Master Course
in Organic Chemistry

2018-19

methods **and design in organic synthesis**

UNIVERSITAT DE BARCELONA

Pere Romea

Blade runner
Ridley Scott, 1982

8. Dreaming the future

I've seen things you people wouldn't believe.

Attack ships on fire off the shoulder of Orion.

I watched C-beams glitter in the dark near the Tannhäuser Gate.

All those moments will be lost in time, like tears in rain.

Time to die.

Tears in the rain, by Roy Batty

Blade Runner

The Dream: Ideal Synthesis


Chapter 1

*An **ideal synthesis** is generally regarded*
as one in which the target molecule is prepared from
readily available, inexpensive starting materials
in one simple, safe, environmental acceptable,
and resource effective operation
that proceeds quickly in a quantitative yield

Hendrickson, J. B. *JACS* **1975**, *97*, 5784; Wender, P. A. *Nature* **2009**, *460*, 197 & *Nat. Prod. Rep.* **2014**, *319*, 433
Baran, P. S. *JOC* **2010**, *75*, 4657

Key Concepts

CHEMO SELECTIVITY

REGIO SELECTIVITY

STEREO SELECTIVITY

Chapter 1, 2 & 7

ATOM ECONOMY

STEP ECONOMY

REDOX ECONOMY

POT ECONOMY

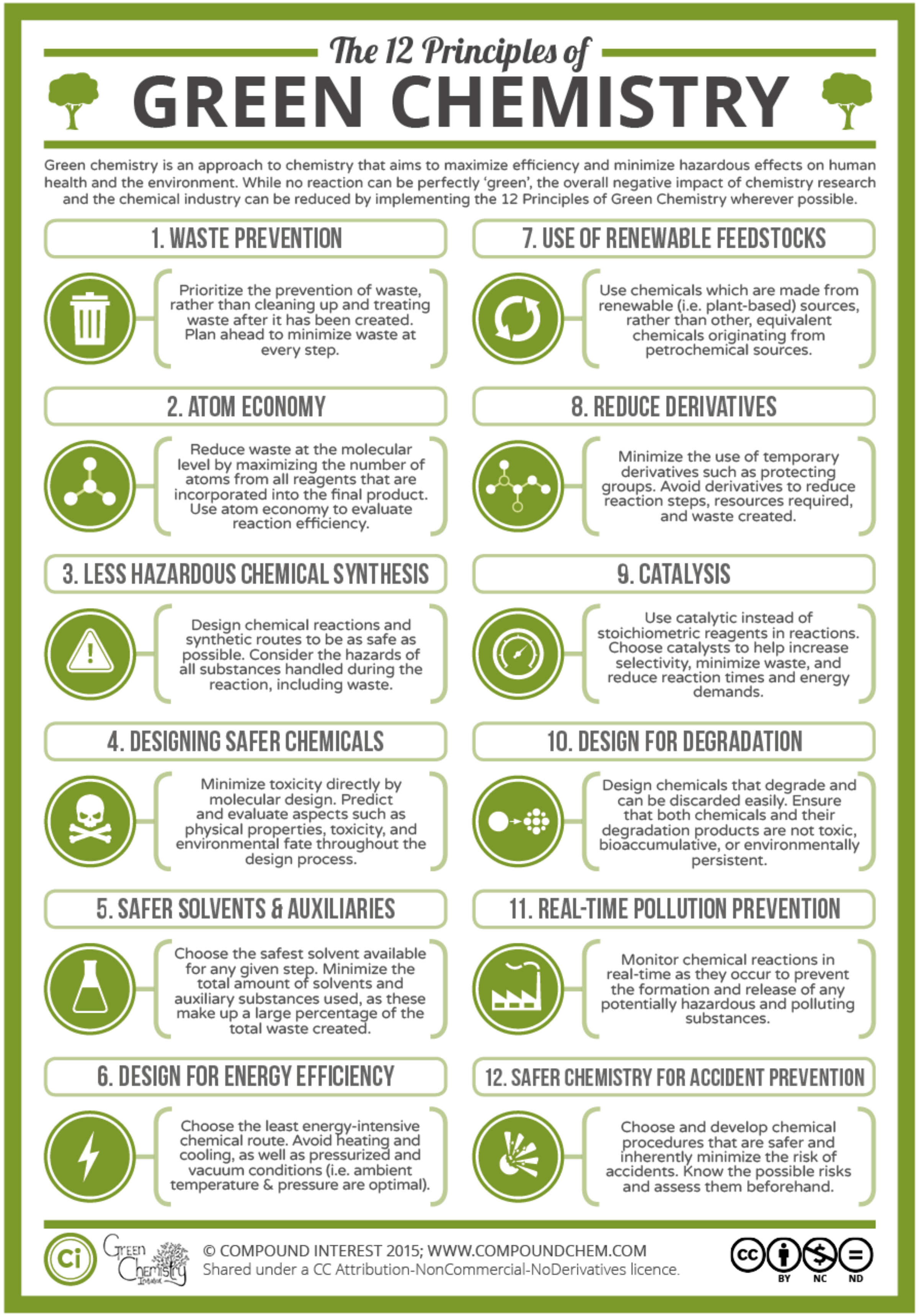
Protecting Group Free Synthesis

Scalability
Practical Synthesis

New chemo, regio, and stereoselective methods are required for the strategic design of a synthetic route to avoid situations where selectivity is a problem

Baran, P. S. *Nat. Prod. Rep.* **2014**, *31*, 419
Allred, T. K. *CR* **2017**, *117*, 11994

Green Chemistry



***Green chemistry** is an ongoing attempt to address the problems that chemicals and chemical processes can sometimes cause*

12 Principles

1. ***Waste Prevention***
2. ***Atom Economy***
3. ***Less Hazardous Chemical Synthesis***
4. ***Designing Safer Chemicals***
5. ***Safer Solvents & Auxiliaries***
6. ***Design for Energy Efficiency***
7. ***Use of Renewable Feedstocks***
8. ***Reduce Derivatives***
9. ***Catalysis***
10. ***Design for Degradation***
11. ***Real Time Pollution Prevention***
12. ***Safer Chemistry for Accident Prevention***

Anastas, P. T. *ACR* **2002**, 35, 686
Lipshutz, B. H. *JOC* **2017**, 82, 2806

Synthetic Metrics

$$\% \textbf{ yield} = \frac{\textit{quantity of product isolated}}{\textit{theoretical quantity of product}} \times 100$$

$$\% \textbf{ atom economy} = \frac{\textit{weight of the desired product}}{\textit{weight of all product}} \times 100$$

$$\textbf{E } (\text{nvironmental}) \textbf{ Factor} = \frac{\textit{mass of waste}}{\textit{mass of product}}$$

Sheldon, R. A. *Green Chem.* **2007**, 9, 1273; Li, C.-J. *PNAS* 2008, 105, 13197
Andraos, J. *OPRD* **2009**, 13, 161; Lipshutz, B. H. *ACIE* **2013**, 52, 10952

$$\% \textbf{ ideality} = \frac{\textit{number of construction rxs + number of strategic redox rxs}}{\textit{total number of steps}} \times 100$$

Baran, P. S. *JOC* **2010**, 75, 4657
[For a recent analysis on *Molecular Complexity*, see Eastgate, M. D. *OBC* **2015**, 13, 7164]

TARGET ORIENTED SYNTHESIS

DIVERSITY ORIENTED SYNTHESIS

DOS was conceived as a novel conceptual alternate to combinatorial chemistry, useful for identifying new targets and for understanding biological functions. It does not rely upon retrosynthetic analysis It includes the development of efficient pathways to a large amount of skeletal and stereochemical diverse small molecules

Schreiber, S. L. *Science* **2000**, *287*, 1964; *Nature* **2009**, *457*, 153
Arya, P. *ACIE* **2001**, *40*, 339

LEAD ORIENTED SYNTHESIS

LOS intends to deliver molecules with specific molecular properties with utility in the drug discovery and optimization process. It pays attention to the physicochemical and FG properties of the target, while also maintaining the synthetic efficiency to allow their cost effective utilization

Churcher, I. *ACIE* **2012**, *51*, 1114

FUNCTION ORIENTED SYNTHESIS

FOS as a strategy to achieve function by design and with synthetic economy.
FOS places an initial emphasis on target design,
thereby harnessing the power of chemists and computers to create new structures with desired functions that could be prepared in a simple, safe, economical, and green, if not ideal, fashion

Wender, P. A. *ACR* **2007**, *41*, 40; **2015**, *48*, 752
Sheng, C. *CR* **2019**, *119*, 4181

BIOLOGICAL ORIENTED SYNTHESIS

The key criterion to generate hypotheses for the design and synthesis of focused compound libraries in BIOS is the biological relevance.
As scaffolds of natural products can be considered as *privileged structures* chosen in evolution, their structures can be viewed as good starting points for compound collection development

Antonchick, A. P.; Waldmann, H. *ACR* **2014**, *47*, 1296

Dreaming the Future

Look beyond what you see

CATALYSIS

STEREOCONTROLLED METHODS

C–H ACTIVATION

LATE-STATE FUNCTIONALIZATION

PHOTOCHEMISTRY