

Green Chemistry: Our Future Challenges in Chemical Synthesis

Great Lakes Pollution-Prevention Roundtable
May 17, 2006

CJ Li
Department of Chemistry
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Canada



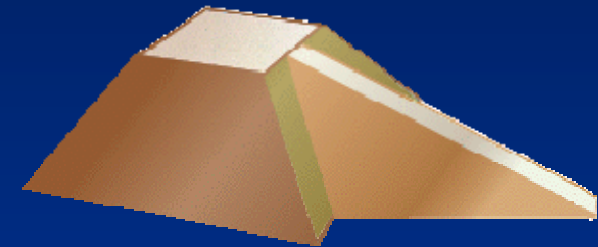
Great Human Achievements

on the Macroscale and Microscale

>2000 years ago, The Great Pyramid



Copyright Lee Krystek, 1999



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Hong Kong, Dec. 2004



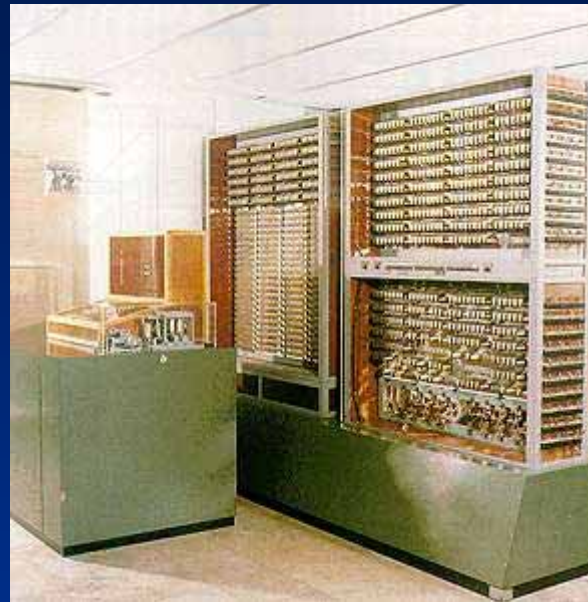
On the nanoscale

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)**



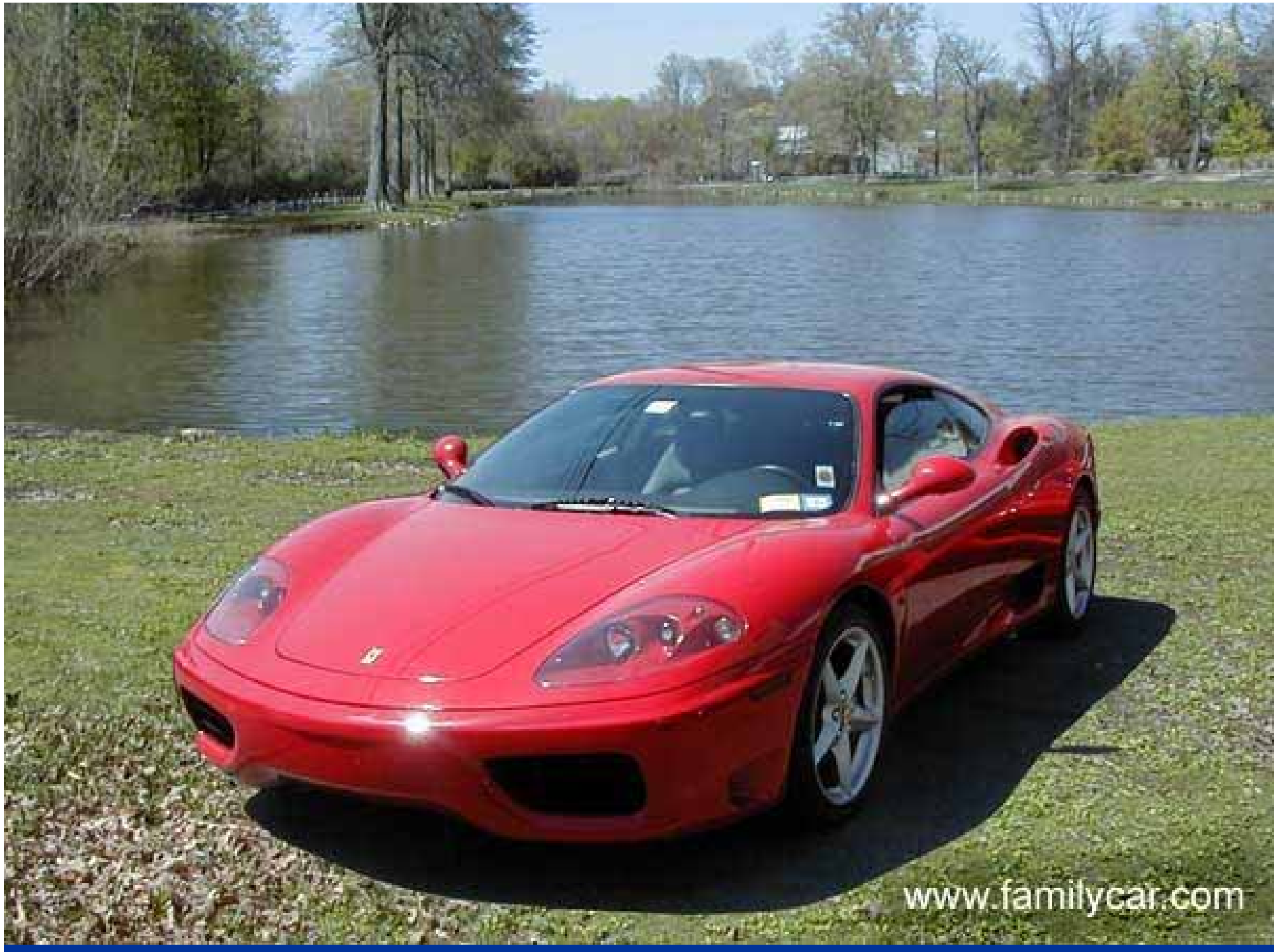
Polyester



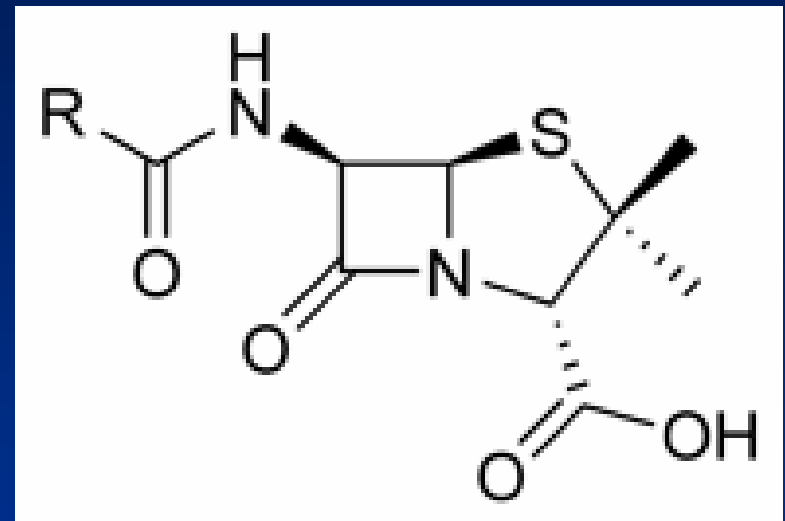
www.supermodels.com

posted to farmphoto.com





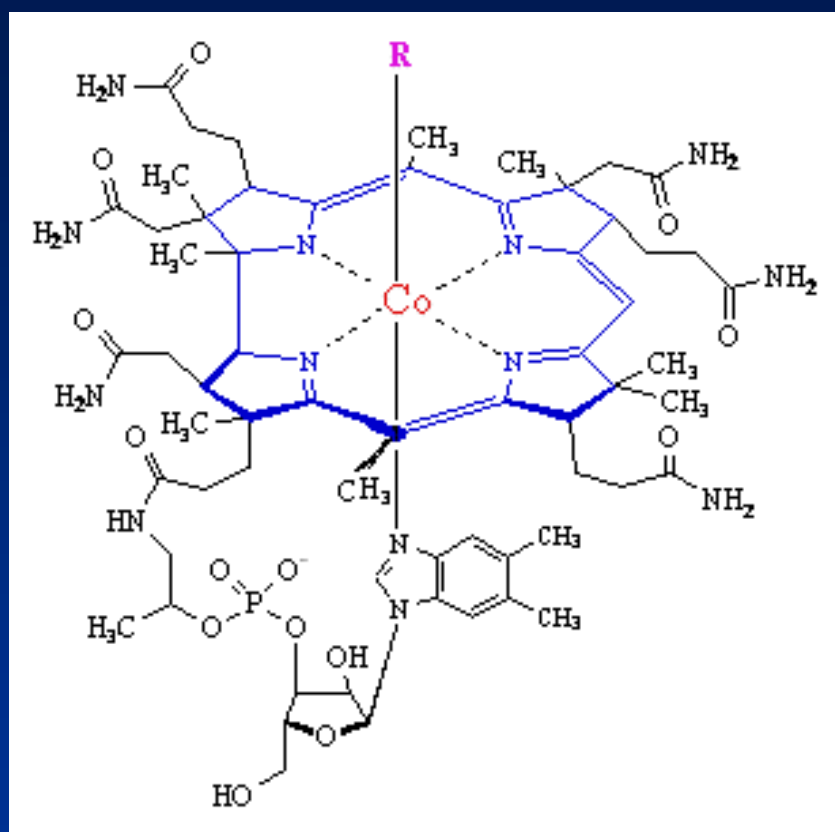
www.familycar.com



<http://www.pbs.org/>

Vitamin B12

On the molecular scale

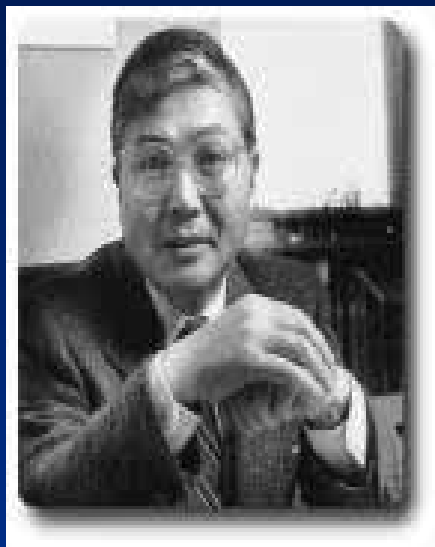


R. B. Woodward (Nobel Prize 1965)

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

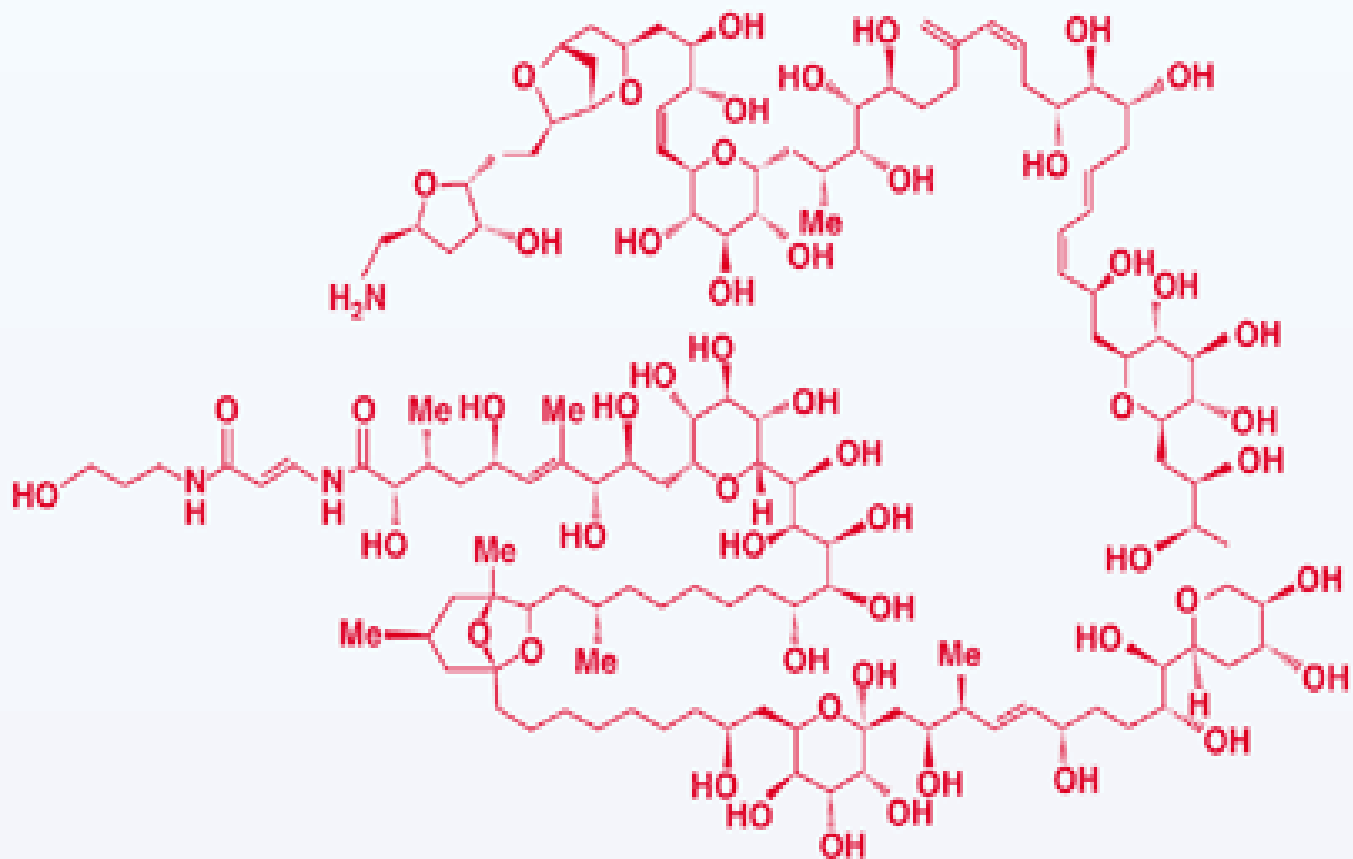
Palytoxin

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:

$2.3 \times 10^{21} = 2300000000000000000000000$ 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

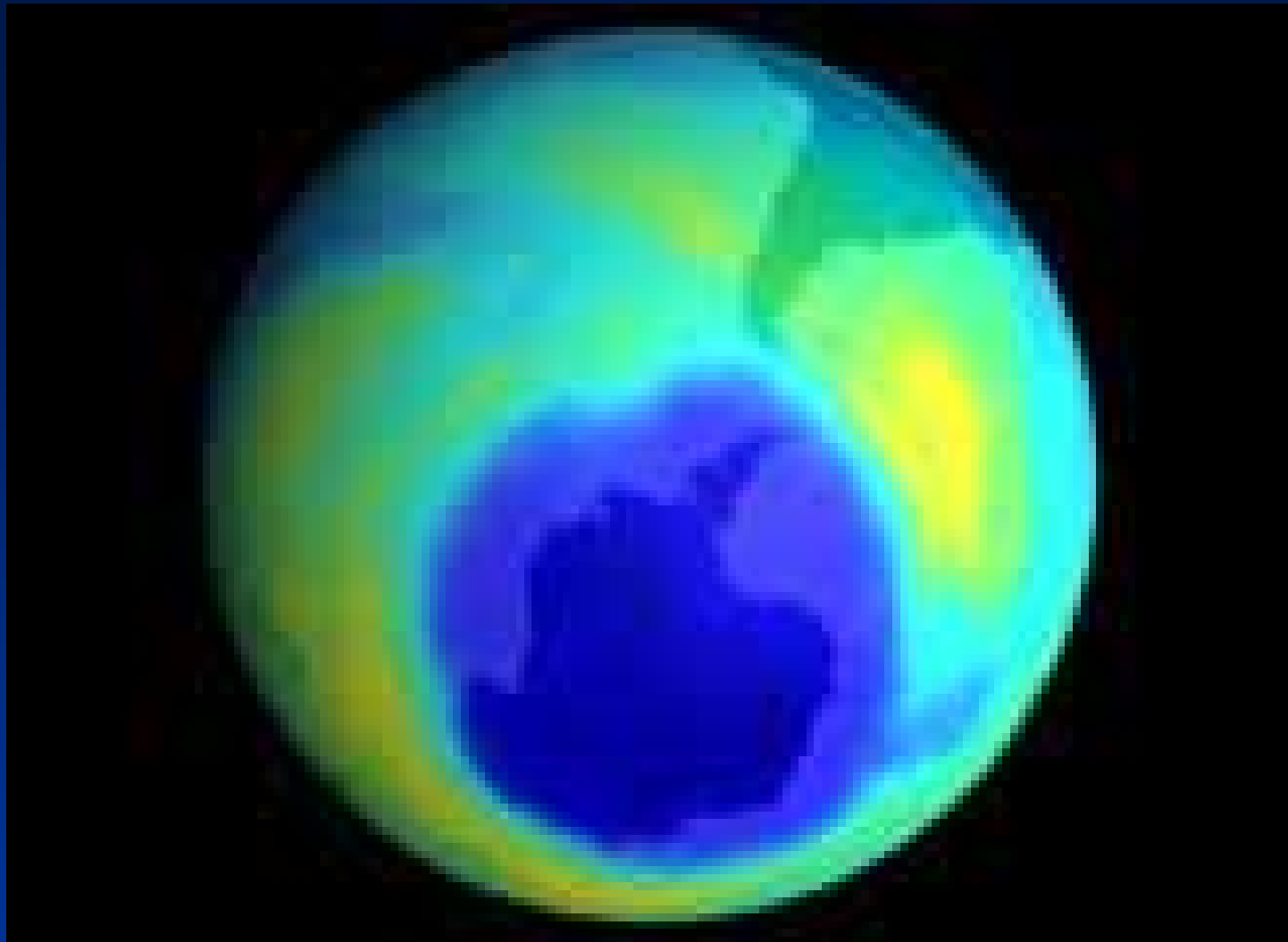
(from Buzz Cue)



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



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



<http://www.coolantarctica.com>



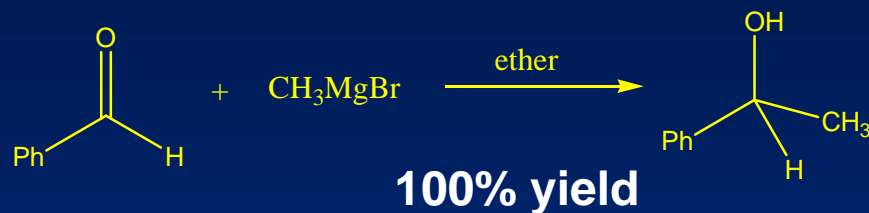
http://www.panda.org/news_facts/education



Wesley Booxe



The Generation of Waste



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)

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

Excluding energy cost and cooling water

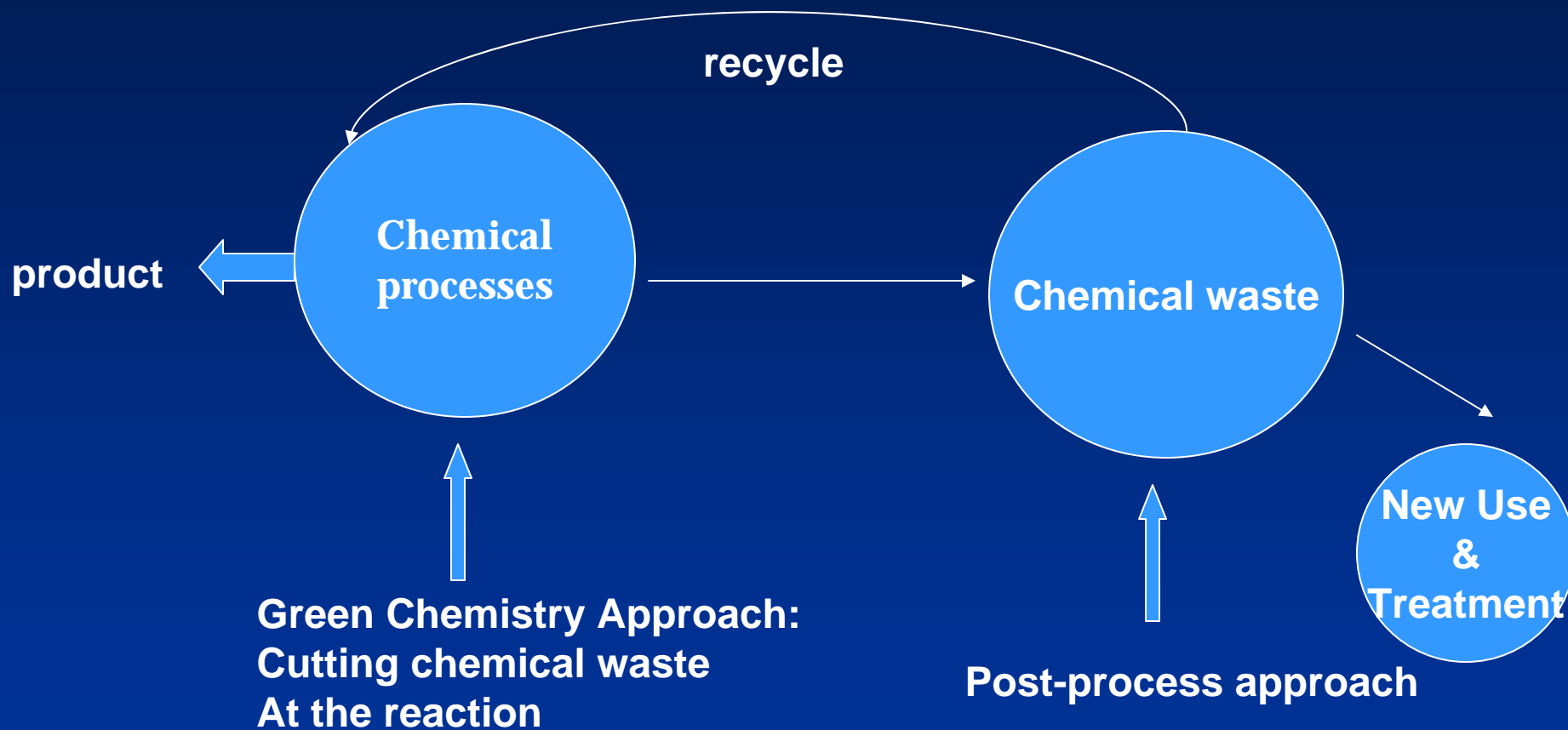
Waste=99.8%

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



ca. 60 steps

Vitamin B12

Starting material



ca. 65 steps

Palytoxin

Synthesis in Nature

Starting material



catalysis/air/water

Vitamin B12

Palytoxin

•The E-Factor:

•(Roger Sheldon)

| Industry segment | Product tonnage | ratio 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+ |

Key Elements in Chemical Syntheses

Media- the solvent- (traditional: organic solvents)

Greener alternatives: water, CO₂, ionic liquids, fluorous.

Separation- (traditional: distillation/crystallization/chromatography)

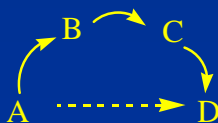
Greener alternatives: self-separation, membrane separation etc.

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 | 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!

CHEMICAL REVIEWS

NONORGANIC, ORGANOMETALLIC, AND TRANSITION-METAL-CATALYZED ORGANIC REACTIONS



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

1993

Chao-Jun Li

Department of Chemistry, Stanford University, Stanford, California 94305-5080

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

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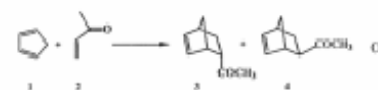


Chao-Jun Li (born in 1963) obtained his B.Sc. in Chemistry from Zhengzhou University, China. After two years of teaching in Henan Medical University, he did his M.Sc. under the supervision of T. H. Chan (McGill University) at the Institute of Chemistry, Academia Sinica, where he received a young Cramer 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.

II. Diels–Alder Reactions and Claisen Rearrangement Reactions

A. Diels–Alder Reactions¹

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.² No further study was carried out until recently. In 1980, Breslow³ 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.⁴ At low concentrations, where both components were completely dissolved, the reaction of cyclopentadiene with butanone 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



I. Introduction

Carbon–carbon bond formation is the essence of organic synthesis. Although the well-known Kolbe synthesis was discovered in 1849⁵ (the first observation was made in 1834 by Faraday),⁶ 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.

1997



Organic
Reactions
in Aqueous
Media

Chao-Jun Li
Tak-Hang Chan

2005

CHEMICAL REVIEWS

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3165

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

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Received January 31, 2005

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10.1021/cr030009a0000 DOI: 10.1039/B400001A © 2005 American Chemical Society
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Research Interests of the Li's Group

Hydrocarbons

CO₂, CO

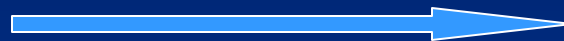
H₂O

N₂, NH₃

Biomass (carbohydrates, lignins)

O₂

Cat.

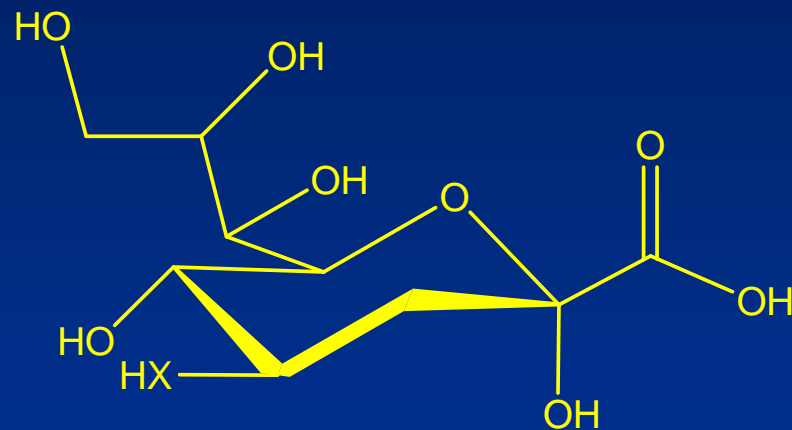


Chemical Products

The environmental, social, economical impact is enormous!

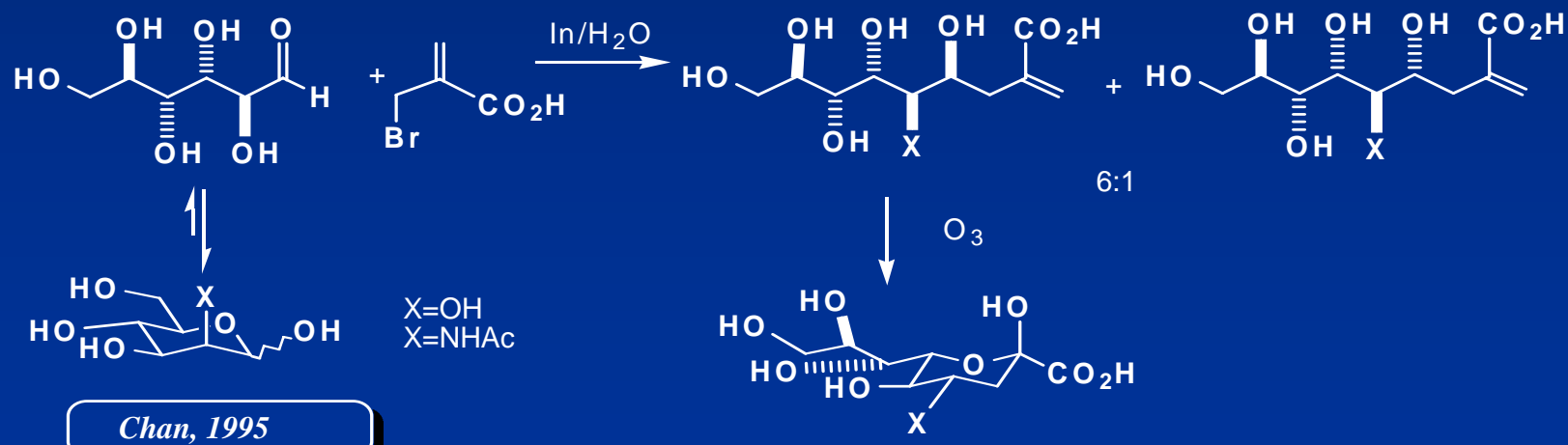
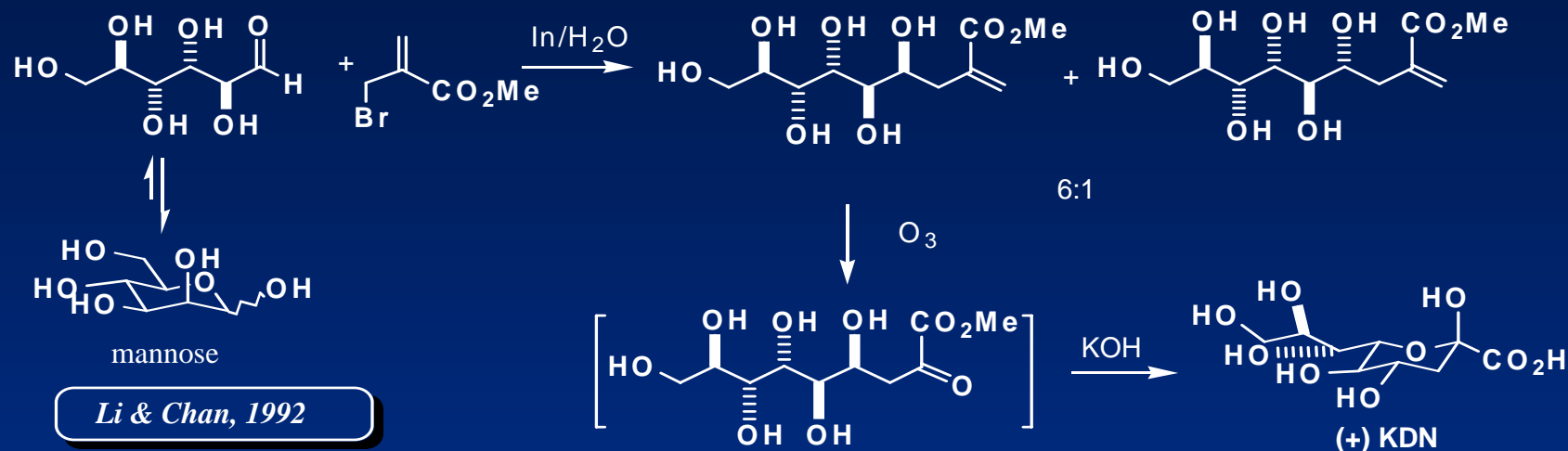
SIALIC ACIDS SYNTHESIS: An Example

Sialic acids

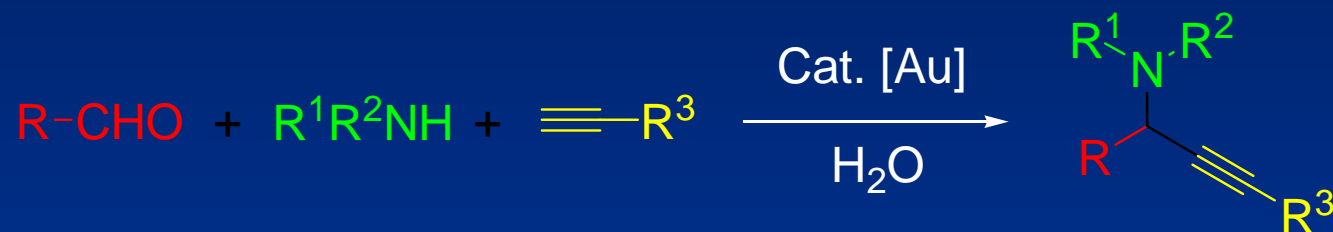


X=O, NH

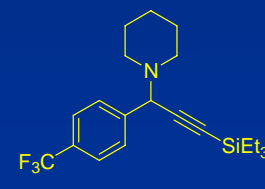
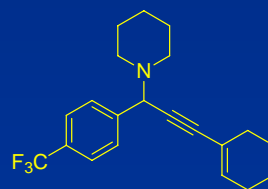
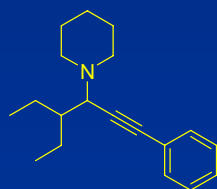
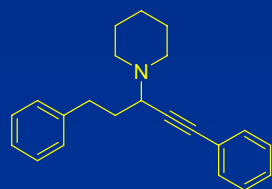
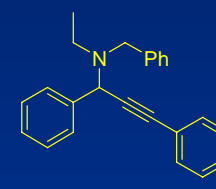
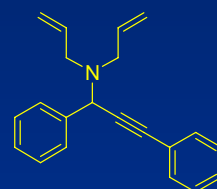
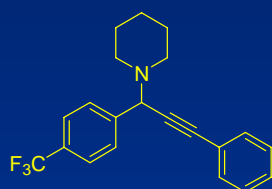
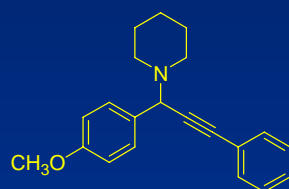
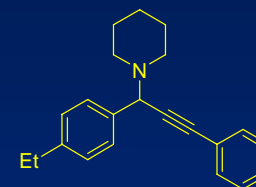
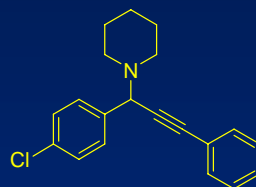
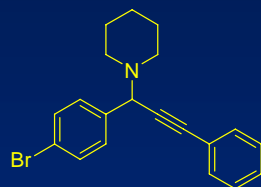
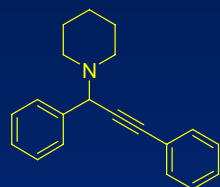
SIALIC ACIDS SYNTHESIS: An Example



Three-Component Coupling of Aldehyde Alkyne and Amine (A³-Coupling) by Gold Catalyst in Water

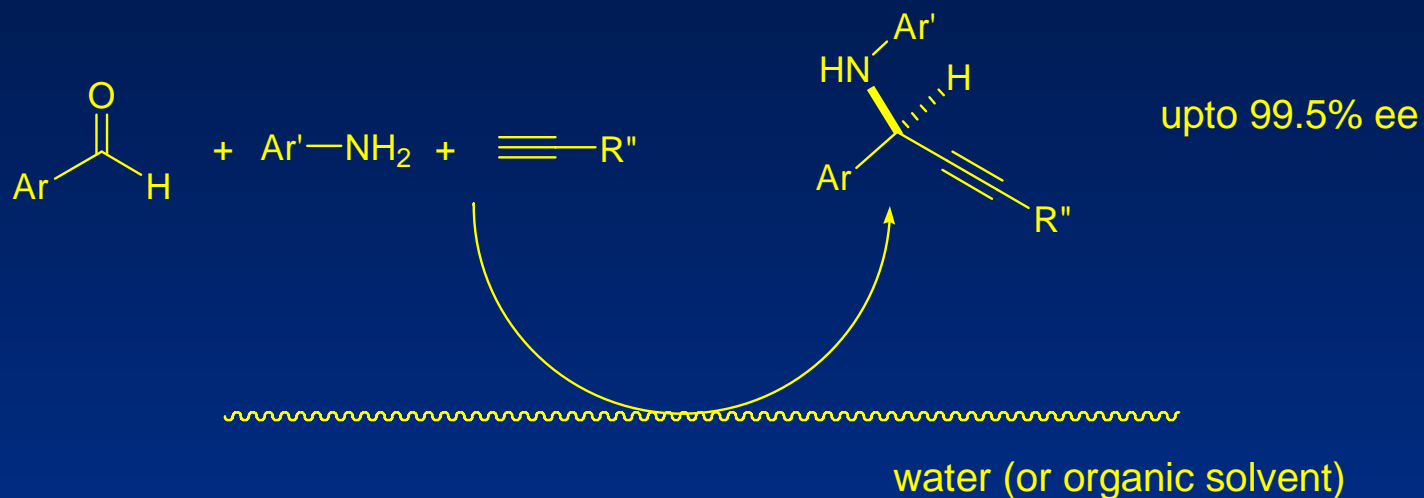


Coupling of Aldehyde, Alkyne and Amine Catalyzed by AuBr₃ in Water

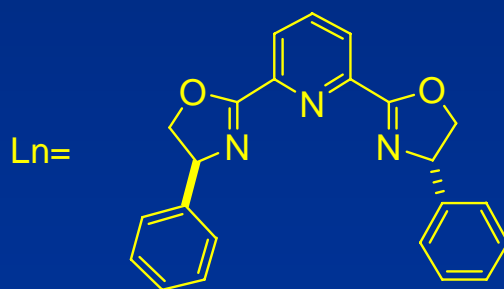


^b Reaction temperature was 70°C.

AA³-Coupling (Asymmetric Aldehyde-Alkyne-Amine Coupling)



cat. $\text{Cu}(\text{OTf})/\text{Ln}$



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.

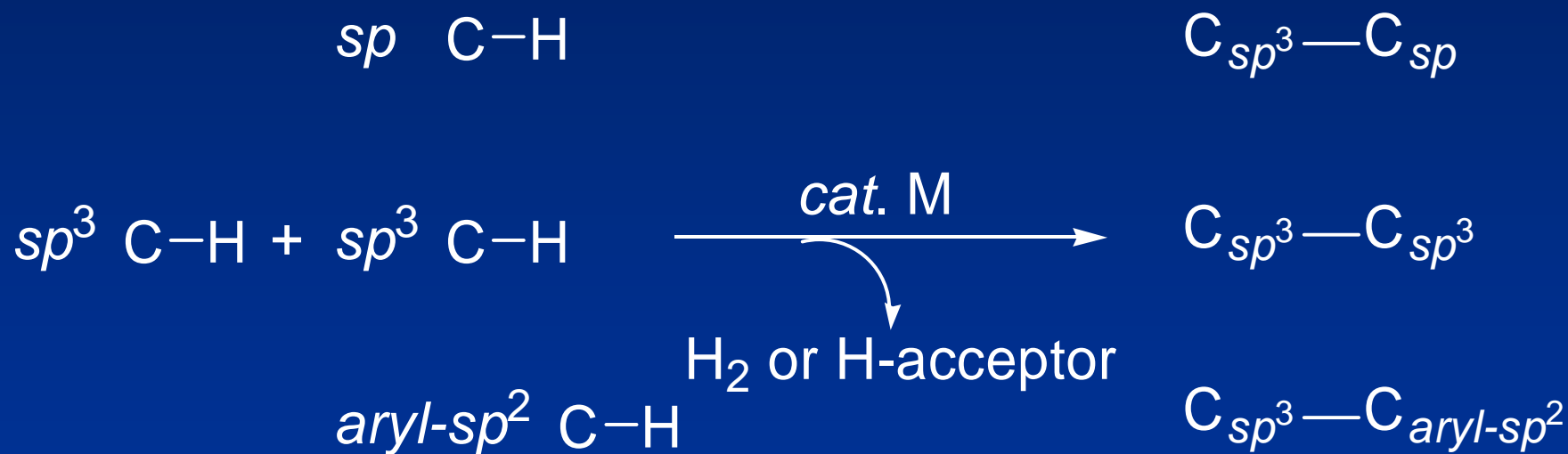
Beyond Functional Group Chemistry?



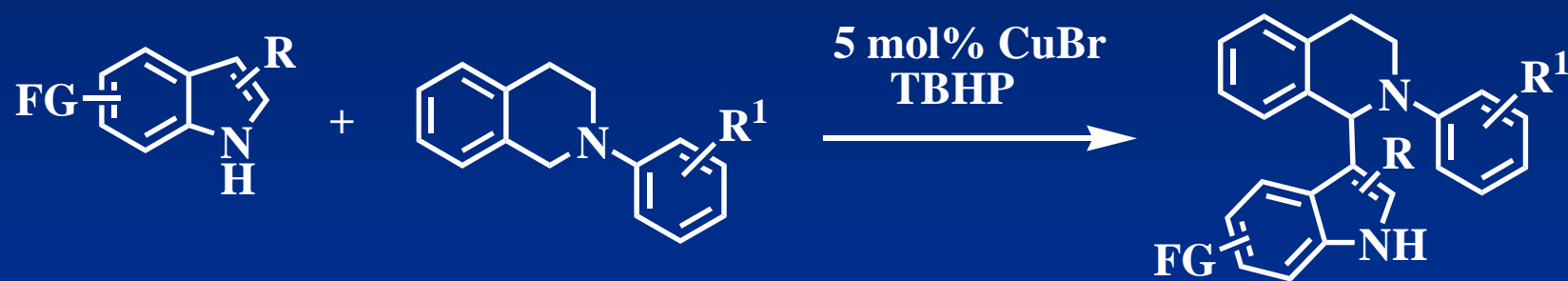
Cross-Dehydrogenative-Coupling (CDC)

Beyond Functional Group Chemistry

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

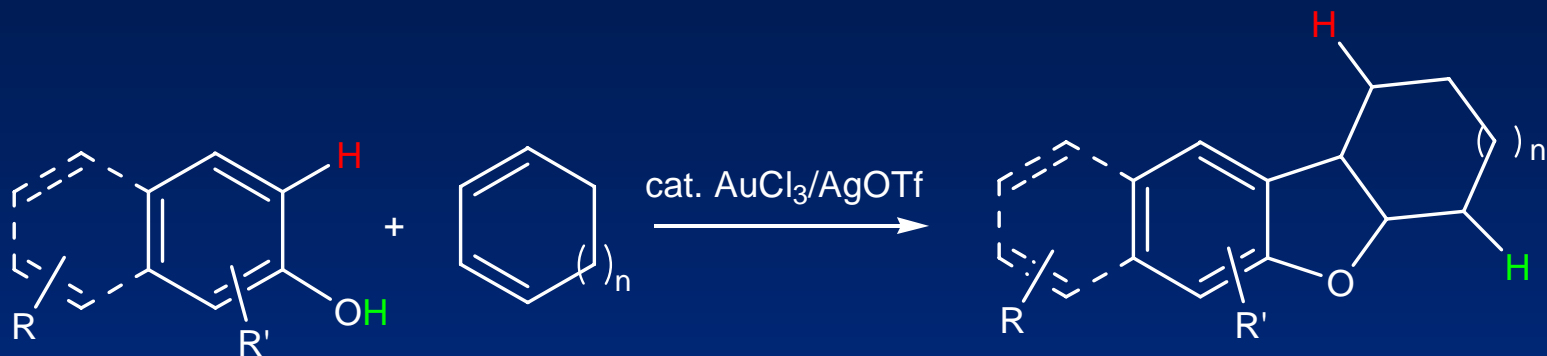


CDC: sp^3 C-H with sp^2 C-H



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

Drug-like products in one step



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

Other researches:

CO₂



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



© 1996-2005
Scientific American



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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](http://artisticportraits.com/churchill.jpg)