

Master Course
in Organic Chemistry

2018-19

methods and design
in organic synthesis



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*

Key Concepts

CHEMO SELECTIVITY

REGIO SELECTIVITY

STEREO SELECTIVITY



**Protecting Group Free
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



Chapter 1, 2 & 7



ATOM ECONOMY

STEP ECONOMY

REDOX ECONOMY

POT ECONOMY



**Scalability
Practical Synthesis**

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

Green Chemistry

The 12 Principles of GREEN CHEMISTRY

Green chemistry is an approach to chemistry that aims to maximize efficiency and minimize hazardous effects on human health and the environment. While no reaction can be perfectly 'green', the overall negative impact of chemistry research and the chemical industry can be reduced by implementing the 12 Principles of Green Chemistry wherever possible.

1. WASTE PREVENTION



Prioritize the prevention of waste, rather than cleaning up and treating waste after it has been created. Plan ahead to minimize waste at every step.

7. USE OF RENEWABLE FEEDSTOCKS



Use chemicals which are made from renewable (i.e. plant-based) sources, rather than other, equivalent chemicals originating from petrochemical sources.

2. ATOM ECONOMY



Reduce waste at the molecular level by maximizing the number of atoms from all reagents that are incorporated into the final product. Use atom economy to evaluate reaction efficiency.

8. REDUCE DERIVATIVES



Minimize the use of temporary derivatives such as protecting groups. Avoid derivatives to reduce reaction steps, resources required, and waste created.

3. LESS HAZARDOUS CHEMICAL SYNTHESIS



Design chemical reactions and synthetic routes to be as safe as possible. Consider the hazards of all substances handled during the reaction, including waste.

9. CATALYSIS



Use catalytic instead of stoichiometric reagents in reactions. Choose catalysts to help increase selectivity, minimize waste, and reduce reaction times and energy demands.

4. DESIGNING SAFER CHEMICALS



Minimize toxicity directly by molecular design. Predict and evaluate aspects such as physical properties, toxicity, and environmental fate throughout the design process.

10. DESIGN FOR DEGRADATION



Design chemicals that degrade and can be discarded easily. Ensure that both chemicals and their degradation products are not toxic, bioaccumulative, or environmentally persistent.

5. SAFER SOLVENTS & AUXILIARIES



Choose the safest solvent available for any given step. Minimize the total amount of solvents and auxiliary substances used, as these make up a large percentage of the total waste created.

11. REAL-TIME POLLUTION PREVENTION



Monitor chemical reactions in real-time as they occur to prevent the formation and release of any potentially hazardous and polluting substances.

6. DESIGN FOR ENERGY EFFICIENCY



Choose the least energy-intensive chemical route. Avoid heating and cooling, as well as pressurized and vacuum conditions (i.e. ambient temperature & pressure are optimal).

12. SAFER CHEMISTRY FOR ACCIDENT PREVENTION



Choose and develop chemical procedures that are safer and inherently minimize the risk of accidents. Know the possible risks and assess them beforehand.

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



Synthetic Metrics

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

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

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

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

$$\% \text{ ideality} = \frac{\text{number of construction rxns} + \text{number of strategic redox rxns}}{\text{total number of steps}} \times 100$$

Baran, P. S. *JOC* **2010**, 75, 4657

[For a recent analysis on *Molecular Complexity*, see Eastgate, M. D. *OBC* **2015**, 13, 7164]

Perspectives on Synthesis

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

Perspectives on Synthesis

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