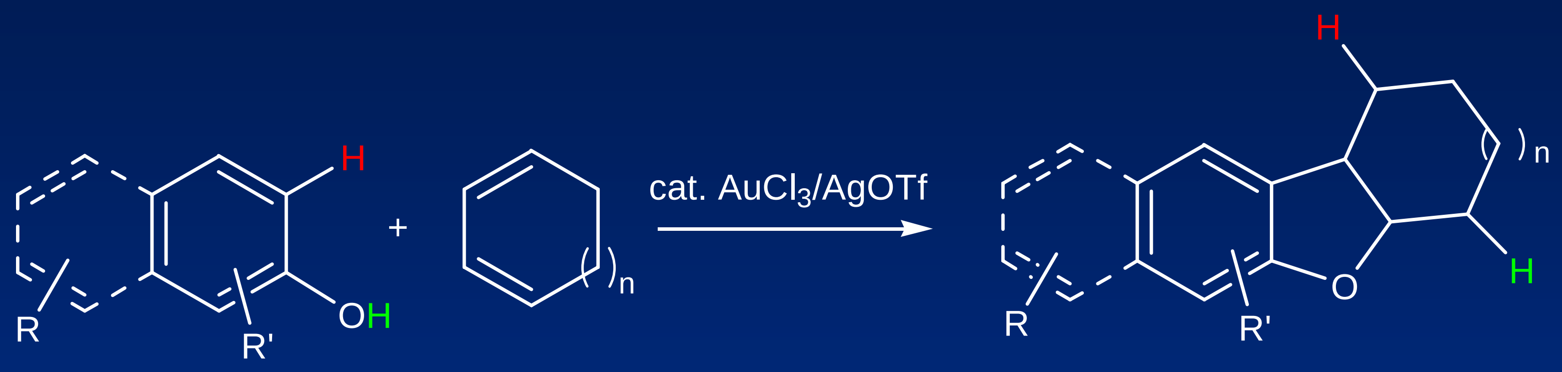
# CDC: $sp^3$ C-H with $sp^2$ C-H




Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.

*C&EN News*, May 23**, 2005**

# Drug-like products in one step




Nguyen, R.;  Li, C.-J. *Org. Lett*. **2006**, 000.

**Other researches:**

**$CO_2$** ⟶ **Fine chemical & polymers**

**biomass** ⟶ **Fine chemicals**

# Materials for Electronics

***CJ Li et al. NASA Report 2005; The SAMPE Meeting (Nov. 2004)***

**Polyimides (wide-range of applications):**

Conventional method

---Increase cost for the feedstock

---Increase cost for the treating the waste

---Increase cost for meeting regulations

---Increase transportation cost

Our solution by new design:

---No waste. No need for treatment, decreased cost for feedstock, decreased cost for meeting regulation.

---Properties are better than or similar to the conventional standard method.

---Now, it has been used in electronics

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"We shall escape the absurdity of growing a whole chicken
in order to eat the breast or wing
[within the next 50 years]
by growing these parts separately
under a suitable medium."

---- Winston Churchill *Fifty Years Hence* (1930)

**Maybe we can apply the same statement to Chemical Synthesis!**

artisticportraits.com/ churchill.jpg