D-Carbonize Workshop & Kick-off

Organic Chemistry

Eduardo García-Verdugo

cepeda@uji.es

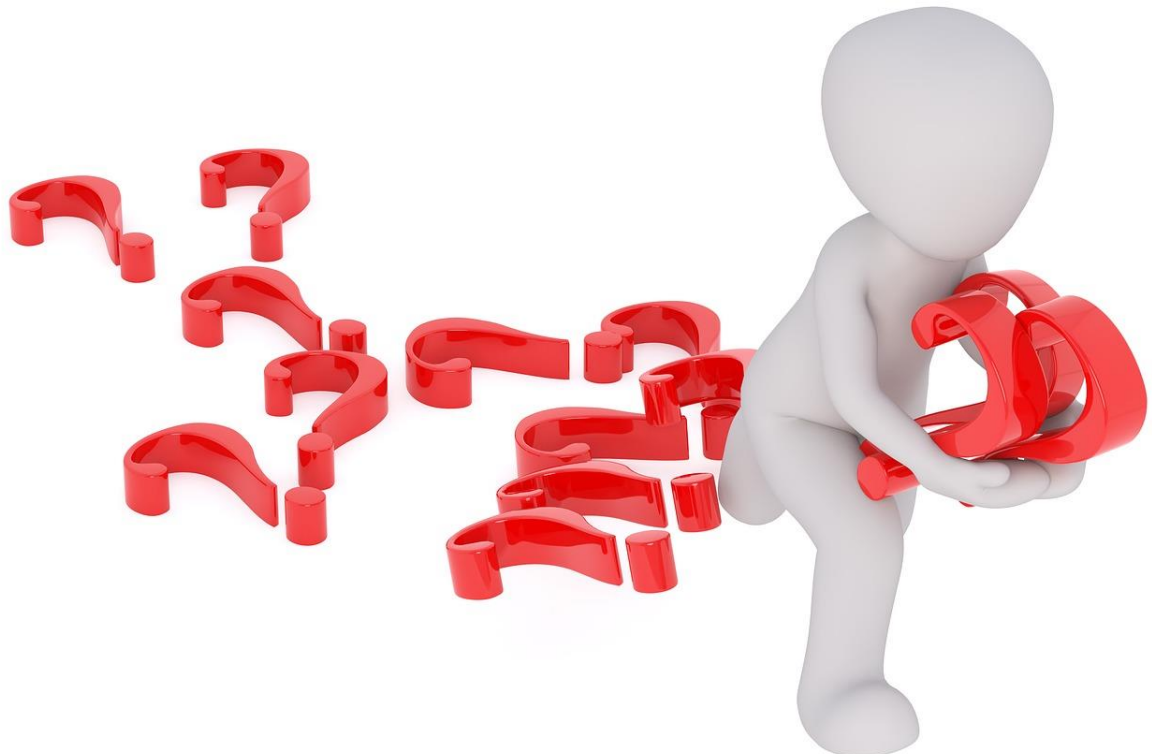
www.quimicasostenible.uji.es
www.miqs.uji.es

Supramolecular and Sustainable Chemistry Group

Grupo de Química Sostenible y Supramolecular

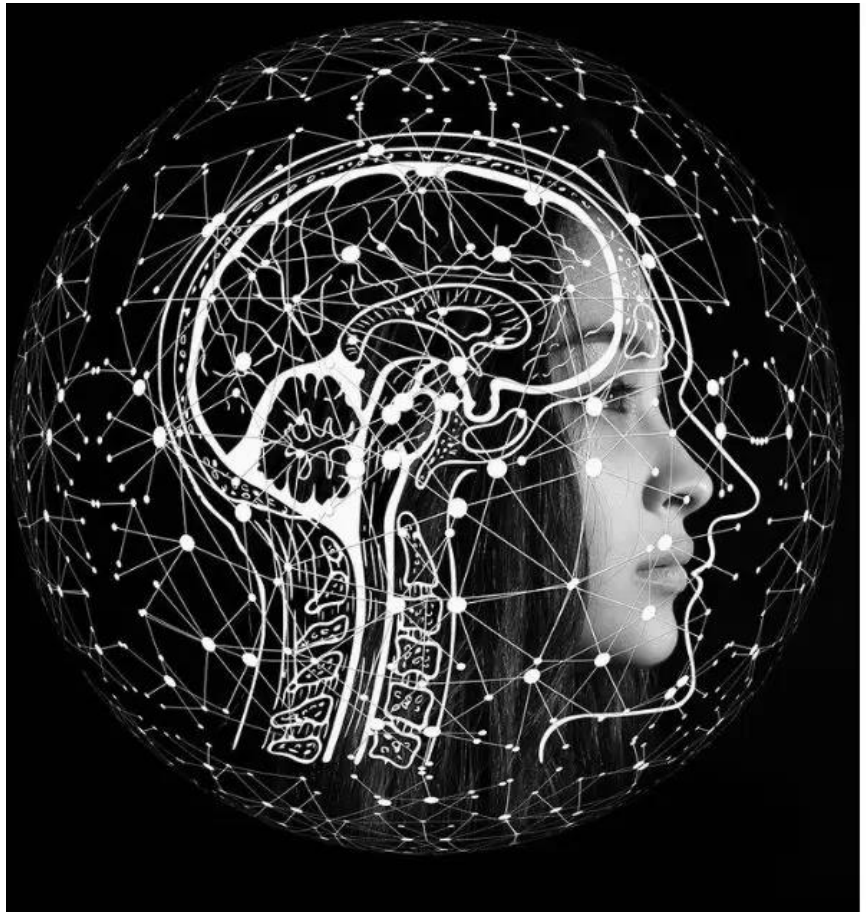
UNIVERSITAT JAUME·I

Introduction to Organic Chemistry



Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

Organic Chemistry



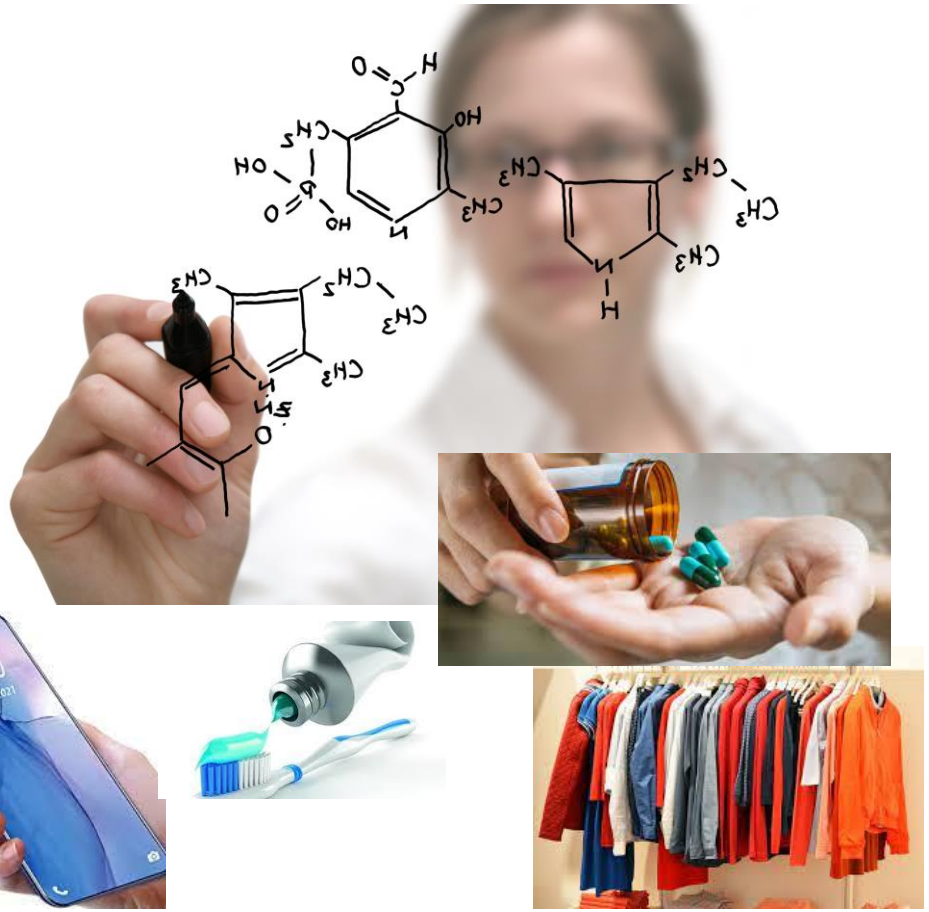
What is an organic Chemist?

Organic chemists investigate the structure, properties, composition, reactions, and synthesis of organic molecules.

Molecules Makers

Their **work is crucial in many fields**, including pharmaceuticals, petrochemicals, food science, and materials science contributing to the development of new drugs, plastics, cleaners, and many other products

We are important



What is an organic Chemist?

What do you think when you read this product label?

INGREDIENTS: WATER (75%), **SUGARS (12%)** (GLUCOSE (48%), FRUCTOSE (40%), SUCROSE (2%), MALTOSE (<1%)), STARCH (5%), FIBRE E460 (3%), **AMINO ACIDS (<1%)** (GLUTAMIC ACID (19%), ASPARTIC ACID (16%), HISTIDINE (11%), LEUCINE (7%), LYSINE (5%), PHENYLALANINE (4%), ARGININE (4%), VALINE (4%), ALANINE (4%), SERINE (4%), GLYCINE (3%), THREONINE (3%), ISOLEUCINE (3%), PROLINE (3%), TRYPTOPHAN (1%), CYSTINE (1%), TYROSINE (1%), METHIONINE (1%)), **FATTY ACIDS (1%)** (PALMITIC ACID (30%), OMEGA-6 FATTY ACID: LINOLEIC ACID (14%), OMEGA-3 FATTY ACID: LINOLENIC ACID (8%), OLEIC ACID (7%), PALMITOLEIC ACID (3%), STEARIC ACID (2%), LAURIC ACID (1%), MYRISTIC ACID (1%), CAPRIC ACID (<1%)), ASH (<1%), PHYTOSTEROLS, E515, OXALIC ACID, E300, E306 (TOCOPHEROL), PHYLLOQUINONE, THIAMIN, **COLOURS** (YELLOW-ORANGE E101 (RIBOFLAVIN), YELLOW-BROWN E160a), **FLAVOURS** (3-METHYLBUT-1-YL ETHANOATE, 2-METHYLBUTYL ETHANOATE, 2-METHYLPROPAN-1-OL, 3-METHYLBUTYL-1-OL, 2-HYDROXY-3-METHYLETHYL BUTANOATE, 3-METHYLBUTANAL, ETHYL HEXANOATE, ETHYL BUTANOATE, PENTYL ACETATE), 1510, NATURAL RIPENING AGENT (ETHENE GAS).

Would you like to buy it?

Chemophobia

AN ALL-NATURAL BANANA

INGREDIENTS: WATER (75%), **SUGARS (12%)** (GLUCOSE (48%), FRUCTOSE (40%), SUCROSE (2%), MALTOSE (<1%)), STARCH (5%), FIBRE E460 (3%), **AMINO ACIDS (<1%)** (GLUTAMIC ACID (19%), ASPARTIC ACID (16%), HISTIDINE (11%), LEUCINE (7%), LYSINE (5%), PHENYLALANINE (4%), ARGININE (4%), VALINE (4%), ALANINE (4%), SERINE (4%), GLYCINE (3%), THREONINE (3%), ISOLEUCINE (3%), PROLINE (3%), TRYPTOPHAN (1%), CYSTINE (1%), TYROSINE (1%), METHIONINE (1%)), **FATTY ACIDS (1%)** (PALMITIC ACID (30%), OMEGA-6 FATTY ACID: LINOLEIC ACID (14%), OMEGA-3 FATTY ACID: LINOLENIC ACID (8%), OLEIC ACID (7%), PALMITOLEIC ACID (3%), STEARIC ACID (2%), LAURIC ACID (1%), MYRISTIC ACID (1%), CAPRIC ACID (<1%)), ASH (<1%), PHYTOSTEROLS, E515, OXALIC ACID, E300, E306 (TOCOPHEROL), PHYLLOQUINONE, THIAMIN, **COLOURS** (YELLOW-ORANGE E101 (RIBOFLAVIN), YELLOW-BROWN E160a), **FLAVOURS** (3-METHYLBUT-1-YL ETHANOATE, 2-METHYLBUTYL ETHANOATE, 2-METHYLPROPAN-1-OL, 3-METHYLBUTYL-1-OL, 2-HYDROXY-3-METHYLETHYL BUTANOATE, 3-METHYLBUTANAL, ETHYL HEXANOATE, ETHYL BUTANOATE, PENTYL ACETATE), 1510, NATURAL RIPENING AGENT (ETHENE GAS).

Diseño original: James Kennedy (jameskennedymonash.wordpress.com)

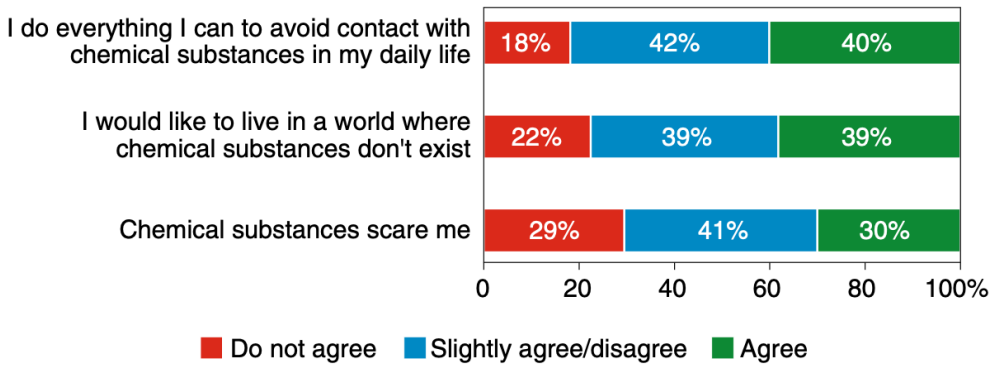
- Chemistry is perceived as synonymous with **'artificial'** and **'dangerous'.**
- A society that **rejects chemistry**.
- The media and the misuse of marketing promote a distorted and unfair vision **"chemical –free"**

comment

Chemophobia in Europe and reasons for biased risk perceptions

Very few consumers are aware that chemistry and synthetic chemicals are indispensable in making everyday goods

Chemophobia: views of European consumers
(n = 5,631)



Siegrist, M., Bearth, A. Chemophobia in Europe and reasons for biased risk perceptions. *Nat. Chem.* **11**, 1071–1072 (2019). https://doi.org/10.1038/s41557-019-0377-8

Chemophobia: A systematic review, R. Rollini, L. Falciola, S. Tortorella, Tetrahedron, 2022, 113, 132758
DOI: 10.1016/j.tet.2022.132758

Describing the public perception of chemistry on twitter,
Chem. Educ. Res. Pract., 2020, **21**, 989-999, 10.1039/C9RP00282K

Chalupa, R., Nesměrák, K. Chemophobia and passion: why chemists should desire Marcel Proust. *Monatsh Chem* **153**, 697–705 (2022), https://doi.org/10.1007/s00706-022-02945-5

Rebranding

I am …

Chemists

Rebranding

I am …

Chemists

Rebranding

I am …

Chemists

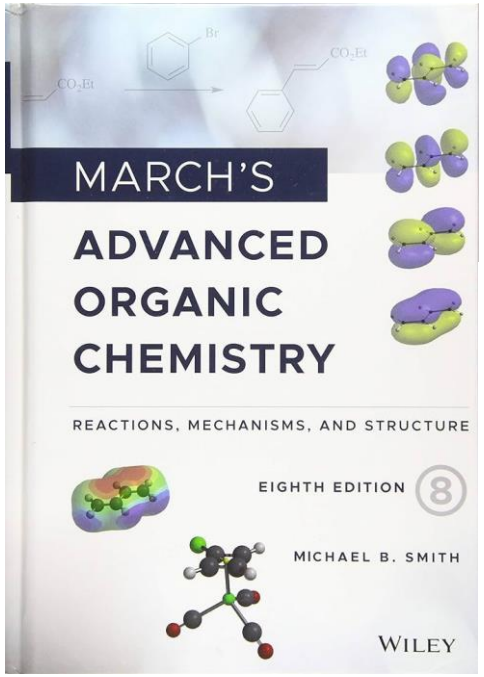
Molecular Designers

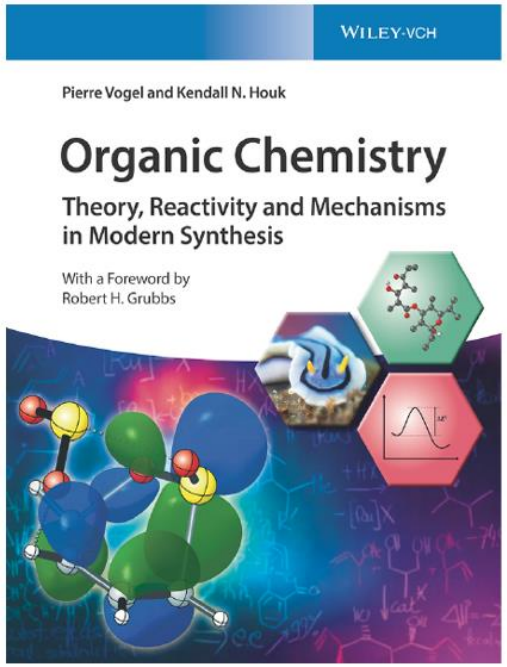
Organic Chemistry

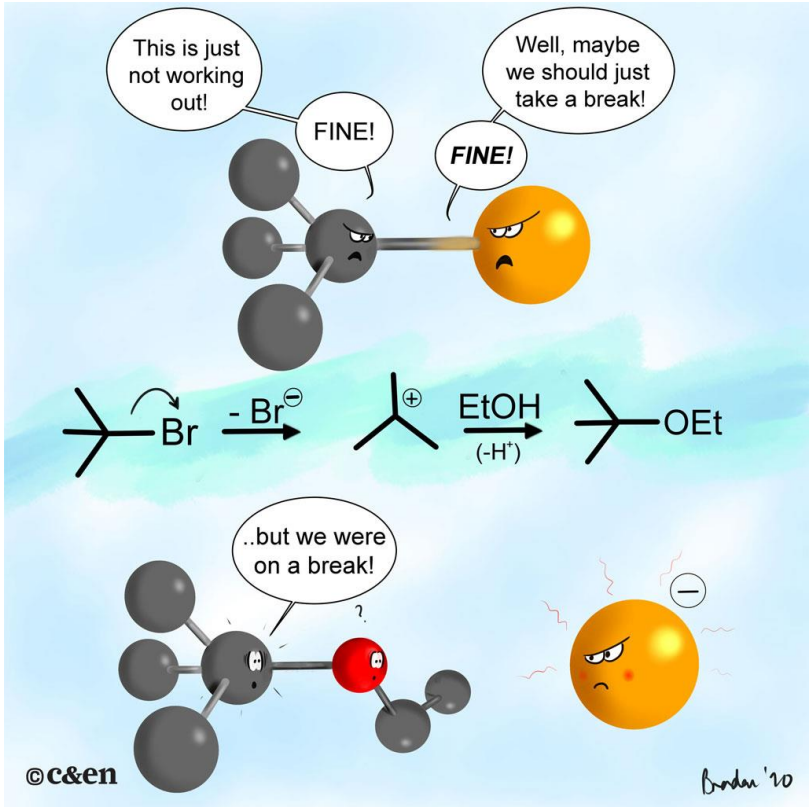
Organic chemists investigate the structure, properties, composition, reactions, and synthesis of organic molecules.

Organic Chemistry

Organic chemists investigate the structure, properties, composition, reactions, and synthesis of organic molecules.

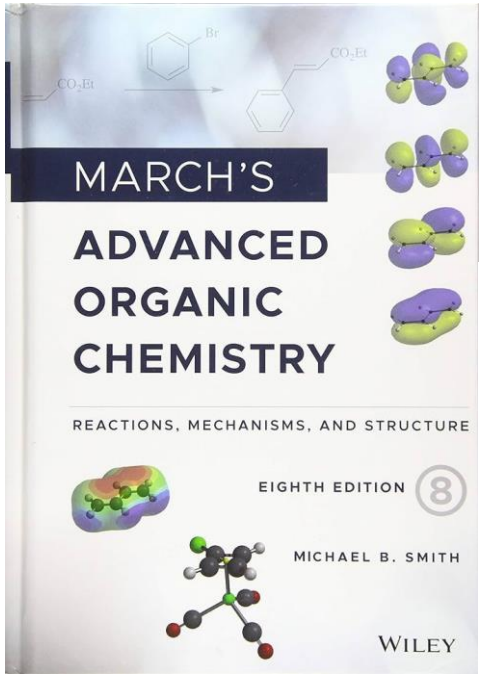


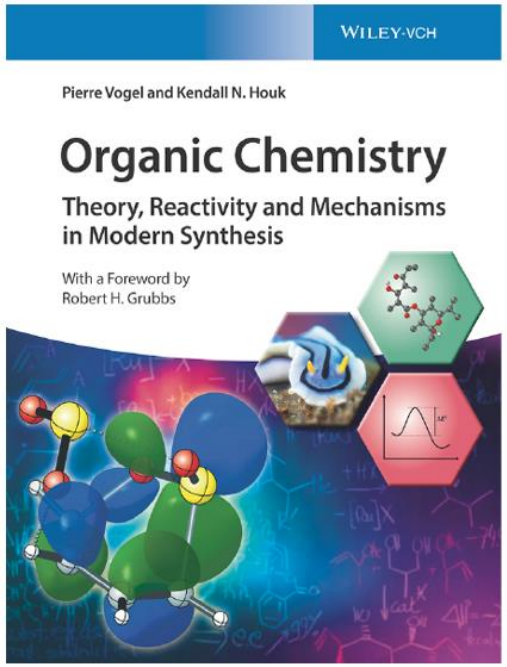


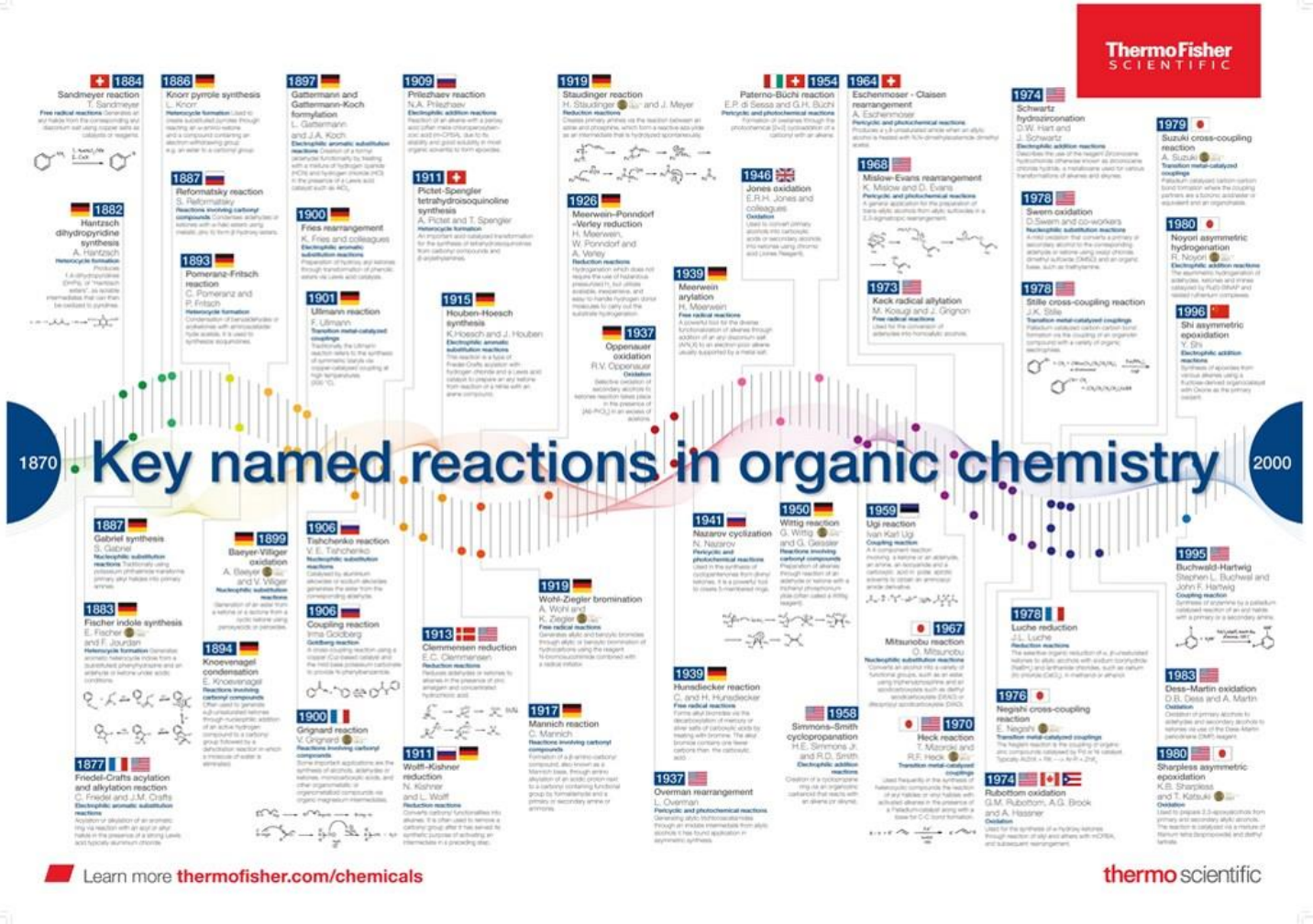


Perception Organic Chemistry

Organic chemistry is known for its complexity and diversity because the carbon atom can form strong bonds with many other types of atoms and can form chains and rings, allowing for the creation of an immense variety of molecules.





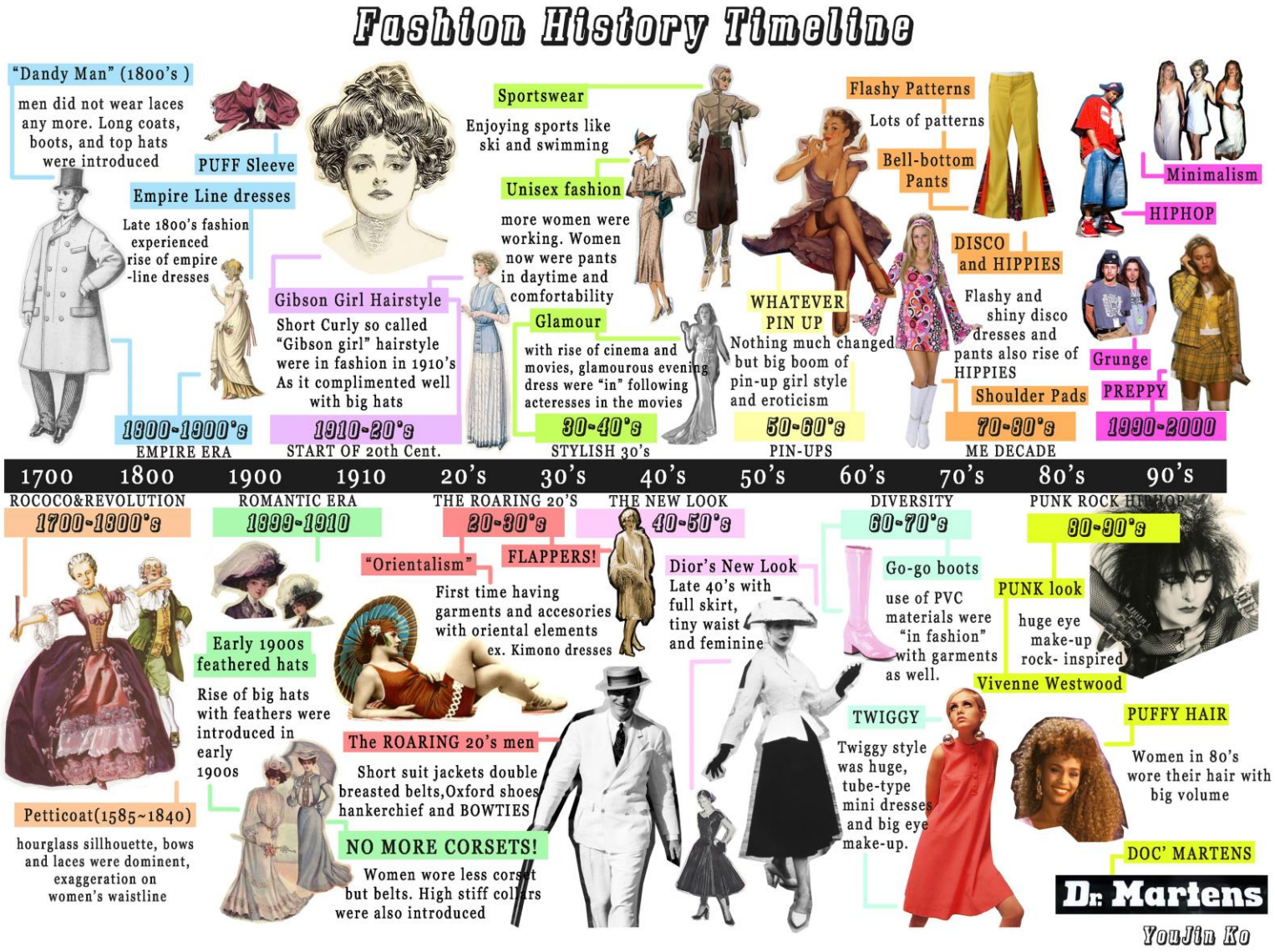


What is the fashion trend in organic Chemist?

Molecular Designers

What is the fashion trend in organic Chemist?

Molecular Designers



Chemists Use Ancient Chemistries !

The evolution of organic chemistry over the years has been marked by significant changes in the types of reactions discovered and utilized by chemists. A hundred years ago, the field was dominated by relatively simple reactions like esterifications and Michael additions. However, from around 1960 to 1980, there was a notable shift towards more complex reaction classes, such as cycloadditions and Pauson–Khand reactions.

A random selection of 100 chemistries in a review of named reactions:

54% *before* World War 1

74% *before* World War 2

91% *before* 1975

9% *during* the 1980's

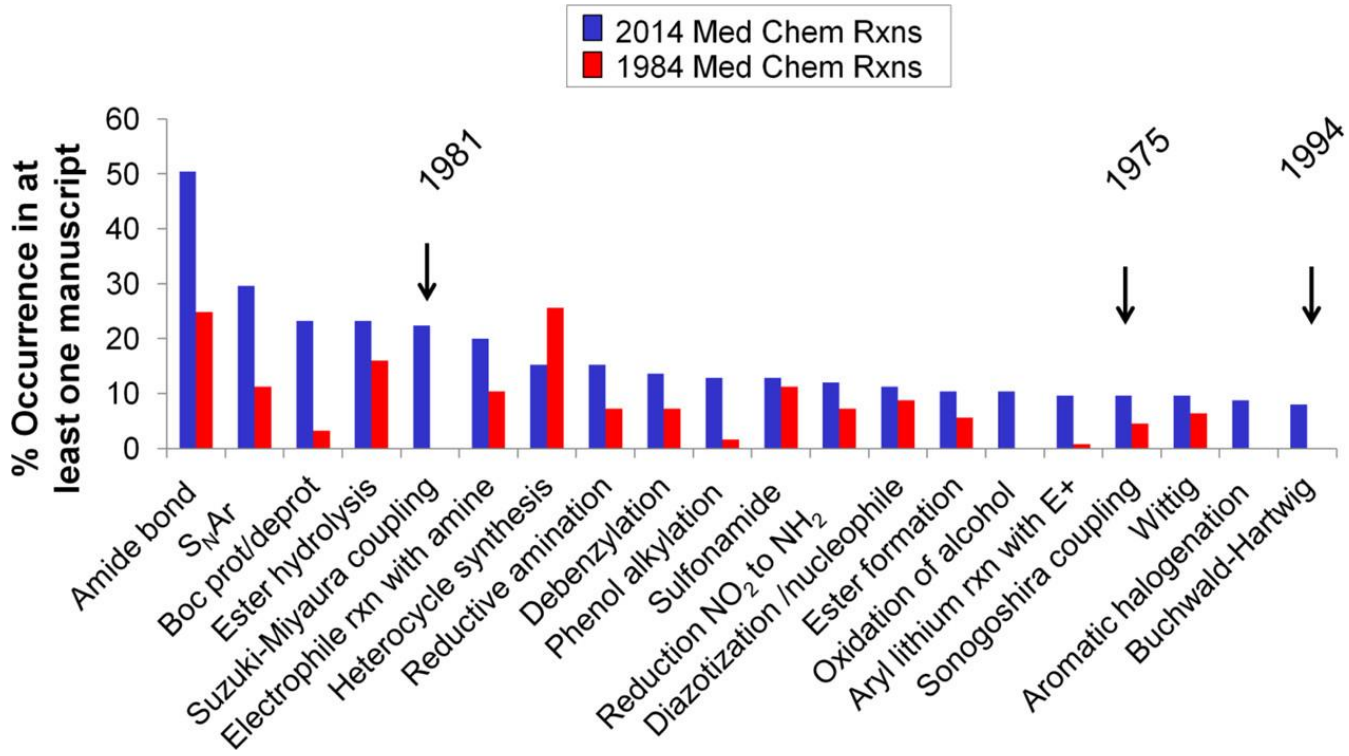
Wurtz, Charles Adolphe
Born: Wolfisheim, 1817
Died: Paris, 1884

Williamson, Alexander William
Born: London, 1824
Died: Hindhead, 1904

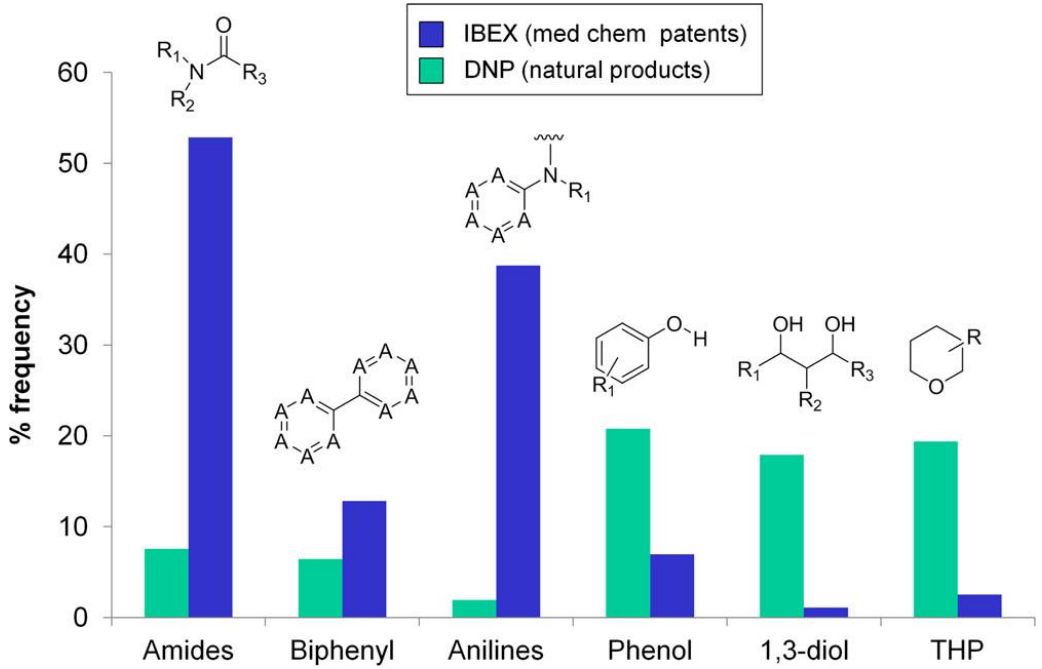
Grignard, François Auguste
Born: Cherbourg, 1871
Died: Lyon, 1935

Reactions types Methodologies on Medicinal Chemistry

two reactions make up over half of all those used in synthesis to discover and develop drugs: the amide formation and the Suzuki–Miyaura cross coupling.



Occurrence of a particular reaction, plotted as the percentage of which it shows up in at least one manuscript (n = 125; representative data set taken from 2014, *J. Med. Chem.*, blue; 1985, *J. Med. Chem.*, red). The arrows (and years) indicated the first citation of this technology in the primary literature.

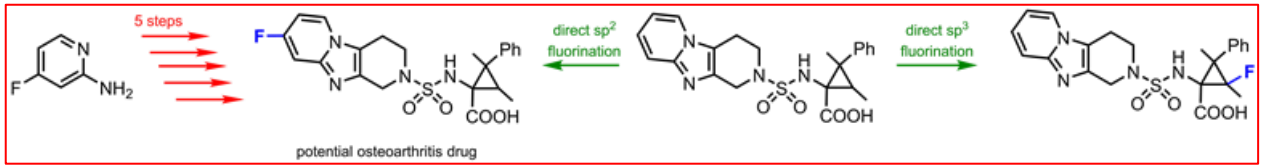


Occurrence of a functional group in the IBEX database (6.2M) records of pharmaceutical drug discovery patents and journals) versus those found in the Dictionary of Natural Products (0.23M records). Where indicated, a nonspecific R group represents a free site at any position. As an example, THP would include any pyranose derivative found in the DNP

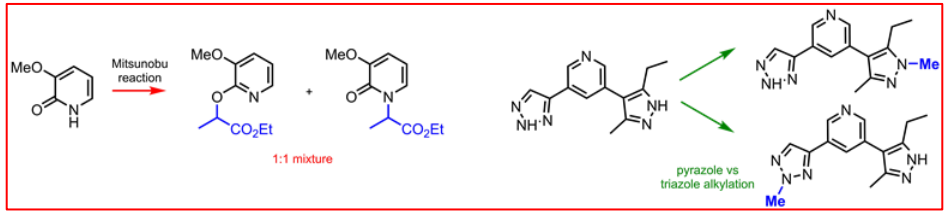
Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?
Dean G. Brown and Jonas Boström, J. Med. Chem. 2016, 59, 10, 4443–4458
https://doi.org/10.1021/acs.jmedchem.5b01409

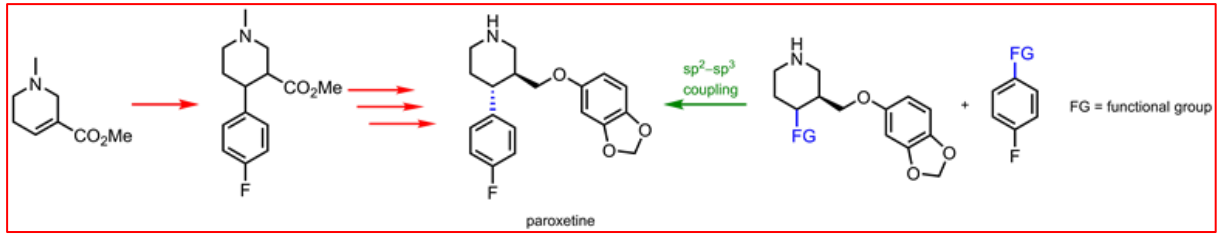
Reactions types: Wish-list

1. Fluorination – Exchanging a specific hydrogen for a fluorine atom in molecules with many functional groups. A reaction that installs a difluoromethyl group would be nice too

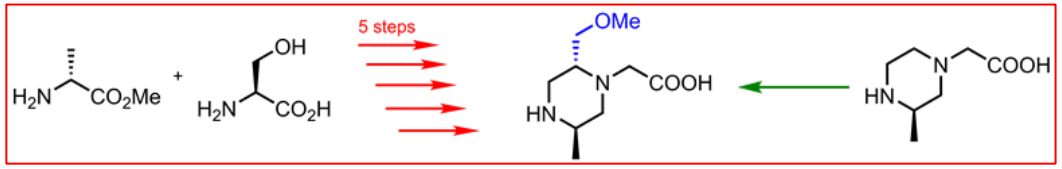


2. Heteroatom alkylation – A reaction that – selectively – attaches an alkyl group onto one heteroatom in rings that have several, such as pyrazoles, triazoles and pyridones.



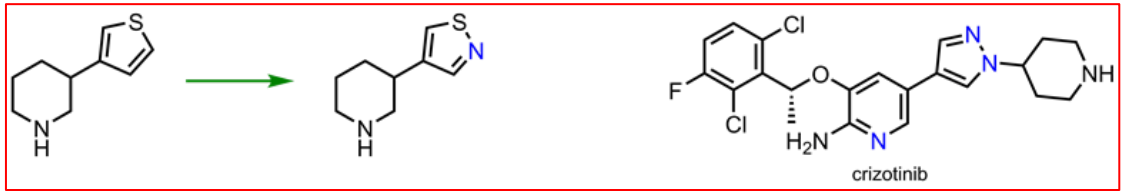


3. Carbon coupling – A reaction as robust and versatile as traditional cross coupling for stitching together aliphatic carbon atoms – ideally with control of chirality, too. Chemists also want more options for the kinds of molecules they can use as coupling precursors



4. Making and modifying heterocycles – A reaction to install functional groups – from alkyl to halogen – anywhere on aromatic and aliphatic heterocycles, such as pyridine, piperidine or isoxazole. Reactions that can make completely new heterocycles from scratch would be a bonus.

5. Atom swapping – A reaction that can exchange individual atoms selectively, like swapping a carbon for a nitrogen atom in a ring. This chemical version of gene editing could revolutionise drug discovery, but is probably furthest from realisation.



https://www.chemistryworld.com/news/the-five-reactions-on-every-organic-chemists-wish-list/3010150.article

What is the fashion trend in organic Chemist?

The reactions might stay the same, but nowadays a lot of effort is put into **moving from simpler to more complex reactions**

What is the fashion trend in organic Chemist?

The reactions might stay the same, but nowadays a lot of effort is put into **moving from simpler to more complex reactions**

- **Green Chemistry**: A stronger focus on sustainability, aiming to reduce the environmental impact of chemical processes and syntheses.

Molecular Designers

Design is a signal of intention

***"Cradle to Cradle" William McDonough* 2002**

What is the fashion trend in organic Chemist?

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

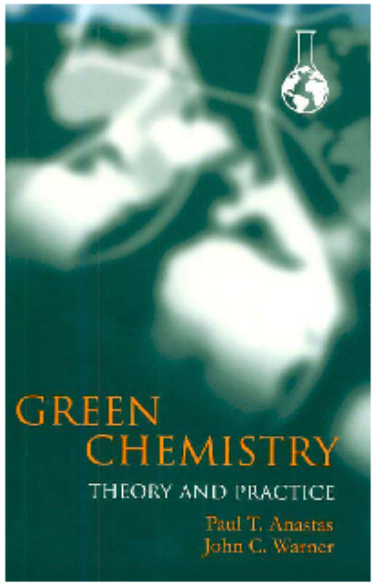
$$A + B \rightarrow C$$

Molecular Designers

Design is a signal of intention

"Cradle to Cradle" William McDonough 2002

What Is Green Chemistry?

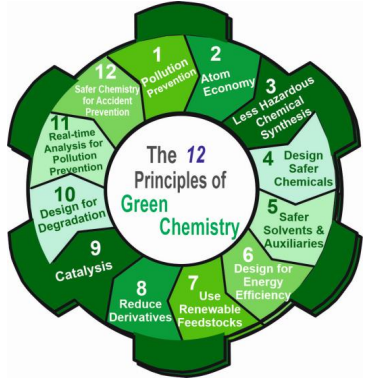


"…the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."

*Source: Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998). ISBN 0 19 850698 8

Twelve Principles of Green Chemistry

(Anastas and Warner 1998)



1. Prevent waste: **Design** chemical syntheses to prevent waste. Leave no waste to treat or clean up.

2. Maximize atom economy: **Design** syntheses so that the final product contains the maximum proportion of the starting materials. Waste few or no atoms.

3. Design less hazardous chemical syntheses: **Design** syntheses to use and generate substances with little or no toxicity to either humans or the environment.

4. Design safer chemicals and products: **Design** chemical products that are fully effective yet have little or no toxicity.

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

6. Increase energy efficiency: Run chemical reactions at room temperature and pressure whenever possible.

7. Use renewable feedstocks: Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.

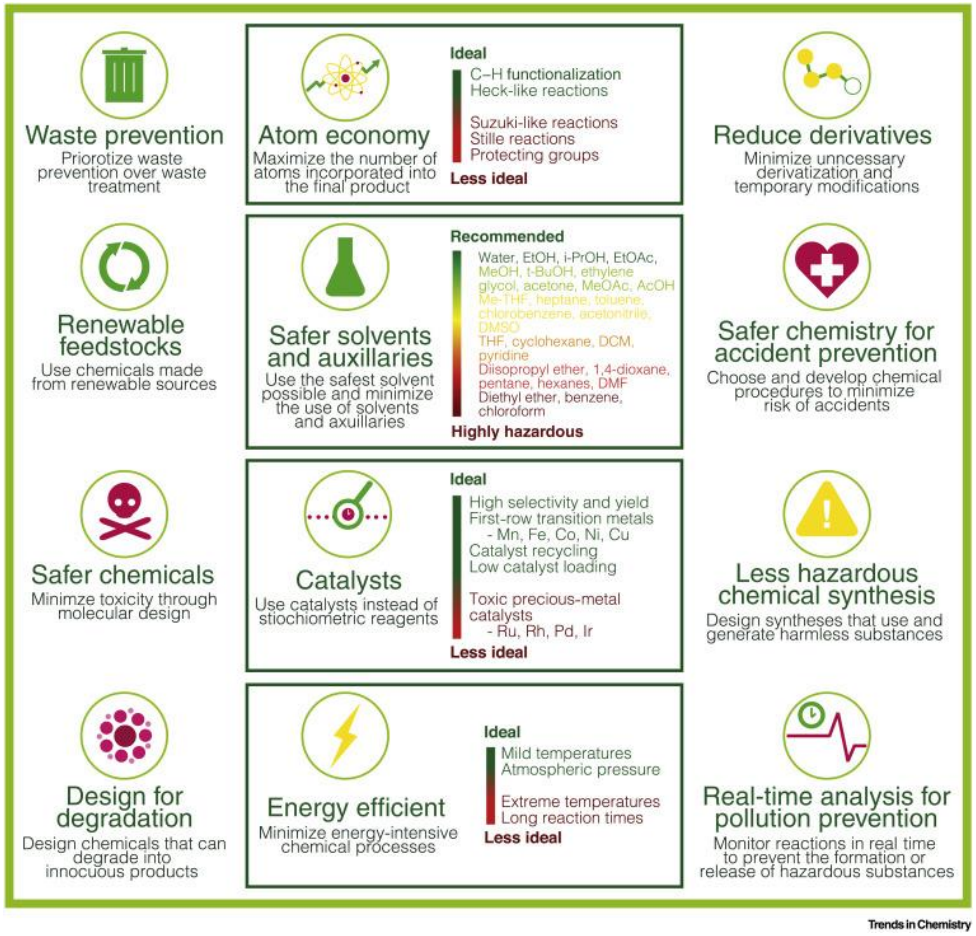
8. Avoid chemical derivatives: Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

9. Use catalysts, not stoichiometric reagents: Minimize waste by using catalytic reactions. Catalysts are effective in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and carry out a reaction only once.

10. Design chemicals and products to degrade after use: **Design** chemical products to break down into innocuous substances after use so that they do not accumulate in the environment.

11. Analyze in real time to prevent pollution: Include in-process, real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.

12. Minimize the potential for accidents: **Design** chemicals and their physical forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases into the environment.



https://doi.org/10.1016/j.trechm.2019.08.002

EPA, United States Environmental Protection Agency – Basics of Green Chemistry, https://www.epa.gov/greenchemistry/basics-green-chemistry

Principles of green chemistry: PRODUCTIVELY

They can be condensed with the acronym **'PRODUCTIVELY'**,
Prof. Sir M. Poliakoff captures the spirit of each of the twelve principles of green chemistry in just two or three words.

Condensed Principles of Green Chem

P Prevent wastes
R Renewable materials
O Omit derivatization steps
D Degradable chemical products
U Use safe synthetic methods Catalytic reagents
T Temperature, pressure ambient
I In-process monitoring
V Very few auxiliary substances
E E-factor , maximise feed in product
L Low toxicity of chemical products
Y Yes, it is safe

https://youtu.be/_KYiLFkMQ_E

Green Chem., 2005,7, 761-762 https://doi.org/10.1039/B513020B

Green Chemistry

https://learning.acsgcipr.org/

Green Chemistry

The traditional approach to hazards focuses on reducing risk by minimizing exposure.

- For example, wearing personal protective equipment or space ventilation if the chemical is volatile.

Green chemistry focuses on reducing risk by reducing hazard.

- If there is no hazard, exposure becomes irrelevant.

↓Risk = ↓Hazard x Exposure

Green chemistry and engineering focus on reducing risk by reducing hazard.

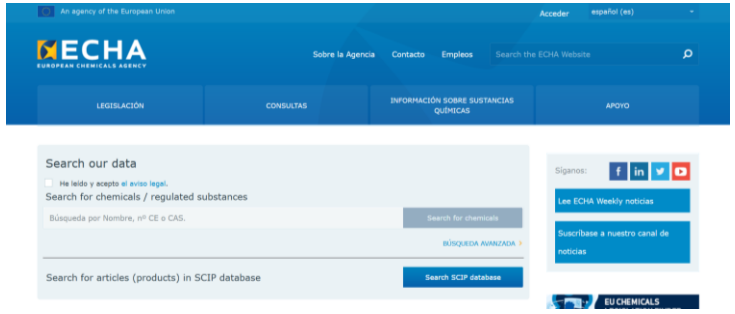
Hazard must be recognized as a flaw in the designing process

12 Principles of Green Chemistry

3. Design less hazardous chemical syntheses: **Design** syntheses to use and generate substances with **little or no toxicity** to either humans or the environment.

4. Design safer chemicals and products: **Design** chemical products that are fully effective yet have **little or no toxicity**.

10. Design chemicals and products to degrade after use: **Design** chemical products to break down into innocuous substances after use so that they **do not accumulate** in the environment.



Physical-chemical properties of a compound or material:

- ❑ State of matter
- ❑ Colour
- ❑ Melting point
- ❑ Boiling point
- ❑ Solubility
- ❑ Electric conductivity

Molecular Designers

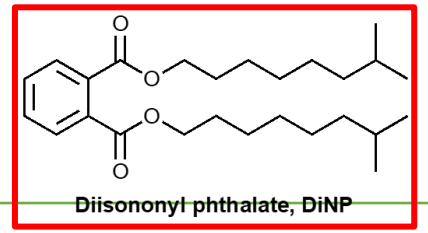
- ➢ Toxicity
- ➢ biodegradability
- ➢ Environment and human Impact

12 Principles of Green Chemistry

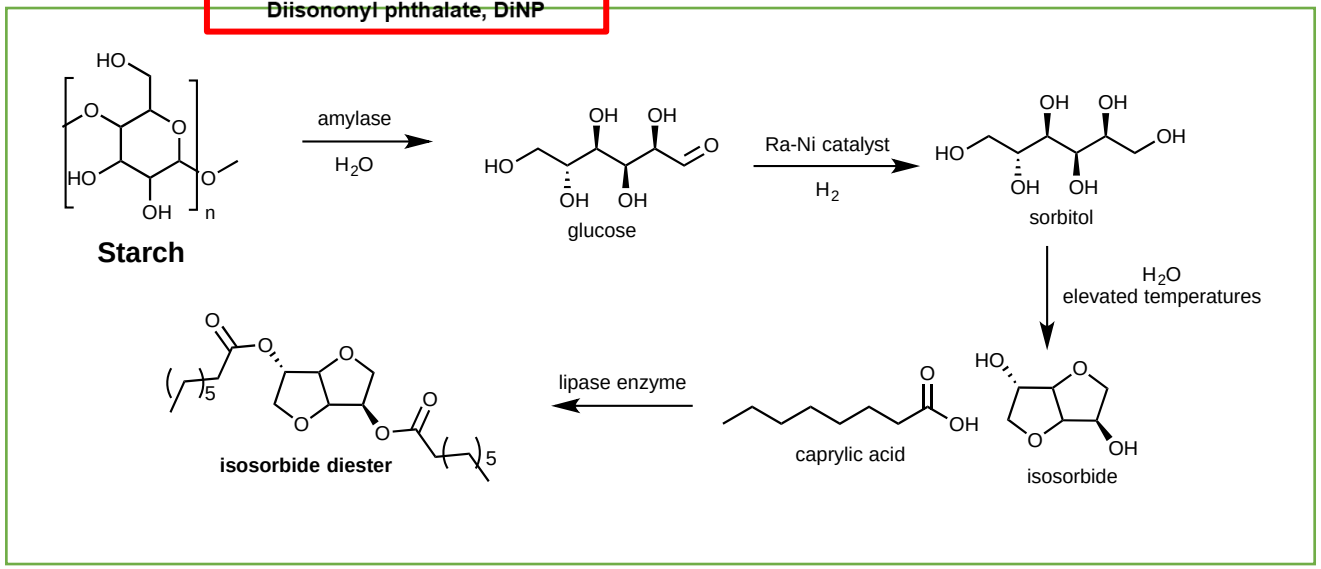
3. Design less hazardous chemical syntheses: **Design** syntheses to use and generate substances with **little or no toxicity** to either humans or the environment.

4. Design safer chemicals and products: **Design** chemical products that are fully effective yet have **little or no toxicity**.

10. Design chemicals and products to degrade after use: **Design** chemical products to break down into innocuous substances after use so that they **do not accumulate** in the environment.



the plasticizer diisononyl phthalate (DiNP) is added to PVC to make it flexible, as well as having other polymer applications. Higher molecular weight plasticisers, including DINP, account for around 60% of the market in Europe, according to trade body European Plasticisers.



Isosorbide Diester provides benefits in performance materials as a safe, specialty plasticizer.
It is an alternative of choice to standard petrochemical-based plasticizers.

Phthalate-free and 100% bio-based, obtained from esterification of isosorbide with plant-based fatty acids.
It offers outstanding compatibility and processability with PVC resins.
An alternative of choice to standard petrochemical-based plasticizers.

This product is registered in REACH regulation. Risk assessment was obtained by conducting a wide range of biodegradability and toxicological protocols. Overall, these studies demonstrated that this new solution is **nontoxic to mammalian life and is readily biodegradable**.

Green Chemistry

Simple Examples of Common Metrics in Chemical Reaction.

Green Chemistry

Simple Examples of Common Metrics in Chemical Reaction.

Porcentaje (%)
Yield (ε)
Selectivity (S)

→ **Reaction Efficiency**

$$A \xrightarrow{\varepsilon_1} B \xrightarrow{\varepsilon_2} C \xrightarrow{\varepsilon 3} D$$

$$\varepsilon_{global} = \varepsilon_1 \times \varepsilon_2 \times \varepsilon_3$$

$$\text{fractional } \varepsilon = \frac{\text{actual } \varepsilon}{\text{theoretical } \varepsilon}$$

$$\text{percentage } \varepsilon = \frac{\text{actual } \varepsilon}{\text{theoretical } \varepsilon} \times 100\%$$

$$\text{reaction } a: \; A + B + \text{catalyst } a \rightarrow C$$

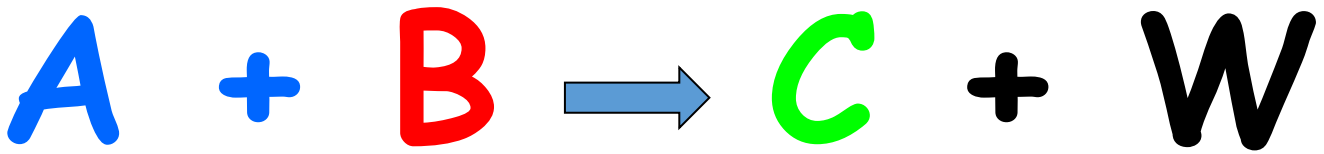
$$\text{reaction } b: \; A + B + \text{catalyst } b \rightarrow D$$

$$S = \frac{\text{amount of desired product}}{\text{amount of substrate converted}} \times 100$$

$$S = \frac{k_a}{k_b} \text{ or } S = \frac{\log k_a}{\log k_b}$$

Green Chemistry

1. Prevent waste: Design chemical syntheses to prevent waste. Leave no waste to treat or clean up.



Reaction Efficiency from a Green Chem. view

Ways to prevent waste?

1. Avoid the generation of W.
2. Find alternatives to A & B to improved overall efficiency of a reaction.
3. Incorporate better catalysts to push the reaction to full completion

Green metrics: based on the 12 principles of green chemistry

.

Metrics are vital –you can't manage what you don't measure

Green metrics have been designed as quantitative tools to evaluate process/product efficiency, while indicating its weaknesses in ecological, economic, and safety terms.

Common Green Metrics

2. Maximize atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. Waste few or no atoms.

$$\text{\% Atom Economy (AE)} = \frac{\text{M.w. (product C)}}{\text{M.w. of A + M.w. of B}} \times 100$$

A + B ⟹ C + by-products

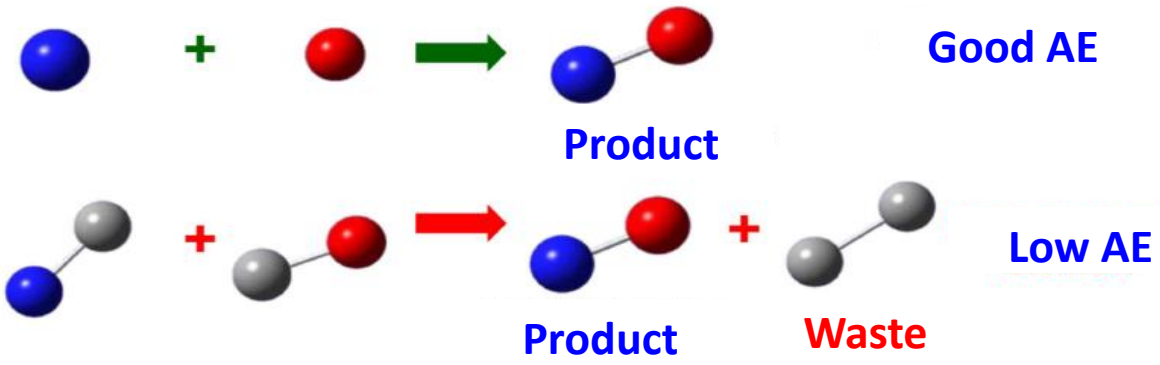
- Defined: 'a calculation of "**how much of the reactants remain in the final product**"
- Simple calculation
- The **larger the number, the higher the percent of all** reactants appearing in the product " (0-100%)
- Does not account for solvents, reagents, reaction yield, and reactant molar excess

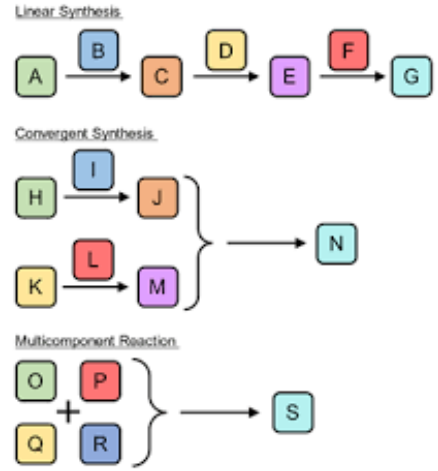
B.M. Trost, *Science*, **1991**, 254, 1471-1477.

Reactions types

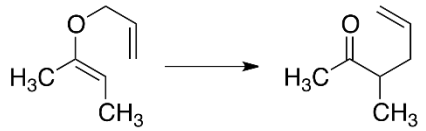
2. Maximize atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. Waste few or no atoms.

"Because an Atom is a Terrible Thing to Waste"





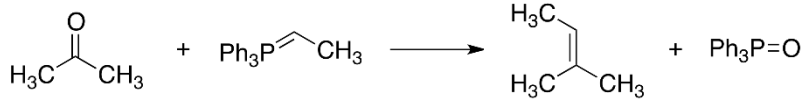
Claisen Rearrangement



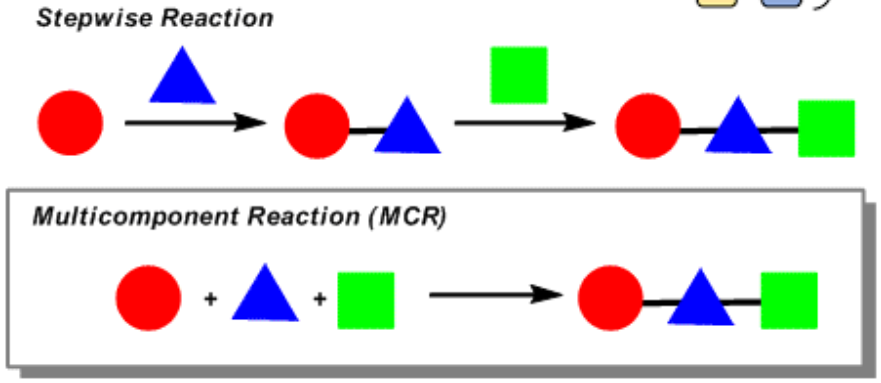
112 g/mol 112 g/mol

Atom Economy	
Claisen	100%
Wittig	20%

Wittig Reaction



58 g/mol 290 g/mol 70 g/mol



Multicomponent reactions: advanced tools for sustainable organic synthesis
R.C. Cioc, E. Ruijter, R. V. A. Orru
Green Chem., 2014, 16, 2958
DOI: 10.1039/C4GC00013G

Common Metrics: E-Factor

1. Prevent waste: Design chemical syntheses to prevent waste. Leave no waste to treat or clean up.

$$\text{E-Factor} = \frac{\text{Total waste (Kg)}}{\text{Product (Kg)}}$$

- ❑ Very useful metric for industry
- ❑ The **smaller the number, the closer to zero waste being** produced
- ❑ Depends on one's definition of 'waste'

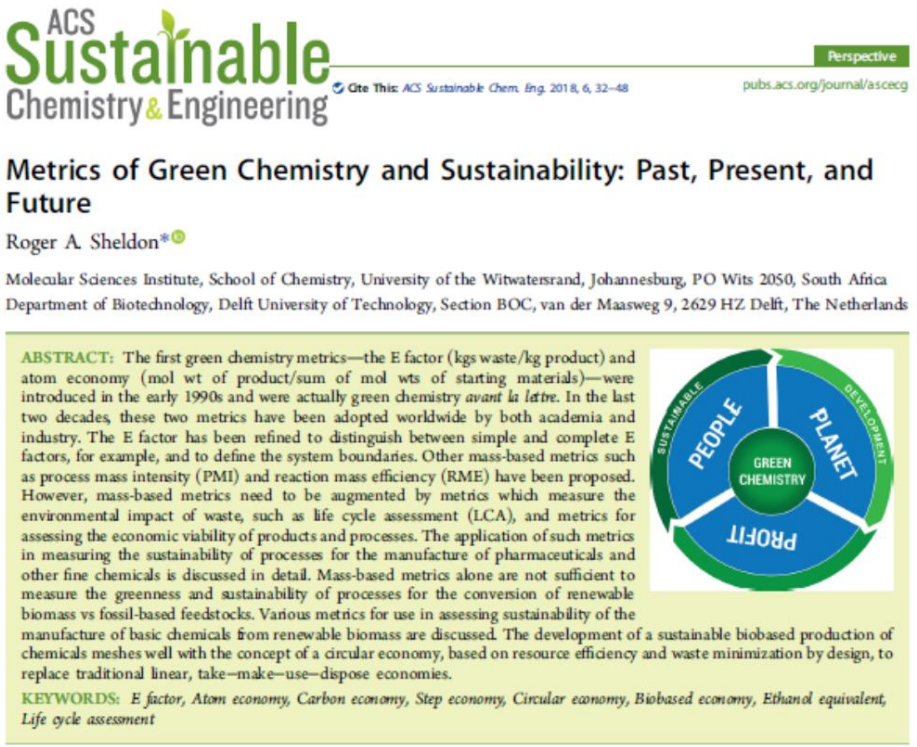
  Process use only or chemicals needed for scrubbing
- ❑ E-factor can be split into different sub-categories:
  - ✓ Organic waste
  - ✓ Aqueous waste (water itself excluded)

R. A. Sheldon, Chem Ind. (London), 1992, 903-906.

Common Metrics: E-Factor

Green Chem., **2007,** 9, 1273-1283
https://doi.org/10.1039/B713736M

Green Chem., 2017,**19**, 18-43
https://doi.org/10.1039/C6GC02157C



ACS Sustainable Chem. Eng. **2018**, 6, 1, 32–48
https://doi.org/10.1021/acssuschemeng.7b03505

12 Principles of Green Chemistry

2. Maximize atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. Waste few or no atoms.

Two views of the same thing: half full or half empty ??

+ **E Factor *vs* Atom Economy** **–**

"atom economy"

Barry Trost

how much of the reactants remain in the final product

"E-factor"

Roger Sheldon

how much waste produce for final product

Common Green Metrics

$$PMI = \frac{1}{RME} = E + 1$$

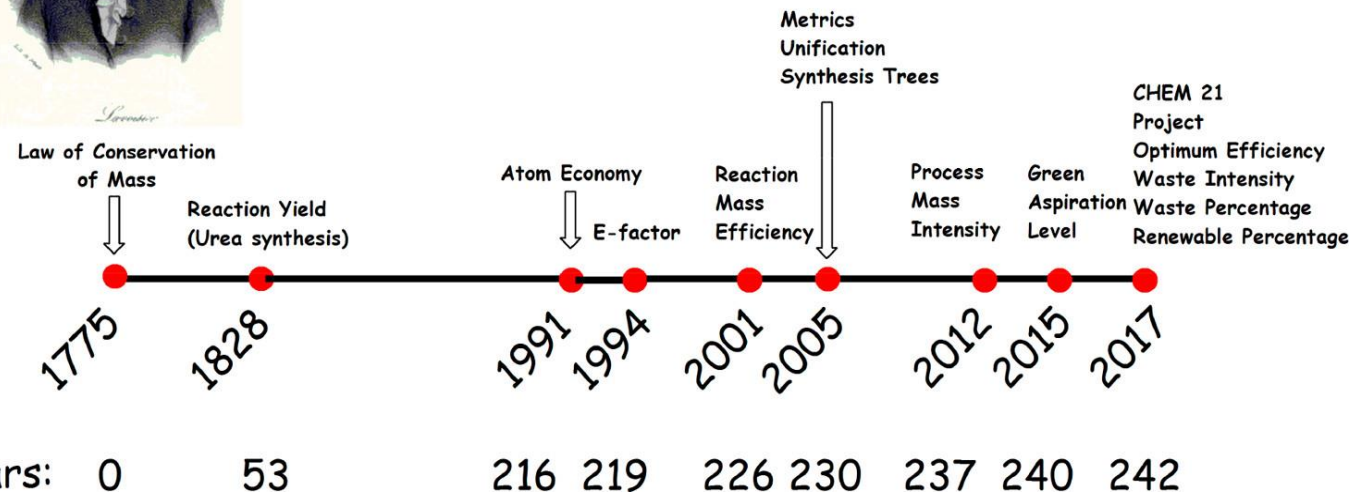
$$LN = \frac{1}{AE} = E_{mw} + 1$$

$$WI = \frac{E}{E+1} = 1 - \frac{1}{PMI}$$

$$\frac{WP}{100} = \frac{E}{(E+1)^2} = \frac{PMI - 1}{(PMI)^2}$$

$$\frac{WP}{100} = WI\,(1 - WI)$$

Evolution of selective sustainability metrics describing material efficiency



E factor (E)[3]

$$E = \frac{\text{Total mass of waste}}{\text{Mass of final product}}$$

Atom Economy (AE)[6]

$$AE\ (\%) = \frac{\text{Mol wt of product} \times 100}{\text{Sum of mol wts of reactants}}$$

Mass Intensity (MI)[31,32]

$$MI = \frac{\text{Total mass in process}}{\text{Mass of product}}$$

Reaction Mass Efficiency (RME)[31]

$$RME\ (\%) = \frac{\text{Mass of product} \times 100}{\text{Total mass of reactants}}$$

Process Mass Intensity (PMI)[34,35]

$$PMI = \frac{\text{Total mass in process (incl } H_2O)}{\text{Mass of product}}$$

Mass Productivity (MP)

$$MP\ (\%) = \frac{\text{Mass of product} \times 100}{\text{Total mass (incl solvents)}}$$

Waste Water Intensity (WWI)

$$WWI = \frac{\text{Mass of process water}}{\text{Mass of product}}$$

Effective Mass Yield (EMY)[33]

$$EMY\ (\%) = \frac{\text{Mass of product}}{\text{Mass of hazardous reactants}}$$

Solvent intensity (SI)

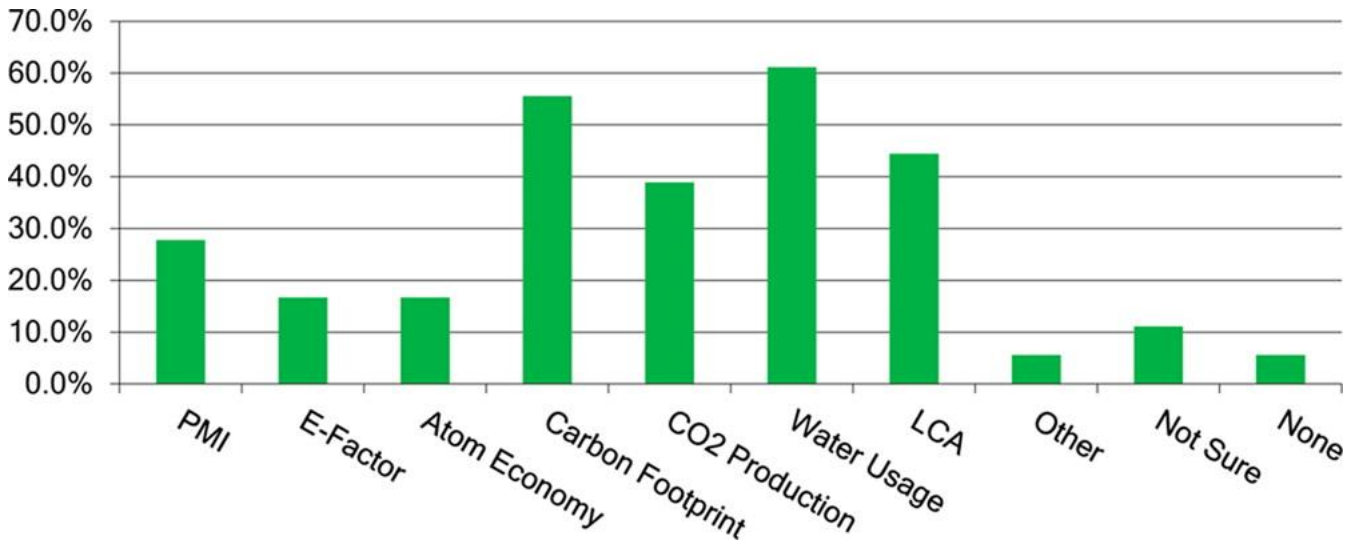
$$SI = \frac{\text{Mass of solvents}}{\text{Mass of product}}$$

Carbon Economy (CE)[31]

$$CE\ (\%) = \frac{\text{Carbon in product} \times 100}{\text{Total carbon in reactants}}$$

Useful Tools for the Next Quarter Century of Green Chemistry Practice: A Dictionary of Terms and a Data Set of Parameters for High Value Industrial Commodity Chemicals
ACS Sustainable Chem. Eng. 2018, 6, 3, 3206–3214
https://doi.org/10.1021/acssuschemeng.7b03360

What Metric?



Green chemistry-related metrics used in chemical manufacturing. Chemical manufacturer responses (*n* = 18) to the 2012 Roundtable survey question "**What green chemistry and engineering related metrics does your company use?** Select all that apply." Percentage of respondents indicating one or more metrics surveyed in use computed as the ratio of [total responses – (not sure + none)]/(total responses).
PMI = process mass intensity = (mass of raw materials)/(mass of final product).
E-factor = (mass of waste)/mass of final product).
LCA = life cycle assessment.

Implementing Green Chemistry in Chemical Manufacturing: A Survey Report
R.J. Giraud; P. A. Williams; A. Sehgal; E. Ponnusamy; A.K. Phillips; J. B. Manley;
ACS Sustainable Chem. Eng. **2014,** 2, 2237-2242.
https://doi.org/10.1021/sc500427d

https://www.acsgcipr.org/tools-for-innovation-in-chemistry/

- ❑ **Green Chemistry Innovation Scorecard Calculator**
- ❑ **Process Mass Intensity (PMI) Metric**
- ❑ **Process Mass Intensity Calculator**
- ❑ **Convergent Process Mass Intensity Calculator**
- ❑ **Process Mass Intensity Life Cycle Assessment**
- ❑ **Process Mass Intensity Prediction Calculator**

Common Metrics: E-Factor

$$\text{E-Factor} = \frac{\text{Total waste (Kg)}}{\text{Product (Kg)}}$$

E-factor for different Industrial sector

Industry	E-factor	Annual Production tonnage
Oil Refining	*ca.* 0.1	10^6 - 10^8
Bulk Chemicals	<1 to 5	10^4 - 10^6
Fine Chemicals	5 to >50	10^2 - 10^4
Pharmaceuticals	25 to >100	10 – 10^3

R. A. Sheldon, *Chem. Ind.*, **1997**, 12 – 15.
E-Factor = Total mass of materials required to produce 1kg product (mass intensity) – 1.
(often does not include water)

Common Metrics: The E Factor

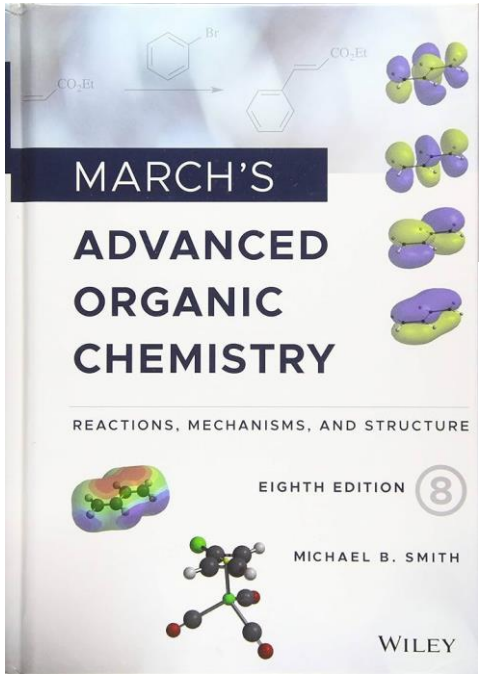
$$\text{E-Factor} = \frac{\text{Total waste (Kg)}}{\text{Product (Kg)}}$$

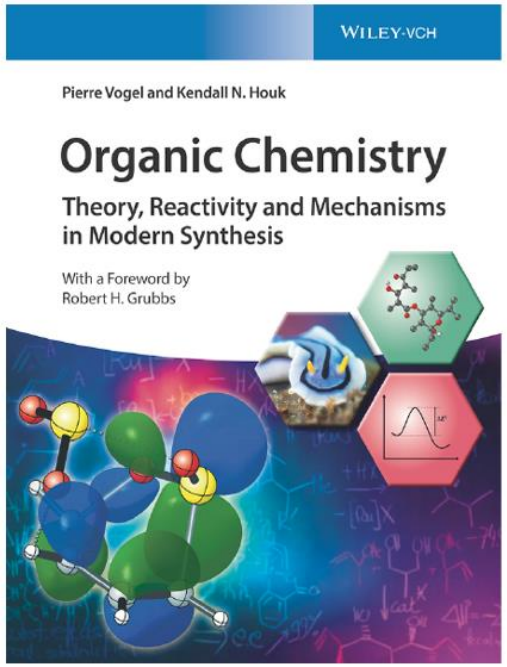
Industry	E-factor	Annual Production tonnes	Total Waste tpa	No of transform-ations	Years of develop-ment
Oil Refining	*ca.* 0.1	10^6 - 10^8	10 million	Separations	100+
Bulk Chemicals	<1 to 5	10^4 - 10^6	5 million	1-2	10 – 50
Fine Chemicals	5 to >50	10^2 - 10^4	0.5 million	3-4	4 - 7
Pharmaceuticals	25 to >100	10 – 10^3	0.1 million	6+	3 - 5

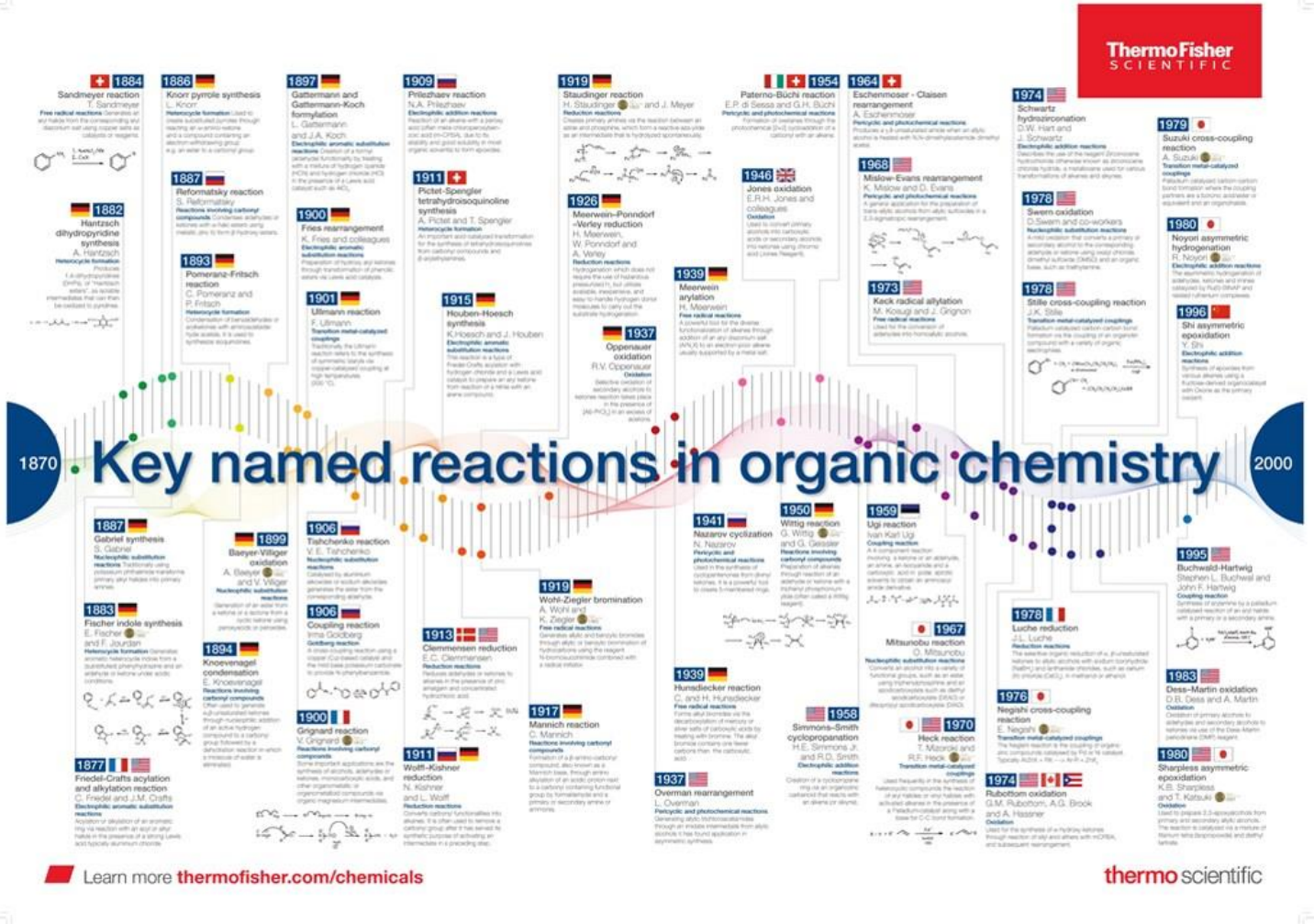
The data indicates that oil companies generate significantly less waste than pharmaceutical companies.
This reflects the oil industry's imperative to minimize waste and repurpose products that would typically be discarded.
The pharmaceutical sector prioritizes manufacturing and molecule quality.
Despite its high-profit margins and less concern over comparatively larger waste volumes (considering the volumes used), it's noted that the pharmaceutical industry still produces less waste tonnage than other sectors.

Reactions types

Organic chemistry is known for its complexity and diversity because the carbon atom can form strong bonds with many other types of atoms and can form chains and rings, allowing for the creation of an immense variety of molecules.







Reactions types

Researchers at GlaxoSmithKline have studied reactions used to prepare molecules of pharmaceutical interest

$$\text{ATOM ECONOMY} = \frac{\text{MW of desired product}}{\text{MW of all reactants}} \times 100\%$$

$$\text{REACTION MASS EFFICIENCY (RME)} = \frac{\text{mass of desired product}}{\text{mass of all reactants}} \times 100\%$$

$$\text{PROCESS MASS INTENSITY (PMI)} = \frac{\text{total input mass (kg)}}{\text{mass of product (kg)}} \times 100\%$$

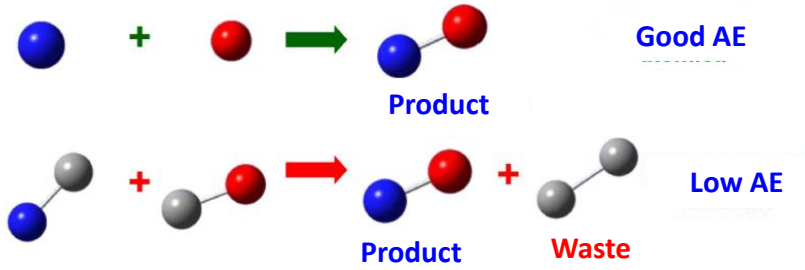
Table 3 Comparison of average atom economy with average reaction mass efficiency for 28 different chemistries

Chemistry type	Atom economy (%)	Reaction mass efficiency (%)	Chemistry type	Atom economy (%)	Reaction mass efficiency (%)
Resolution	40	31	Epoxidation	83	58
N-Dealkylation	64	27	Bromination	84	63
Elimination	72	45	Hydrogenation	84	74
N-Alkylation	73	60	S-Alkylation	84	61
Chlorination	74	46	O-Arylation	85	58
Borohydride	75	58	N-Acylation	86	62
Lithal	76	52	Amination	87	54
Grignard	76	42	C-Alkylation	88	61
Hydrolysis (acid)	76	50	Iodination	89	56
Cyclisation	77	56	Knoevenagel	89	66
Cyanation	77	65	Sulfonation	89	69
Decarboxylation	77	68	Esterification	91	67
C-Acylation	81	51	Base salt	100	80
Hydrolysis (base)	81	52	Acid Salt	100	83

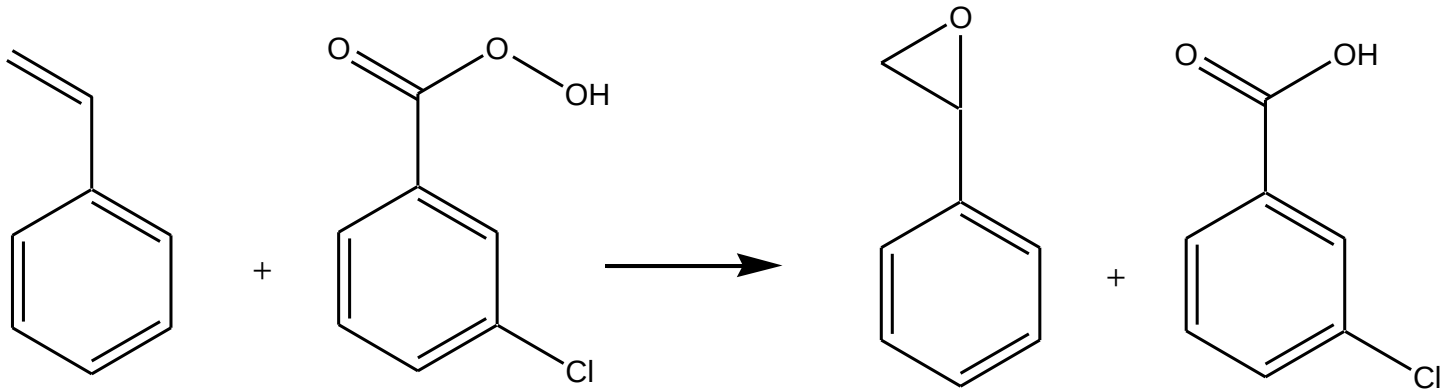
D. Curzons, D. J. C. Constable, D. N. Mortimer, V. L. Cunningham,
So you think your process is green, how do you know?—Using principles of sustainability to determine what is green–a corporate perspective
Green Chem., 2001,3, 1-6
https://doi.org/10.1039/B007871I

12 Principles of Green Chemistry

2. Maximize atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. Waste few or no atoms.



Example: Epoxidation of styrene



styrene | 3-Chloroperbenzoic acid MCPBA | desired epoxide | waste

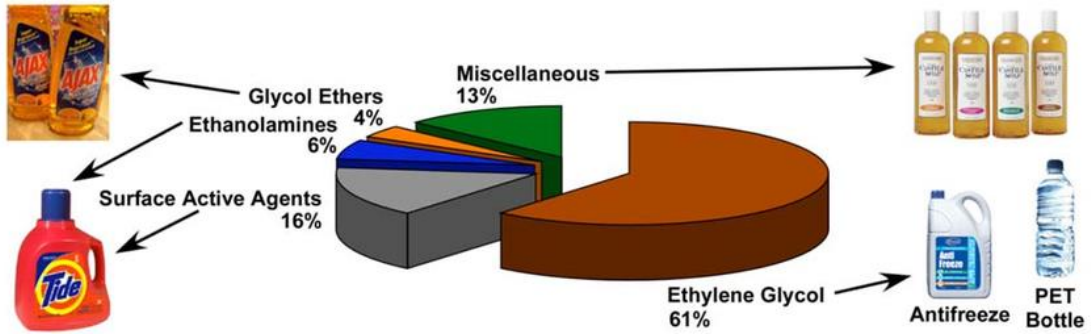
- Assume 100% yield.
- 100% of the desired epoxide product is recovered.
- 100% formation of the co-product: m-chlorobenzoic acid.
- A.E. of this reaction is 23%.
- 77% of the products are waste.

12 Principles of Green Chemistry

1. Prevent waste: Design chemical syntheses to prevent waste. Leave no waste to treat or clean up.

Case study: Production of ethylene oxide

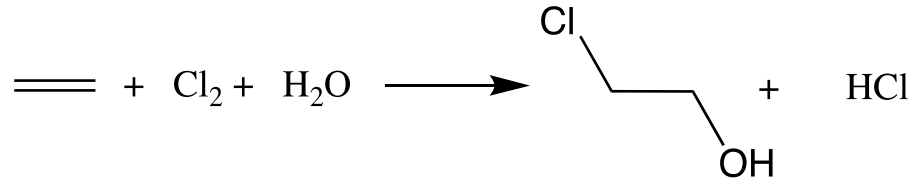
Ethylene oxide is used as an intermediate in the production of several industrial chemicals, the most notable of which is ethylene glycol.
It is also used as a fumigant in certain agricultural products and as a sterilant for medical equipment and supplies.



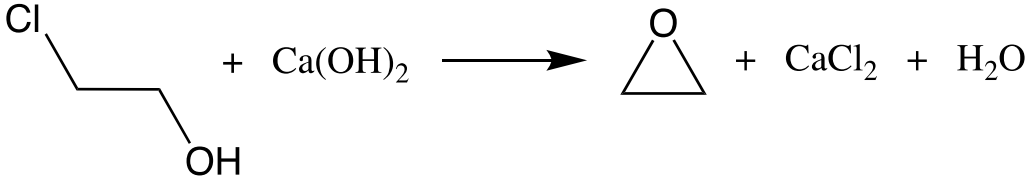
Conventional ethylene oxide synthesis included:

- A 2-step synthesis with a chlorohydrin intermediate.
- For each kilogram of product, 5 Kg of waste were disposed.

Step 1:



Step 2:



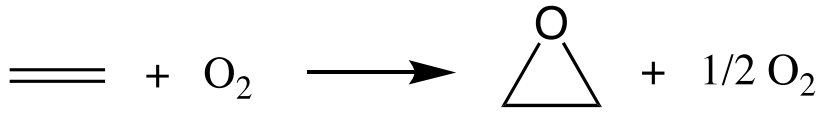
12 Principles of Green Chemistry

1. Prevent waste: Design chemical syntheses to prevent waste. Leave no waste to treat or clean up.

Case study: Production of ethylene oxide

Alternative production of ethylene oxide:

- Use of molecular oxygen removes the need for chlorine.
- New process generates more than **16 times less waste** than the original one and eliminates the formation of wastewater.

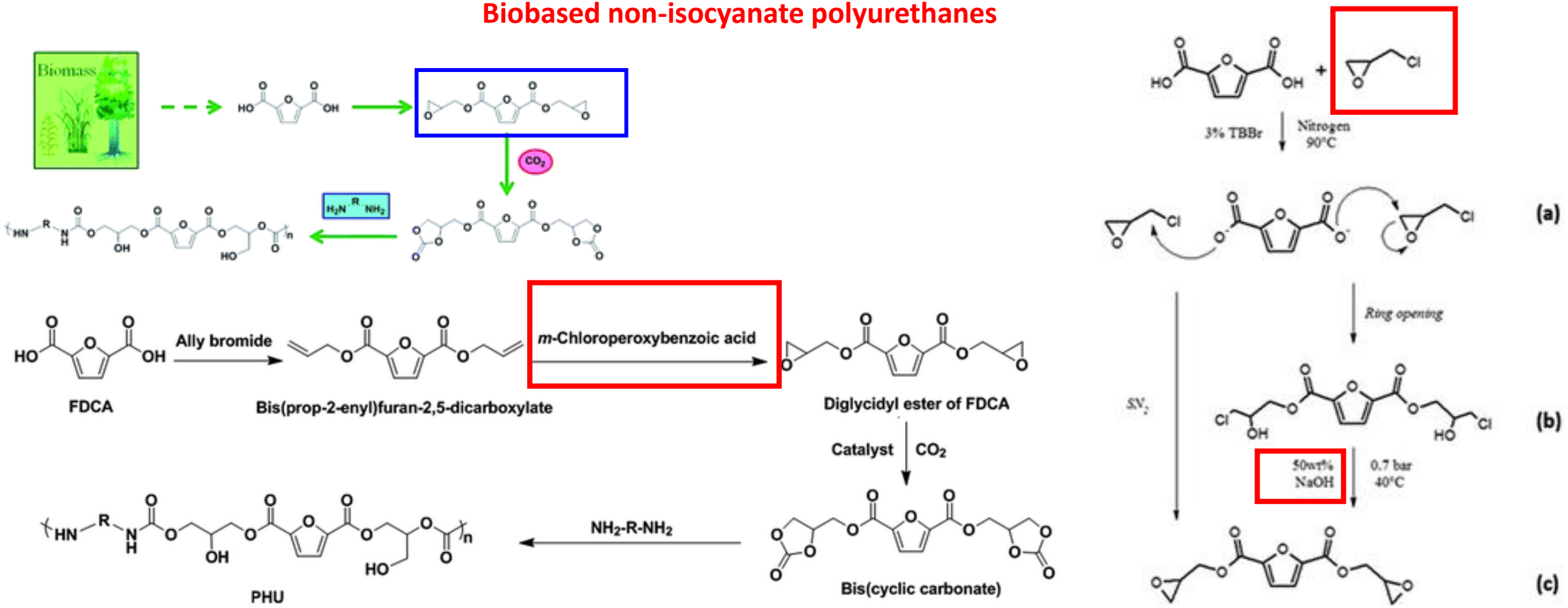


E-factor = 0.3

12 Principles of Green Chemistry

2. Maximize atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. Waste few or no atoms.

Biobased non-isocyanate polyurethanes



RSC Adv., 2017,7, 37-46 https://doi.org/10.1039/C6RA25045A

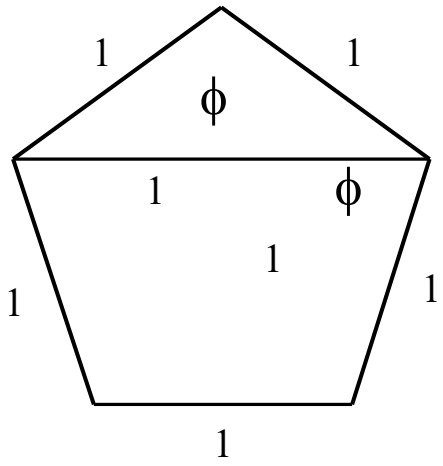
Golden Ratio / Golden Section

Green chemistry = Golden chemistry

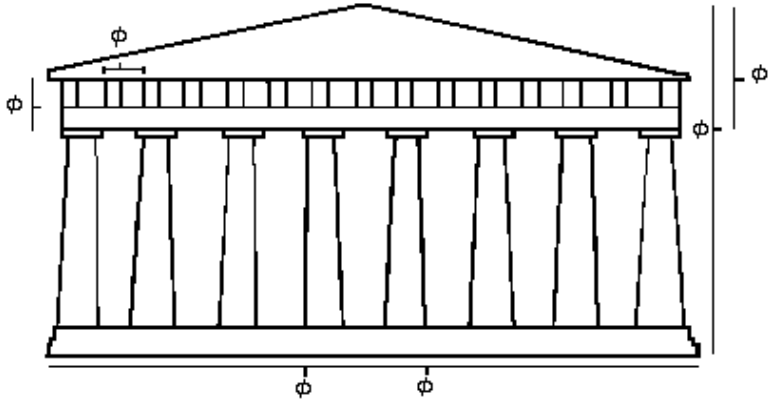
Determining the material efficiency of a reaction relative to a "golden" economy of atoms (a reference to the "golden ratio" known to mathematicians for centuries).

$$\frac{BC}{AC} = \frac{AB}{BC} = \phi = \frac{\sqrt{5}-1}{2} = 0.618\ldots$$

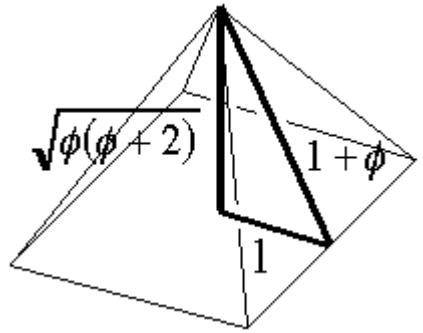
Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to Reaction Discovery
Org. Process Res. Dev. 2005, 9, 4, 404–431
https://doi.org/10.1021/op050014v



Pentagon



Parthenon



Great Pyramid

Golden Ratio / Golden Section
Green chemistry = Golden chemistry

The 'golden' threshold for a single-step reaction is given by Equation

$$RME = \varepsilon \times AE \geq 0.618$$

Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to Reaction Discovery
Org. Process Res. Dev. 2005, 9, 4, 404–431
https://doi.org/10.1021/op050014v

(1) **AE>61.8%** so that **AE>E_{MW}**

(2) **RME>61.8%** so that **RME>E_{MW}**

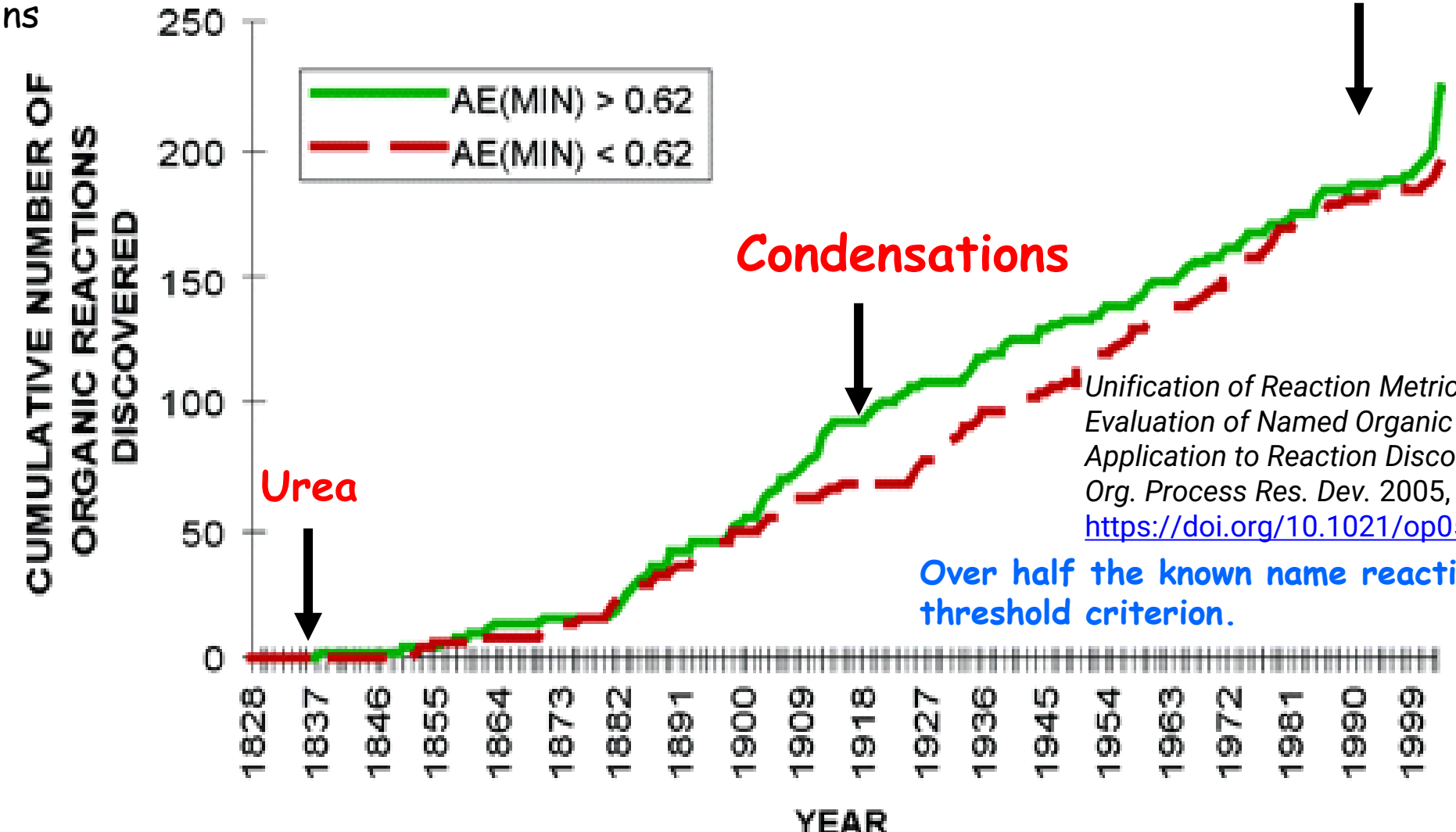
(3) Reaction **solvents and all post-reaction materials** used in the work-up and purification stages **must be reclaimed and/or eliminated**

$$AE = \frac{1}{1 + E_{mw}} \qquad RME = \frac{1}{1 + E\ factor}$$

Golden Ratio / Golden Section

Green chemistry = Golden chemistry

The concept of minimum atom economy $(AE)_{min}$ and maximum environmental impact factor has been introduced and applied to a database of over 400 named organic reactions



Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to Reaction Discovery
Org. Process Res. Dev. 2005, 9, 4, 404−431
https://doi.org/10.1021/op050014v

Over half the known name reactions satisfy this threshold criterion.

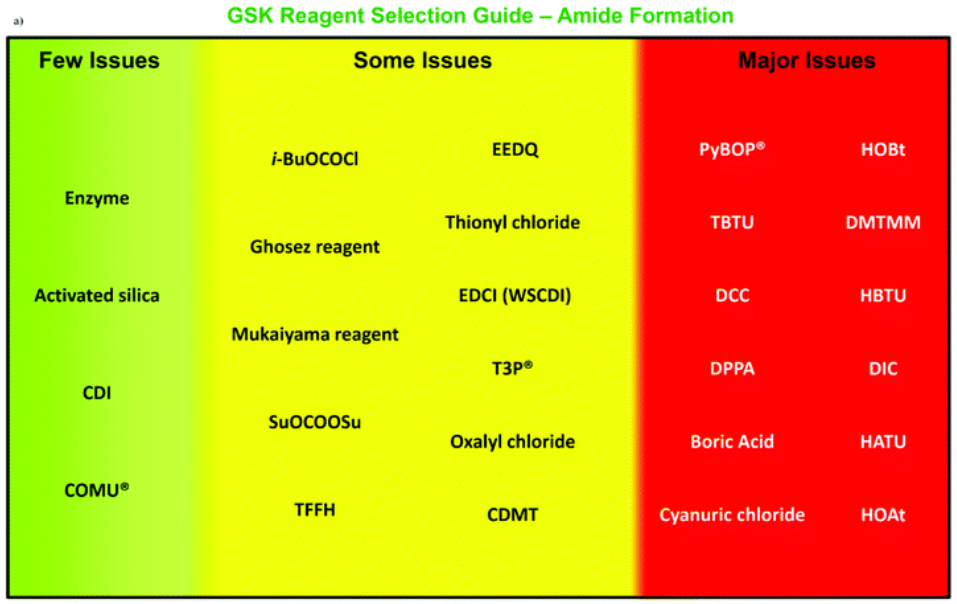
Reactions types

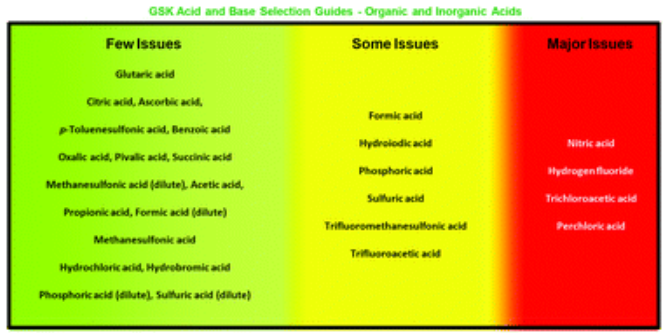
Table 3. Summary of Atom Economical Efficiency Trends for Various Reaction Classifications

Reaction Classification	General Trends
Multi-component reactions	• Most highly atom economical reaction type of all
Carbon–carbon bond forming reactions	• Atom economy increases as the molecular weights of the combining fragments increase
Non-carbon-carbon bond forming reactions	• Atom economy increases as the molecular weights of the combining fragments increase
Condensations	• Highly atom economical since small molecules of water or alcohol are liberated • Atom economy increases as the molecular weights of the combining fragments increase • For cyclization reactions such as the Dieckmann condensation and the synthesis of cyclic ethers from straight chain diols the atom economy increases with increasing ring size
Oxidations or reductions with respect to substrate	• Worst atom economical performance of all (exceptions are catalytic hydrogenation and oxidation with molecular oxygen or hydrogen peroxide) • Characterized by the production of significant waste byproducts that are the result of oxidation or reduction of reducing and oxidizing reagents, respectively • Recycling of byproducts back to the original oxidizing or reducing reagents necessarily involves at least another redox couple
Rearrangements	• Rearrangements of substrates always have atom economies of 100% • Some rearrangement reactions involve rearrangements of intermediates along their reaction pathways and so their corresponding atom economies are less than 100%
Substitutions	• Atom economy increases if the in-coming group is heavier than the leaving group, otherwise it will decrease • The caveat is that good leaving groups tend to be large
Fragmentations/eliminations	• Proportion of high atom economical reactions is low since these reactions are the reverse of skeletal building up reactions • Atom economy decreases as the molecular weight of the leaving fragment increase

12 Principles of Green Chemistry

- Reagent selection guides assist the user in selecting the 'greenest' reagent for a particular transformation.
- individual ranking or grouping within the guides allows you to make an informed decision as to the most appropriate choice for your needs





J. P. Adams, C. M. Alder, I. Andrews, A. M. Bullion, M. Campbell-Crawford, M. G. Darcy, J. D. Hayler, R. K. Henderson, C. A. Oare, I. Pendrak, A. M. Redman, L. E. Shuster, H. F. Sneddon and M. D. Walker, Development of GSK's reagent guides – embedding sustainability into reagent selection, Green Chem., 2013, 15, 1542-1549.

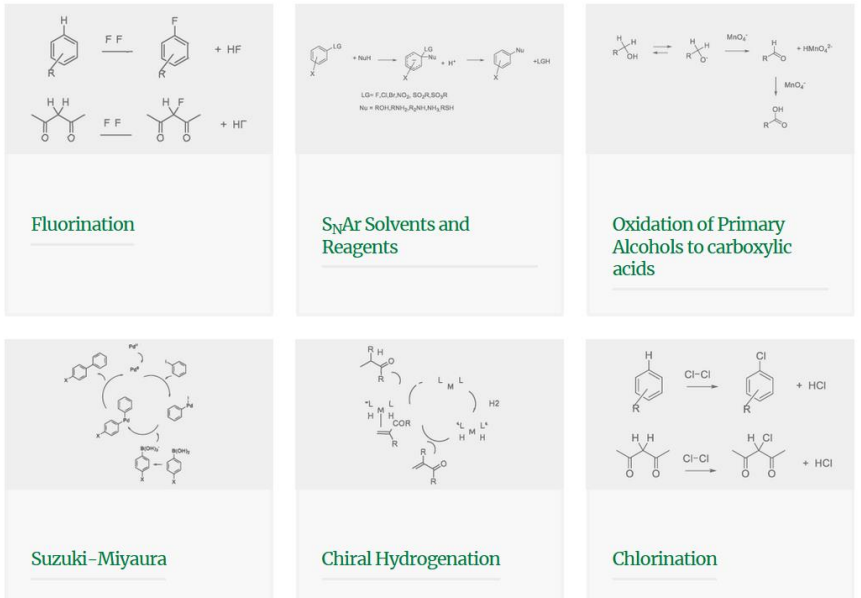
K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, P. H. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation, Green Chem., 2008, 10, 31-36.

ACS Green Chemistry Institute Pharmaceutical Roundtable

https://www.acsgcipr.org/tools-for-innovation-in-chemistry/

Reagent Selection Guides

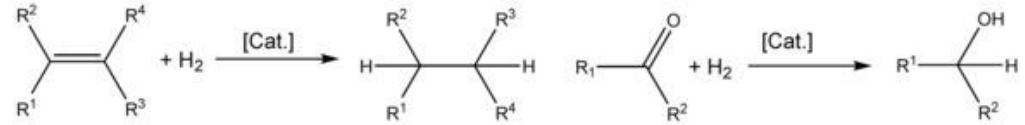
https://reagents.acsgcipr.org/reagent-guide



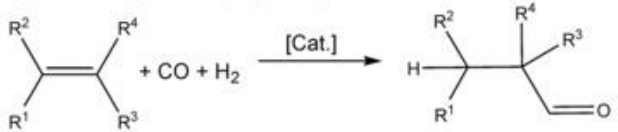
Reactions types

organic transformations run on multi-million-ton scales is mainly driven by not losing carbon from the starting material and not producing unwanted by-products or waste

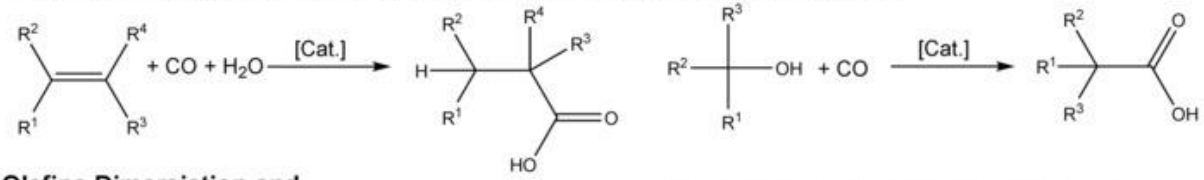
Hydrogenation (e.g. Cyclohexane, Oxo-Alcohols)



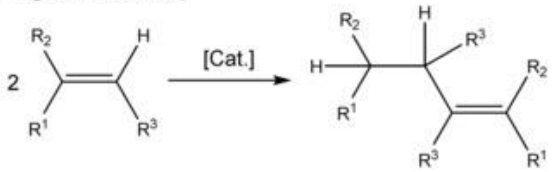
Hydroformylation (e.g. Propanal, Butanal, higher Aldehydes)



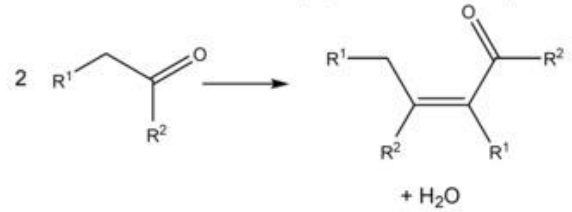
Carbonylation (e.g. Propionic Acid, Methacrylic Acid, Acetic Acid, Formic Acid)



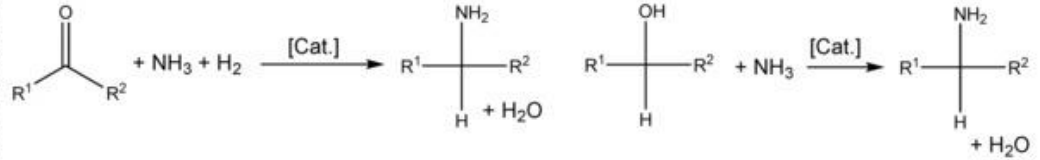
Olefine Dimersiation and Oligomerisation (e.g.Octenes, Higher Olefines)



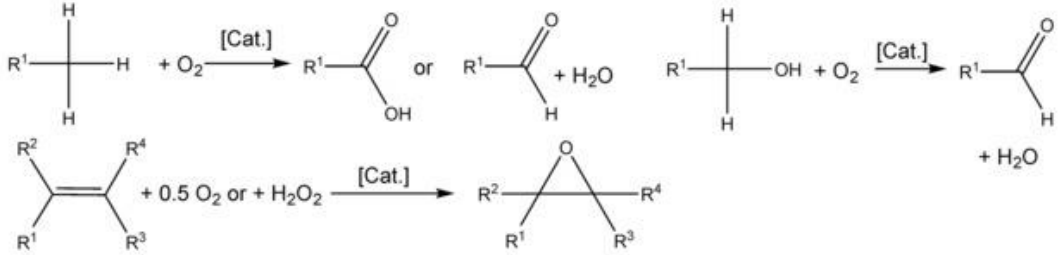
Aldol Condensation (e.g. Oxo-Alcohols)



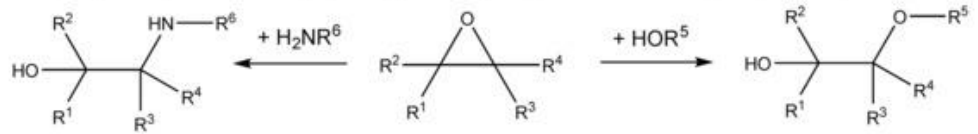
Amination (e.g. Aliphatic Amines)



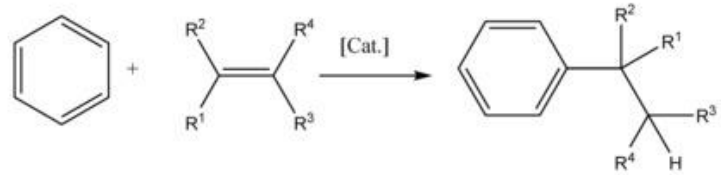
Oxidation (e.g. Phthalic Acid, Acrylic Acid, Ethylene- and Propylene Oxide)



Ring Opening Oxiranes (e.g. Ethylene Glycol, Alkanolamines, Polyethers)



Alkylation of Aromatics (e.g. Ethylbenzene, Cumene)



Efficient Industrial Organic Synthesis and the Principles of Green Chemistry,
T. Schaub, *Chem. Eur. J.* **2021**, *27*, 1865.
https://doi.org/10.1002/chem.202003544

Reactions types

Molecular Designers

(1) **minimize the overall number of steps**, preferably using nested MCRs as far as possible as the main strategy in a synthetic plan to a complex target;

(2) **maximize yield** per step to be no lower than **75%**;

(3) **maximize atom economy** per step keeping $(AE)_{min}$ above the **"golden" threshold of 61.8%** and E_{max} below 0.618;

(4) operate under **stoichiometric** conditions if possible, keeping SF equal to 1 for each reaction;

(5) minimize overall E_{mw} factor and maximize overall AE in **multistep syntheses**: (a) by **maximizing** frequency of **condensations**, **MCRs, rearrangements, carbon–carbon and non-carbon–carbon bond-forming reactions** and (b) by **minimizing** frequency of **substitutions** (protecting group strategies) and redox reactions;

(6) if forced to use **oxidations**, opt for hydrogen **peroxide or molecular oxygen** as oxidant;

(7) if forced to use **reductions**, opt for **molecular hydrogen** as reductant;

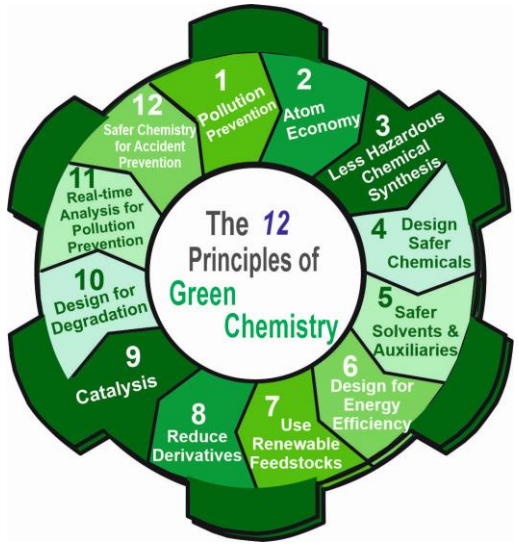
(8) devise **electrochemical** transformations;

(9) devise **catalytic methods** where catalysts are recycled and reused;

(10) devise **regio- and stereoselective** synthetic strategies particularly regio- and stereoselective MCRs;

(11) opt for **solventless** reactions, **recycle solvents**, or use **benign solvents** (e.g., ionic liquids, supercritical media);

(12) **minimize energy demands** such as heating, cooling, and carrying out reactions under pressure exceeding 1 atm; aim for reactions run under standard temperature and pressure conditions (room temperature and 1 atm).

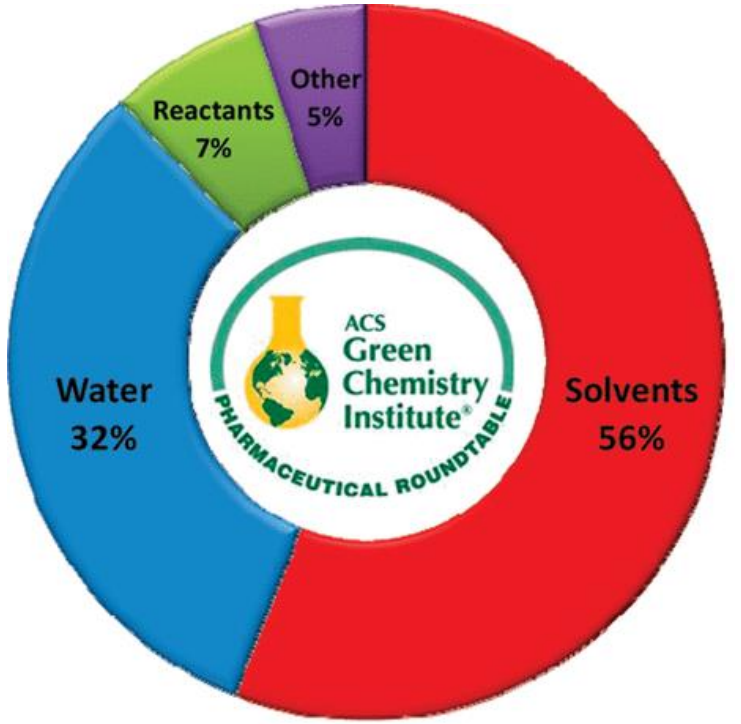


Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to Reaction Discovery
Org. Process Res. Dev. 2005, 9, 4, 404−431
https://doi.org/10.1021/op050014v

12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

- ❑ Solvent and water accounts for 80%-90% of mass utilized in a typical pharmaceutical chemical operation.
- ❑ Solvents are dominant in determining the toxicity of the process
- ❑ Finding a green replacement for traditional solvents remains a big challenge
- ❑ elimination/substitution of hazardous solvents



Process Mass Intensity Benchmark

What is a green solvent? A comprehensive framework for the environmental assessment of solvents
C. Capello, U. Fischer, K. Hungerbühler
Green Chem., **2007,** 9, 927-934
https://doi.org/10.1039/B617536H

Green and Sustainable Solvents in Chemical Processes
C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl, J. P. Hallett,
Chem. Rev. **2018**, 118, 2, 747–800
https://doi.org/10.1021/acs.chemrev.7b00571

12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

Solvent Selection

Recommended	Water, EtOH, i-PrOH, *n*-BuOH, EtOAc, i-PrOAc, *n*-BuOAc, anisole, sulfolane.
Recommended or problematic?	MeOH, *t*-BuOH, benzyl alcohol, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, MeOAc, AcOH, Ac_2O.
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylenes, chlorobenzene, acetonitrile, DMPU, DMSO.
Problematic or hazardous?	MTBE, THF, cyclohexane, DCM, formicacid, pyridine.
Hazardous	Diisopropyl ether, 1,4-dioxane, DME, pentane, hexane, DMF, DMAc, NMP, methoxy-ethanol, TEA.
Highly hazardous	Diethyl ether, benzene, chloroform, CCl_4, DCE, nitromethane.

CHEM21 selection guide of classical- and less classical-solvents,
Green Chem. 2016, 18, 288–296.
https://doi.org/10.1039/C5GC01008J

ACS Green Chemistry Institute Pharmaceutical Roundtable

https://www.acsgcipr.org/tools-for-innovation-in-chemistry/

❑ Solvent Selection Tool

https://www.acsgcipr.org/tools-for-innovation-in-chemistry/solvent-tool/

Toward a More Holistic Framework for Solvent Selection
Org. Process Res. Dev. 2016, 20, 4, 760–773
Publication Date:February 18, 2016
https://doi.org/10.1021/acs.oprd.6b00015

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

GSK solvent guide

Classification	Solvent	CAS number	Melting point °C	Boiling point °C	Waste recycling, incineration, VOC, and biotreatment issues	Environmental Impact fate and effects on the environment	Health acute and chronic effects on human health and exposure potential	Flammability & Explosion storage and handling	Reactivity/ Stability factors affecting the stability of the solvent	Life Cycle Score Environmental impacts to produce the solvent	Legislation Flag alerts regulatory restrictions
Greenest	Water	7732-18-5	0	100	4	10	10	10	10	10	
Alcohols	1-Butanol	71-36-3	-89	118	5	7	5	8	9	5	
	2-Butanol	78-92-2	-115	100	4	6	8	7	9	6	
	Ethanol/IMS	64-17-5	-114	78	3	8	8	6	9	9	
	t-Butanol	75-65-0	25	82	3	9	6	6	10	8	
	Methanol	67-56-1	-98	65	4	9	5	5	10	9	
	2-Propanol	67-63-0	-88	82	3	9	8	6	8	4	
	1-Propanol	71-23-8	-127	97	4	7	5	7	10	7	
	2-Methoxyethanol	109-86-4	-85	124	3	8	2	7	6	7	
Ester	t-Butyl acetate	540-88-5	-78	95	6	9	8	6	10	8	
	Isopropyl acetate	108-21-4	-73	89	5	7	7	6	9	7	
	Propyl acetate	109-60-4	-92	102	5	7	8	6	10	4	
	Dimethyl carbonate	616-38-6	-1	91	4	8	7	6	10	8	
	Ethyl acetate	141-78-6	-84	77	4	8	8	4	8	6	
	Methyl acetate	79-20-9	-98	57	3	9	7	4	9	7	
Ketone	Methylisobutyl ketone	108-10-1	-84	117	6	6	6	7	8	2	
	Acetone	67-64-1	-95	56	3	9	8	4	9	7	
	Methylethyl ketone	78-93-3	-87	80	3	7	8	4	8	3	
Organic Acids	Propionic acid	79-09-4	-21	141	4	8	6	8	8	7	
	Acetic acid (glacial)	64-19-7	17	118	4	8	6	8	7	8	
Aromatics	p-Xylene	106-42-3	-13	138	7	2	6	5	10	7	
	Toluene	108-88-3	-95	111	6	3	4	4	10	7	
	Benzene	71-43-2	6	80	5	6	1	3	10	7	
Hydrocarbons	Isooctane	540-84-1	-107	99	6	4	8	3	10	7	
	Cyclohexane	110-82-7	7	81	5	5	7	2	10	7	
	Heptane	142-82-5	-91	98	6	3	8	3	10	7	
	2-Methylpentane	107-83-5	-153	60	5	4	7	2	10	7	
	Hexane	110-54-3	-95	69	5	3	4	2	10	7	
	Petroleum spirit	8032-32-4	-73	55	6	2	2	3	10	7	
Ethers	t-Butyl methyl ether	1634-04-4	-109	55	4	5	5	3	9	8	
	Cyclopentyl methyl ether	5614-37-9	-140	106	6	4	4	5	8	4	
	2-Methyl THF	96-47-9	-137	78	4	5	4	3	6	4	
	Diethyl ether	60-29-7	-116	35	4	4	5	2	4	6	
	Bis(2-methoxyethyl) ether	111-96-6	-68	162	4	5	2	8	4	6	
	1,4-Dioxane	123-91-1	12	102	3	4	4	4	5	6	
	Tetrahydrofuran	109-99-9	-108	65	3	5	6	3	4	4	
	1,2-Dimethoxyethane	110-71-4	-58	85	4	5	2	4	4	7	
	Diisopropyl ether	108-20-3	-86	68	4	3	8	1	1	9	
Dipolar aprotics	Dimethyl sulfoxide	67-68-5	19	189	5	5	7	9	2	6	
	Dimethyl formamide	68-12-2	-61	153	4	6	2	9	9	7	
	N-Methylformamide	123-39-7	-4	200	4	6	2	10	10	7	
	N-Methyl pyrrolidone	872-50-4	-24	202	5	6	3	9	8	4	
	Dimethyl acetamide	127-19-5	-20	165	5	6	2	10	8	2	
	Acetonitrile	75-05-8	-45	82	2	6	6	6	10	3	
Chlorinated	Carbon tetrachloride	56-23-5	-23	77	4	5	3	4	10	7	
	Dichloromethane	75-09-2	-95	40	3	6	4	6	9	7	
	Chloroform	67-66-3	-64	61	3	6	3	6	9	6	
	1,2-Dichloroethane	107-06-2	-36	84	4	4	2	6	10	7	

Legislation Flag	
	Substitution recommended - There are no current restrictions but future regulatory restrictions may apply
	Substitution recommended - existing regulatory restrictions apply
	Must be substituted - A regulatory ban applies

Updating and further expanding GSK's solvent sustainability guide
Green Chem., **2016**, 18, 3879-3890
https://doi.org/10.1039/C6GC00611F

Sanofi's Solvent Selection Guide

Organic Process Research & Development

Article

pubs.acs.org/OPRD

Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes

Denis Prat,*,† Olivier Pardigon,‡ Hans-Wolfram Flemming,§ Sylvie Letestu,∥ Véronique Ducandas,† Pascal Isnard,⊥ Eberhard Guntrum,⊥ Thomas Senac,⊥ Stéphane Ruisseau,† Paul Cruciani,¶ and Patrik Hosek†

recommendation:

- Green: recommended solvent (most often these solvents are in the A list of the HSE guide)
- Yellow: substitution advisable. These can be used on an industrial scale with some constraints.
- Red: substitution requested. These can still be used in the pilot plant, but their use on industrial level for new processes has to be justified on the basis of unsuccessful substitution experiments.

Table 13. Example of sustainability improvement during Drug Candidate development

STEP	Discovery	Study batch	GMP1 batch
Triflatation	DMF	THF	THF
Suzuki coupling	Dioxane	Dioxane	Acetonitrile
N-arylation	DMF	DMF	Acetonitrile
Purification of API	Diethyl ether	DCM	Isopropanol

Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes
Org. Process Res. Dev. **2013**, 17, 12, 1517–1525
https://doi.org/10.1021/op4002565

Solvents Guide	ETHERS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Diethyl ether	Banned	5000	OEBV2	SHB5	EHB2	Peroxides, VOC
Diisopropyl ether	Substitution advisable	Not listed	OEBV2	SHB5	EHB3	Peroxides
Dibutyl ether	Substitution advisable	Not listed	OEBV2	SHB5	EHB3	Peroxides, odor
THF	Substitution advisable	720	OEBV3 Sk	SHB4	EHB2	VOC, miscible with water, peroxides
Methyl-THF	Recommended	Not listed	OEBV2	SHB4	EHB3	Peroxides, cost
Dioxane	Substitution requested	380	OEBV3 Sk	SHB5	EHB2	Miscible with water, peroxides
Anisole	Recommended	5000	OEBV2	SHB3	EHB2	Odor
MTBE	Substitution advisable	5000	OEBV3 Sk	SHB5	EHB3	VOC
ETBE	Substitution requested	Not listed	OEBV4	SHB5	EHB3	Peroxides, lack of data
CPME	Substitution requested	Not listed	OEBV3	SHB5	EHB3	Peroxides, one supplier only
Dimethoxy ethane	Substitution requested	100	OEBV4 G2	SHB4	EHB2	CMR (R1B), peroxides
Diglyme	Substitution requested	Not listed	OEBV4 G2	SHB4	EHB2	CMR (R1B), peroxides
Diethoxymethane	Substitution requested	Not listed	OEBV4	SHB5	Not available	Reactive, considered as CMR

12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

Pfizer solvent selection guide

PERSPECTIVE www.rsc.org/greenchem | Green Chemistry

Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation†

Kim Alfonsi,[a] Juan Colberg,[b] Peter J. Dunn,*[c] Thomas Fevig,[d] Sandra Jennings,[a] Timothy A. Johnson,[b] H. Peter Kleine,[d] Craig Knight,[c] Mark A. Nagy,[d] David A. Perry*[b] and Mark Stefaniak[c]

Received 1st August 2007, Accepted 30th October 2007
First published as an Advance Article on the web 16th November 2007
DOI: 10.1039/b711717e

Influencing and improving the environmental performance of a large multi-national pharmaceutical company can be achieved with the help of electronic education tools, backed up by site champions and strong site teams. This paper describes the development of two of those education tools.

Table 1 Red category solvents

Red solvent	Flash point	Reason
Pentane	−49 °C	Very low flash point, good alternative available.
Hexane(s)	−23 °C	More toxic than the alternative heptane, classified as a hazardous airborne pollutant (HAP) i
Diisopropyl ether	−12 °C	Very powerful peroxide former, good alternative ethers available.
Diether ether	−40 °C	Very low flash point, good alternative ethers available.
Chloroform	N/A	Carcinogen, classified as a HAP in the US.
Dichloroethane	15 °C	Carcinogen, classified as a HAP in the US.
Dimethyl formamide	57 °C	Toxicity, strongly regulated by EU Solvent Directive, classified as a HAP in the US.
Dimethyl acetamide	70 °C	Toxicity, strongly regulated by EU Solvent Directive.
N-Methyl pyrrolidinone	86 °C	Toxicity, strongly regulated by EU Solvent Directive.
Pyridine	20 °C	Carinogenic/mutagenic/reprotoxic (CMR) category 3 carcinogen, toxicity, very low threshold limit value TLV for worker exposures.
Dioxane	12 °C	CMR category 3 carcinogen, classified as HAP in US.
Dichloromethane	N/A	High volume use, regulated by EU solvent directive, classified as HAP in the US.
Dimethoxyethane	0 °C	CMR category 2 carcinogen, toxicity.
Benzene	−11 °C	Avoid use : CMR category 1 carcinogen, toxic to humans and environment, very low TLV (0.5 ppm), strongly regulated in the EU and the US (HAP).
Carbon tetrachloride	N/A	Avoid use : CMR category 3 carcinogen, toxic, ozone depleter, banned under the Montreal protocol, not available for large-scale use, strongly regulated in the EU and US (HAP).

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	Methyl *t*-butyl ether	Dichloromethane
Ethyl acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MethylTHF	Dimethyl formamide
Methyl ethyl ketone	Tetrahydrofuran	*N*-Methylpyrrolidinone
1-Butanol	Xylenes	Pyridine
t-Butanol	Dimethyl sulfoxide	Dimethyl acetate
	Acetic acid	Dioxane
	Ethylene glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Fig. 1 Pfizer solvent selection guide for medicinal chemistry.

CrossMark click for updates

Cite this: *Green Chem.*, 2014, **16**, 4546

A survey of solvent selection guides

Denis Prat,*[a] John Hayler[b] and Andy Wells[c]

A survey of solvent selection guides,
Green Chem., 2014,16, 4546-4551
https://doi.org/10.1039/C4GC01149J

CHEM21 solvent selection guide

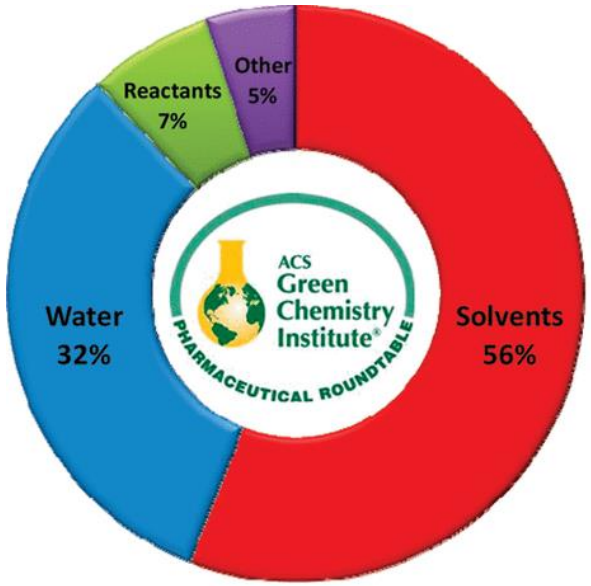
Family	Solvent	BP (°C)	FP (°C)	Worst H3xx[a]	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion[b]
Water	Water	100	na	None	None	1	1	1	Recommended	Recommended
Alcohols	MeOH	65	11	H301	None	4	7	5	Problematic	Recommended
	EtOH	78	13	H319	None	4	3	3	Recommended	Recommended
	i-PrOH	82	12	H319	None	4	3	3	Recommended	Recommended
	n-BuOH	118	29	H318	None	3	4	3	Recommended	Recommended
	t-BuOH[c]	82	11	H319	None	4	3	3	Recommended	Recommended
	Benzyl alcohol	206	101	H302	None	1	2	7	Problematic	Problematic
	Ethylene glycol	198	116	H302	None	1	2	5	Recommended	Recommended
Ketones	Acetone	56	−18	H319	None	5	3	5	Problematic	Recommended
	MEK	80	−6	H319	None	5	3	3	Recommended	Recommended
	MIBK	117	13	H319	None	4	2	3	Recommended	Recommended
	Cyclohexanone	156	43	H332	None	3	2	5	Recommended	Problematic
Esters	Methyl acetate	57	−10	H302	None	5	3	5	Problematic	Problematic
	Ethyl acetate	77	−4	H319	None	5	3	3	Recommended	Recommended
	i-PrOAc	89	2	H319	None	4	2	3	Recommended	Recommended
	n-BuOAc	126	22	H336	None	4	2	3	Recommended	Recommended
Ethers	Diethyl ether	34	−45	H302	None	10	3	7	Hazardous	HH
	Diisopropyl ether	69	−28	H336	None	9	3	5	Hazardous	Hazardous
	MTBE	55	−28	H315	None	8	3	5	Hazardous	Hazardous
	THF	66	−14	H351	None	6	7	5	Problematic	Problematic
	Me-THF	80	−11	H318	None	6	5	3	Problematic	Problematic
	1,4-Dioxane	101	12	H351	None	7	6	3	Problematic	Hazardous
	Anisole	154	52	None	None	4	1	5	Problematic	Recommended
	DME	85	−6	H360	None	7	10	3	Hazardous	Hazardous
Hydrocarbons	Pentane	36	−40	H304	H411	8	3	7	Hazardous	Hazardous
	Hexane	69	−22	H361	H411	8	7	7	Hazardous	Hazardous
	Heptane	98	−4	H304	H410	6	2	7	Problematic	Problematic
	Cyclohexane	81	−17	H304	H410	6	3	7	Problematic	Problematic
	Me-cyclohexane	101	−4	H304	H411	6	2	7	Problematic	Problematic
	Benzene	80	−11	H350	None	6	10	3	Hazardous	HH
	Toluene	111	4	H351	None	5	6	3	Problematic	Problematic
	Xylenes	140	27	H312	None	4	2	5	Problematic	Problematic
Halogenated	DCM	40	na	H351	None	1	7	7	Hazardous	Hazardous
	Chloroform	61	na	H351	None	2	7	5	Problematic	HH
	CCl_4	77	na	H351	H420	2	7	10	Hazardous	HH
	DCE	84	13	H350	None	4	10	3	Hazardous	HH
	Chlorobenzene	132	29	H332	H411	3	2	7	Problematic	Problematic
Aprotic polar	Acetonitrile	82	2	H319	None	4	3	3	Recommended	Problematic
	DMF	153	58	H360	None	3	9	5	Hazardous	Hazardous
	DMAc	166	70	H360	None	1	9	5	Hazardous	Hazardous
	NMP	202	96	H360	None	1	9	7	Hazardous	Hazardous
	DMPU	246	121	H361	None	1	6	7	Problematic	Problematic
	DMSO[c]	189	95	None	None	1	1	5	Recommended	Problematic
	Sulfolane[c]	287	177	H360	None	1	9	7	Hazardous	Hazardous
	HMPA	>200	144	H350	None	1	9	7	Hazardous	HH
	Nitromethane	101	35	H302	None	10	2	3	Hazardous	HH
Miscellaneous	Methoxy-ethanol	125	42	H360	None	3	9	3	Hazardous	Hazardous
	Carbon disulfide	46	−30	H361	H412	9	7	7	Hazardous	HH
Acids	Formic acid	101	49	H314	None	3	7	3	Problematic	Problematic
	Acetic acid	118	39	H314	None	3	7	3	Problematic	Problematic
	Ac_2O	139	49	H314	None	3	7	3	Problematic	Problematic
Amines	Pyridine	115	23	H302	None	4	2	3	Recommended	Hazardous
	TEA	89	−6	H314	None	6	7	3	Problematic	Hazardous

CHEM21 selection guide of classical- and less classical-solvents,
Green Chem. 2016, 18, 288–296.
https://doi.org/10.1039/C5GC01008J

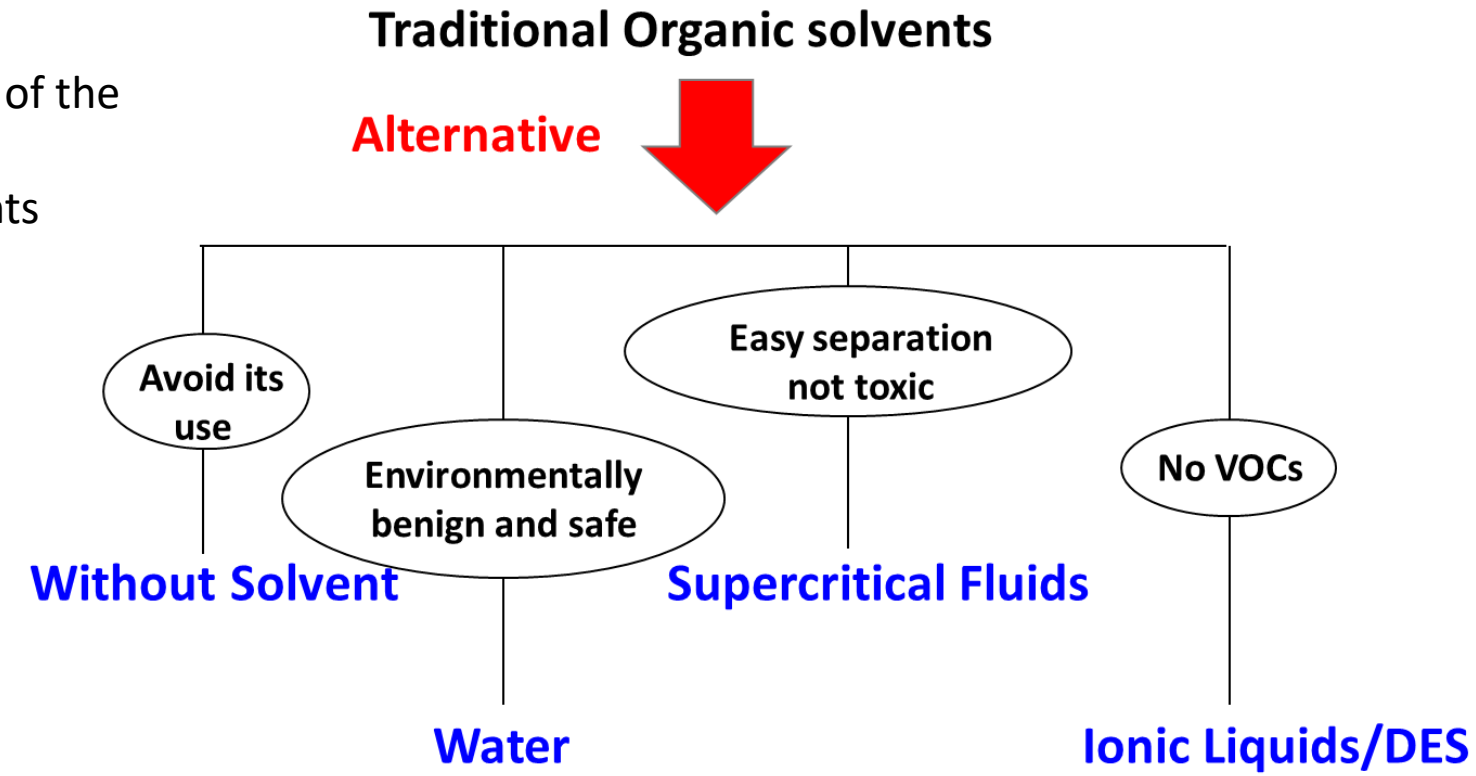
12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

- Solvent and water accounts for 80%-90% of mass utilized in a typical pharmaceutical chemical operation.
- Solvents are dominant in determining the toxicity of the process
- Finding a green replacement for traditional solvents remains a big challenge
- elimination/substitution of hazardous solvents



Process Mass Intensity Benchmark



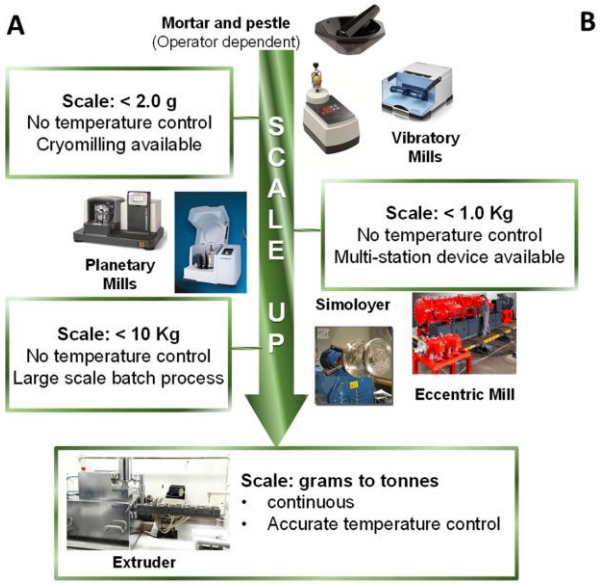
What is a green solvent? A comprehensive framework for the environmental assessment of solvents
C. Capello, U. Fischer, K. Hungerbühler
Green Chem., **2007,** 9, 927-934
https://doi.org/10.1039/B617536H

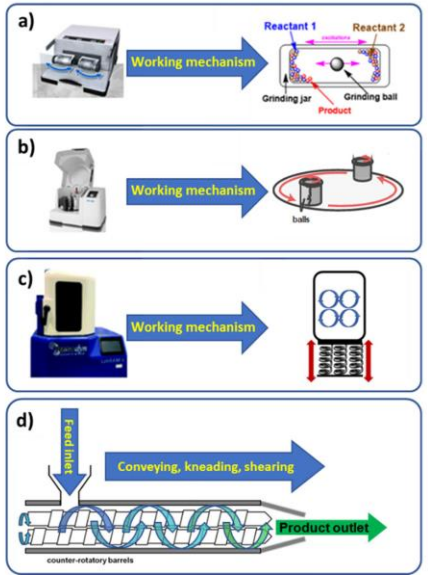
Green and Sustainable Solvents in Chemical Processes
C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl, J. P. Hallett,
Chem. Rev. **2018**, 118, 2, 747–800
https://doi.org/10.1021/acs.chemrev.7b00571

12 Principles of Green Chemistry

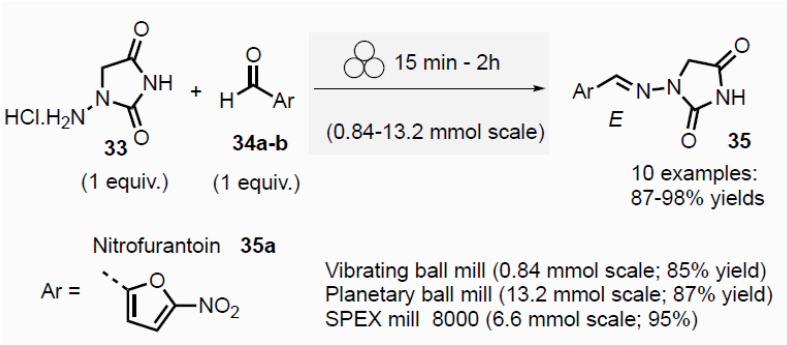
5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

6. Increase energy efficiency: Run chemical reactions at room temperature and pressure whenever possible.

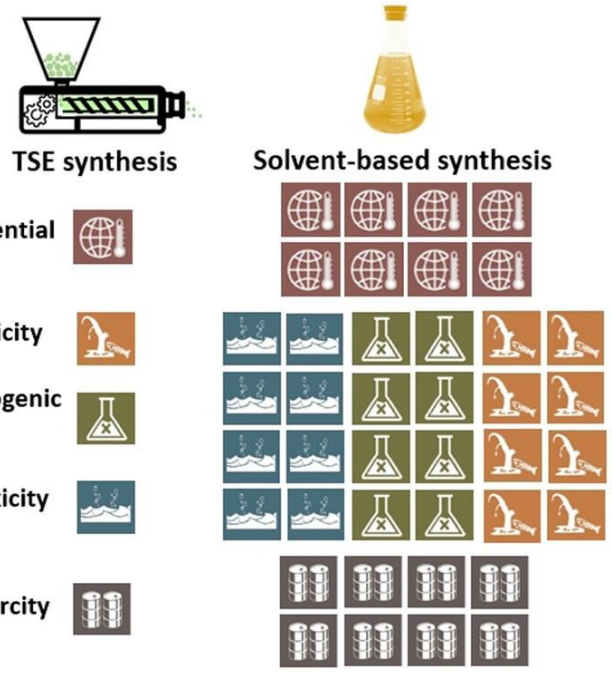


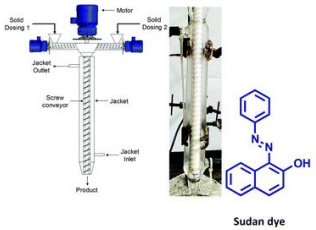


Mechanochemistry is an environmentally benign approach to chemical processes, which has steadily gained momentum at both laboratory and preparative scales



Schematic representation of the life cycle environmental impacts for the cradle-to-gate production of 1 kg of **nitrofurantoin** by TSE synthesis and batch solvent-based synthesis





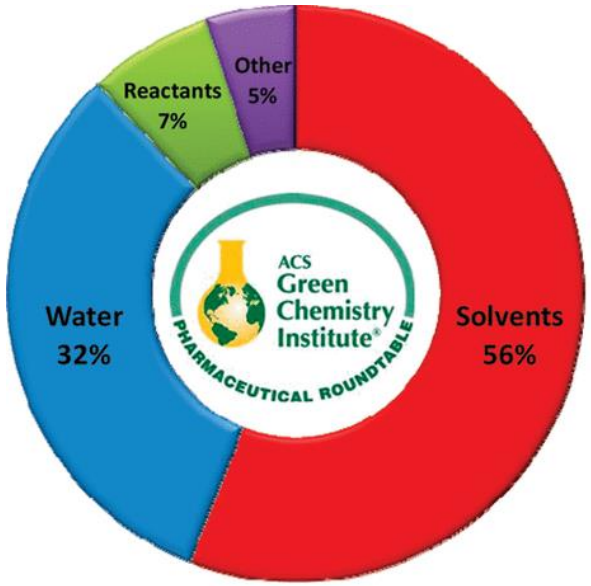
Batch and continuous flow mechanochemical synthesis of organic compounds including APIs
R. S. Atapalkarab, A. A. Kulkarnihttps,
React. Chem. Eng., 2024,9, 10-25
https://doi.org/10.1039/D2RE00521B

Tinkering with Mechanochemical Tools for Scale Up
J. F. Reynes, V. Isoni, F. García
Angew. Chem. Int. Ed. 2023, 62, e202300819.
https://doi.org/10.1002/anie.202300819

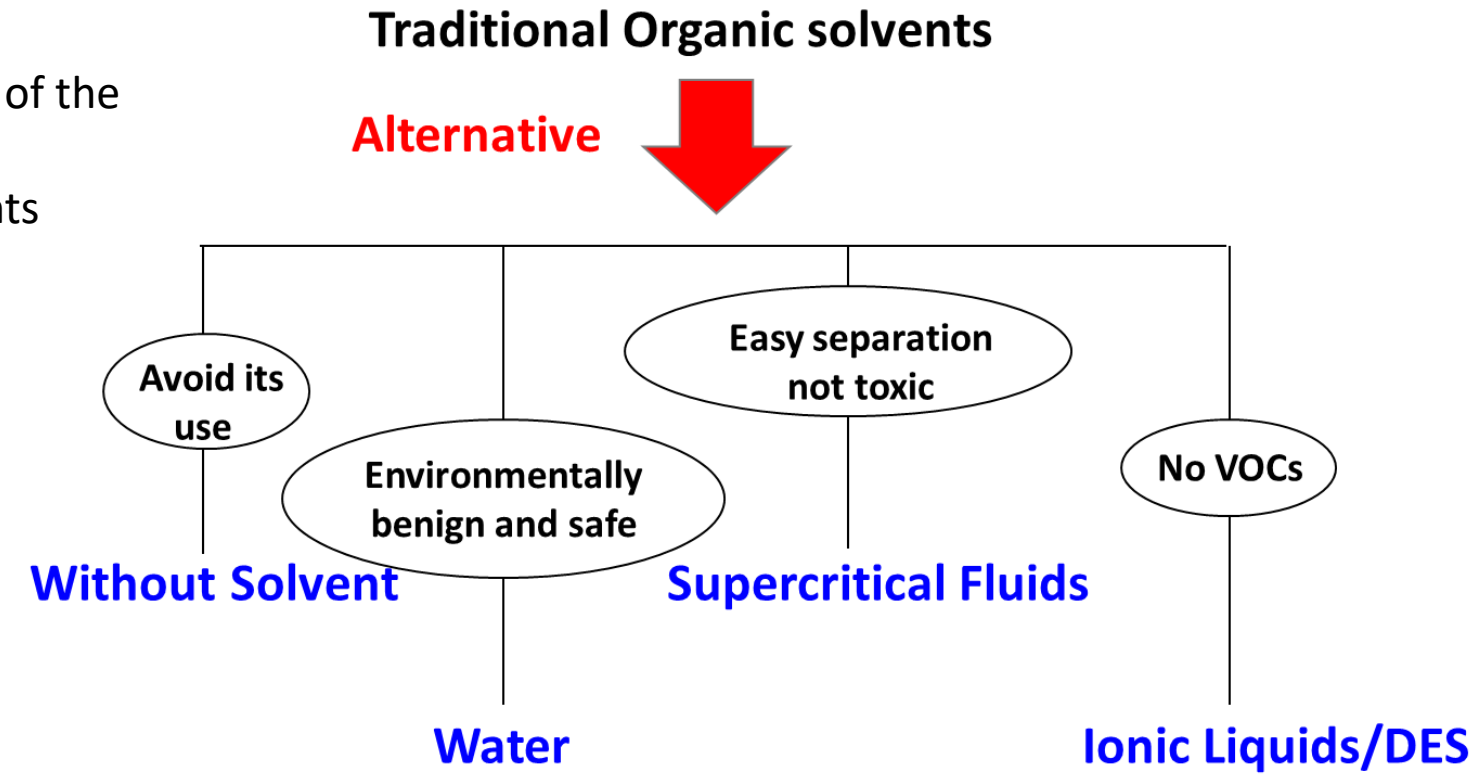
12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

- Solvent and water accounts for 80%-90% of mass utilized in a typical pharmaceutical chemical operation.
- Solvents are dominant in determining the toxicity of the process
- Finding a green replacement for traditional solvents remains a big challenge
- elimination/substitution of hazardous solvents



Process Mass Intensity Benchmark



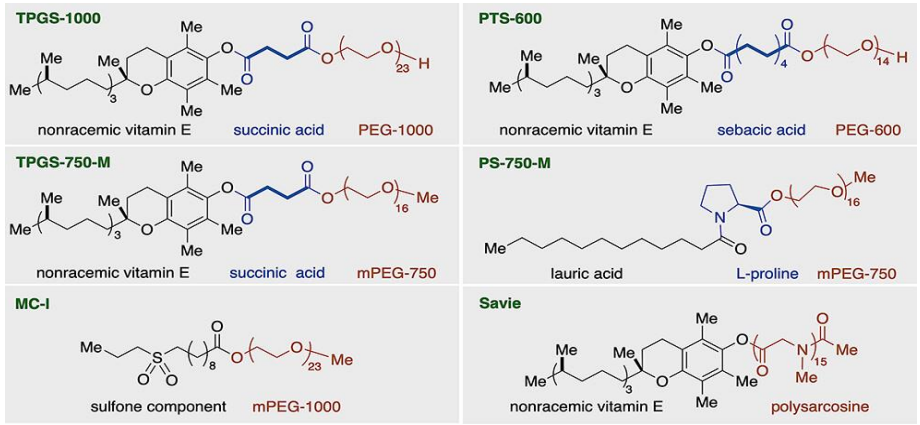
What is a green solvent? A comprehensive framework for the environmental assessment of solvents
C. Capello, U. Fischer, K. Hungerbühler
Green Chem., **2007,** 9, 927-934
https://doi.org/10.1039/B617536H

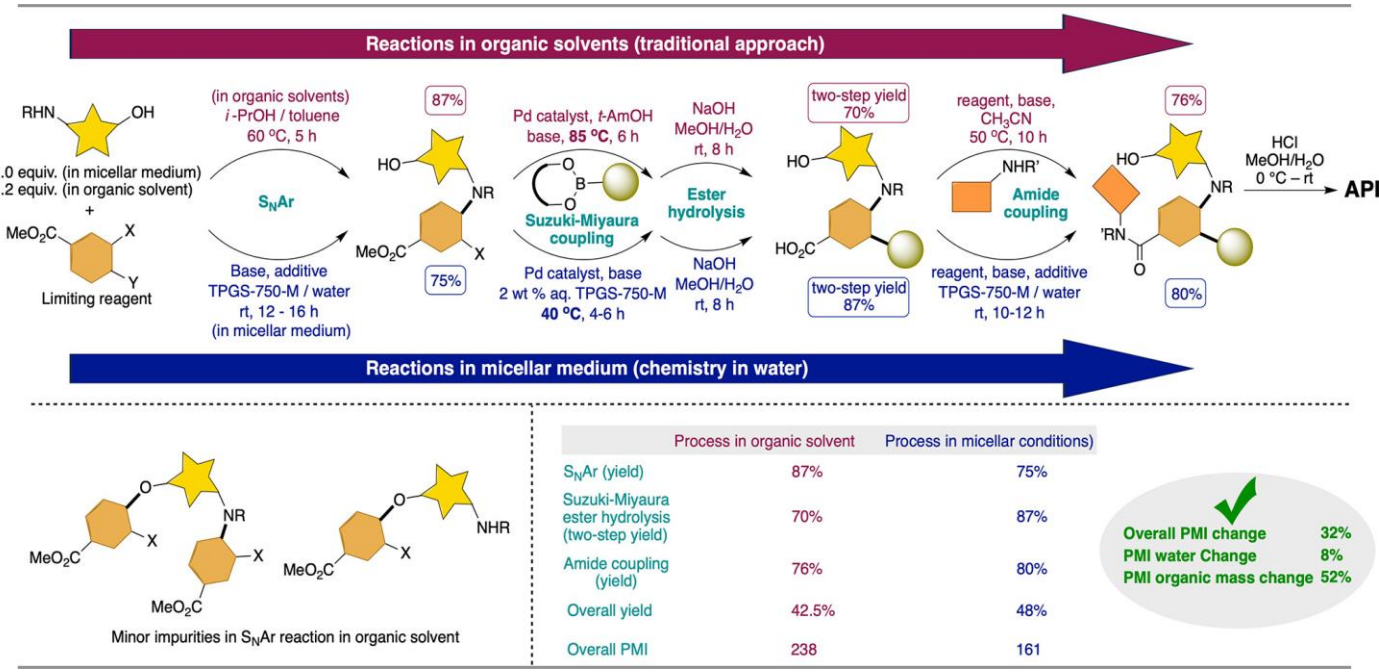
Green and Sustainable Solvents in Chemical Processes
C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl, J. P. Hallett,
Chem. Rev. **2018**, 118, 2, 747–800
https://doi.org/10.1021/acs.chemrev.7b00571

12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

Surfactant in water as a valuable alternative



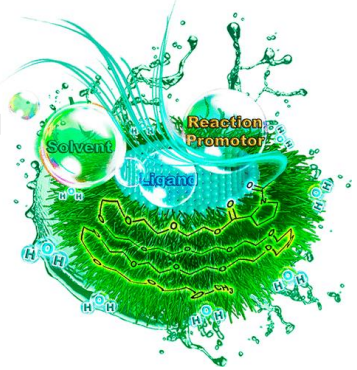


	Process in organic solvent	Process in micellar conditions)
S_NAr (yield)	87%	75%
Suzuki-Miyaura ester hydrolysis (two-step yield)	70%	87%
Amide coupling (yield)	76%	80%
Overall yield	42.5%	48%
Overall PMI	238	161

Overall PMI change 32%
PMI water Change 8%
PMI organic mass change 52%

Reactions in Water Involving the "On-Water" Mechanism
T. Kitanosono, S. Kobayashi, Chem. Eur. J. 2020, 26, 9408.
https://doi.org/10.1002/chem.201905482

Organic synthesis reactions on-water at the organic–liquid water interface
R. N. Butle, A. G. Coyne
Org. Biomol. Chem., 2016, 14, 9945-9960
https://doi.org/10.1039/C6OB01724J



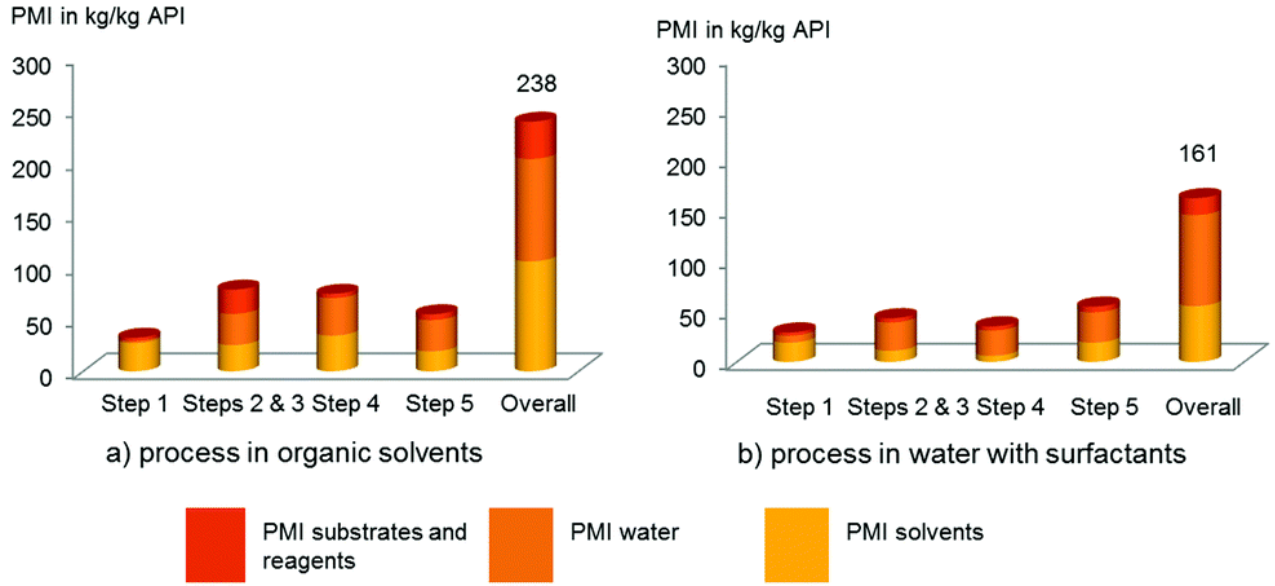
Aqueous Micelles as Solvent, Ligand, and Reaction Promoter in Catalysis
Jagdeep K. Virdi, Ashish Dusunge, and Sachin Handa*
JACS Au 2024, XXXX, XXX, XXX-XXX
Publication Date:January 16, 2024
https://doi.org/10.1021/jacsau.3c00605

Where Chemocatalysis Meets Biocatalysis: In Wate, H. Gröger, F. Gallou, B.H. Lipshutz,
Chem. Rev. 2023, 123, 9, 5262–5296
https://doi.org/10.1021/acs.chemrev.2c00416

12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

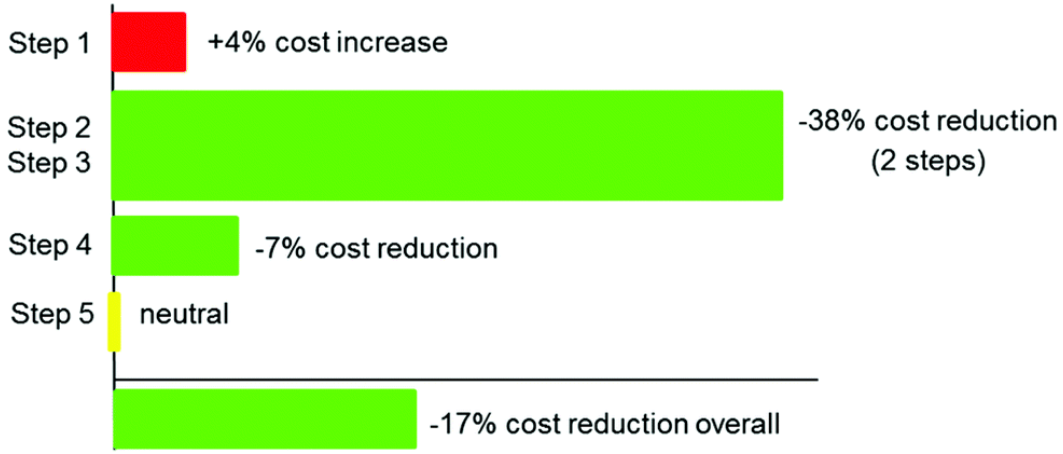
Surfactant in water as a valuable alternative



Comparison of evolution of the Process Mass Intensity (PMI): (

Table 2 Comparison of the cycle time for each transformation of our API in organic solvent *vs.* TPGS-750-M in water

	Cycle time (h)	
Step	Organic solvent	TPGS-750-M/water
S_NAr to **3**	104	61
Cross-coupling to **5**	61	24
hydrolysis to **6**	137	53
Amide-bond formation to **8**	105	76
Final deprotection to API	62	62
Total	469 (19.5 days)	276 (11.5 days)



Cost variation from surfactant-water process vs. organic solvent process.

From an environmental standpoint, the overall PMI also decreased by ca. 30% (from 238 to 161.5).
reduction in solvent usage by about 50% (from 105 to 55).
the surfactant technology minimizes the requirement for an organic solvent to that of a mere solubilizer for extraction purposes

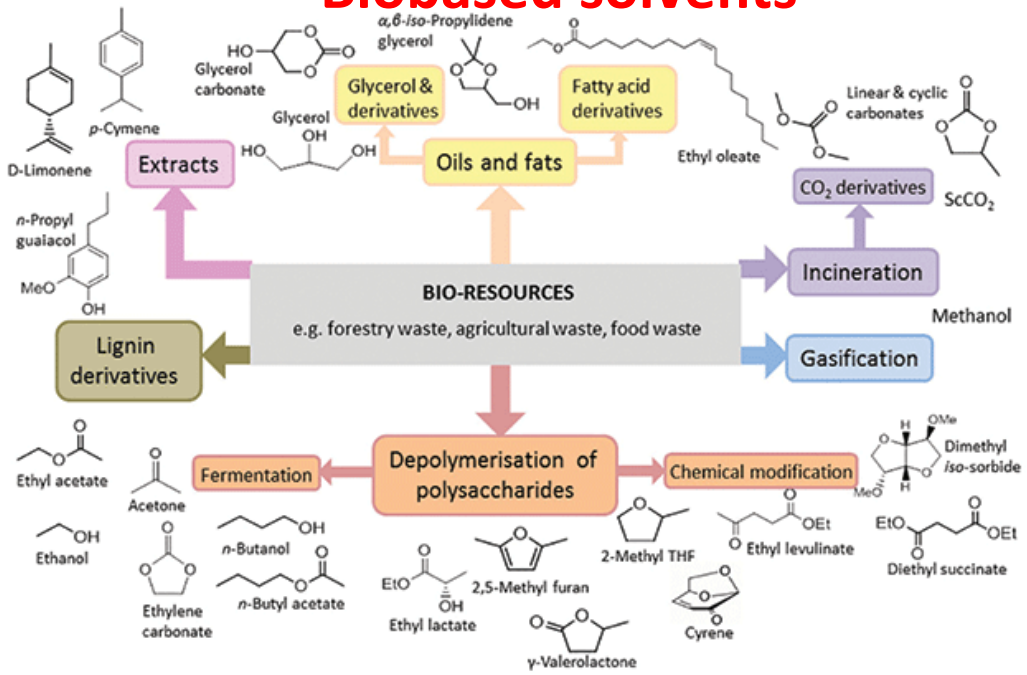
12 Principles of Green Chemistry

5. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.

Traditional Organic solvents

Alternative

Biobased solvents



Although bio-derived solvents are **not always safe and non-toxic**, as they are renewable they reduce concerns about the use of finite resources such as oil and natural gas

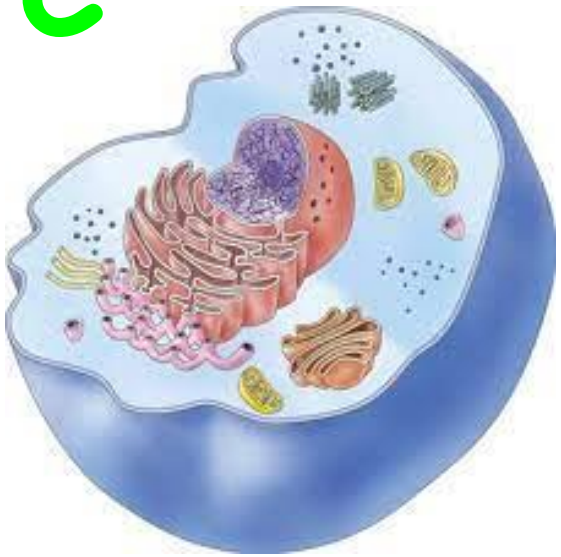
12 Principles of Green Chemistry

6. Increase energy efficiency: Run chemical reactions at room temperature and pressure whenever possible.

- Energy requirements should be recognized for their environmental and economic impacts and should be minimized.
- In a process most energy is used for heating, cooling, separations and pumping.

A + B → C

Ideally, all reactions are performed at '**ambient' conditions – room temperature and atmospheric pressure"** – in order to minimize energy usage.

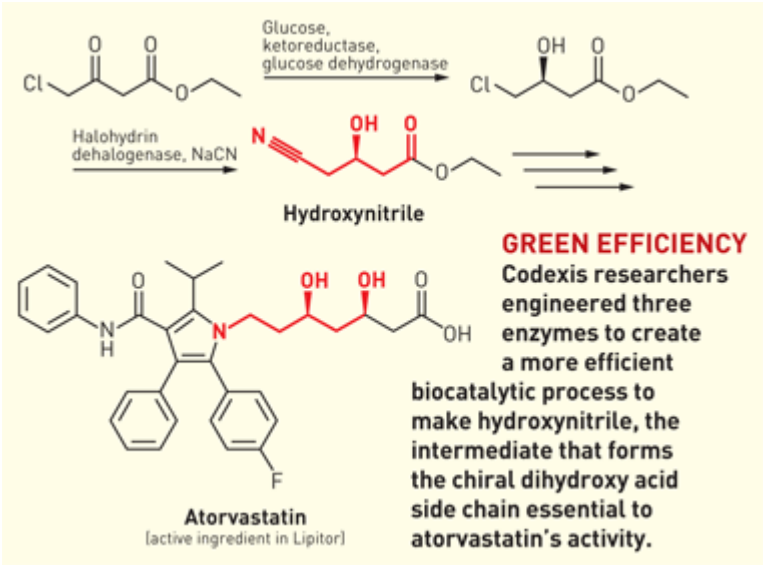


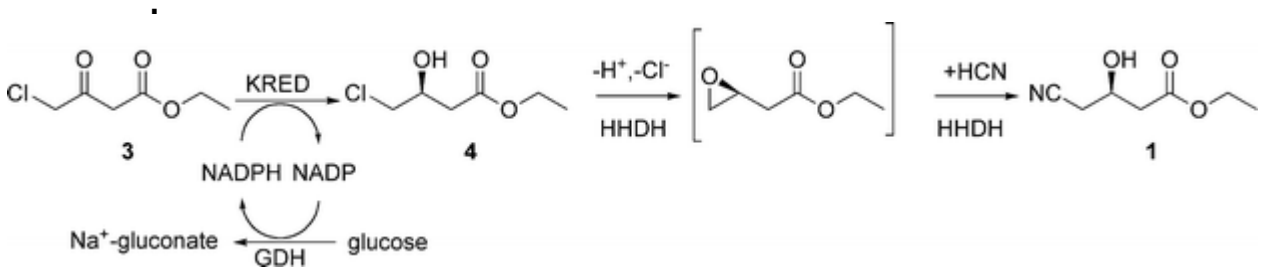
12 Principles of Green Chemistry

6. Increase energy efficiency: Run chemical reactions at room temperature and pressure whenever possible.

Atorvastatin, a cholesterol-lowering drug, suffers from an energy-demanding synthesis as a result of two cryogenic reactions at - 70 °C.

La New ***biocatalytic*** synthesis uses enzyme DERA and shortens the process by removing two energy intensive chemical steps.





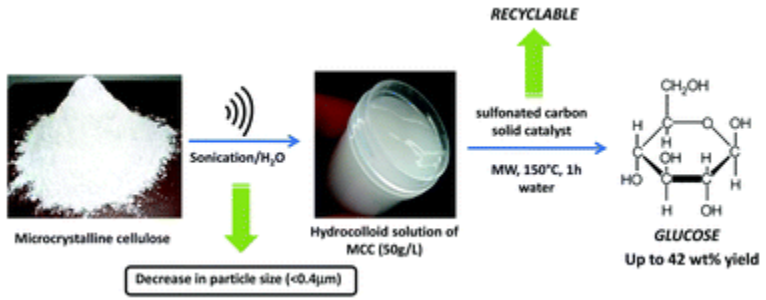
12 Principles of Green Chemistry

6. Increase energy efficiency: Run chemical reactions at room temperature and pressure whenever possible.

Sono-, microwave-, and photo-assisted chemistry are known to save energy, improve reaction time, and catalytic activity.

Sonochemistry:

- Uses of high frequency (20-100 kHz) sound waves to promote chemical reaction.
- The collapse of bubbles formed in a solution generates a very high temperature and a higher pressure than conventional heating.
- Used in the production of triglycerides from methyl transesterification.



Green Chem., 2013,15, 963-969
https://doi.org/10.1039/C3GC36643J

Microwave:

- Uses a high-frequency electric field to heat or cool the local environment with electrical charges.
- Avoids unnecessarily prolonged residence time at a given temperature.

Green Chem., 2019,21, 6043-6050
https://doi.org/10.1039/C9GC02534K

Photo-assisted:

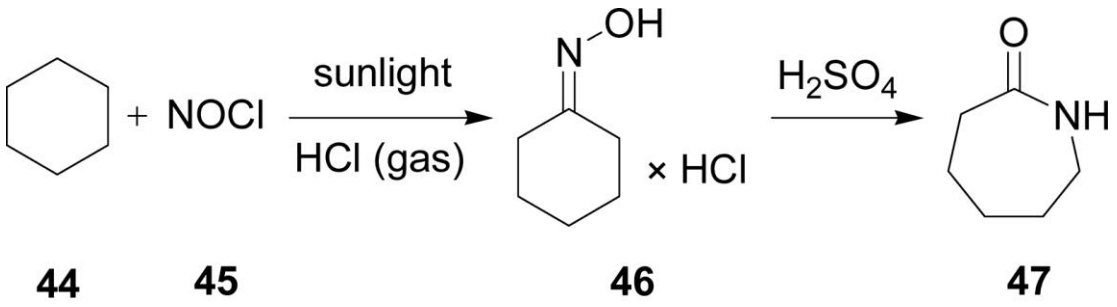
- Naturally occurring, such as using the sun as a catalyst.
- Used in photo-driven acylation for the production of valuable synthetic intermediates and commercial fragrances in bulk.
- Used by BASF to develop automotive primer coating, a precursor readily able to be crosslinked under photo irradiation, as opposed to its conventional energy-intensive thermally driven variation.

Chem. Rev. 2016, 116, 17, 9664–9682
https://doi.org/10.1021/acs.chemrev.5b00720

12 Principles of Green Chemistry

6. Increase energy efficiency: Run chemical reactions at room temperature and pressure whenever possible.

Photo-assisted:



5.5 L cyclohexane (HCl saturated)
2.8-7.59×10^{-6} kg/s of NOCl; 1:1-1.3:1 ratio HCl:NOCl
61-84% yields of **46** after 1-4$^1/_4$ h in a solar furnace (DLR)

Solar Photooximation of Cyclohexane (**44**) and Subsequent Conversion to ε-Caprolactam (**47**)

The reaction is of significant industrial importance for the synthesis of ε-caprolactam and consequently nylon-6. For 1991, an annual production of 160 000 t was realized by Toray in Japan.

The solar reaction was performed in a specialized titanium vessel that was fitted with glass windows for the incoming and exiting solar beam. The device was encased by a glass cooling water mantle, which also functioned as an effective IR filter. Cyclohexane was initially saturated with hydrochloric acid before a fine stream of nitrosyl chloride entered the reactor vessel from the bottom. During solar exposure, cyclohexanone oxime hydrochloride precipitated as an oily substance. Solar exposure for 1–4.25 h furnished the desired oxime in good yields of 61–84% and with excellent selectivity.

DOI: (10.1021/acs.chemrev.5b00720)

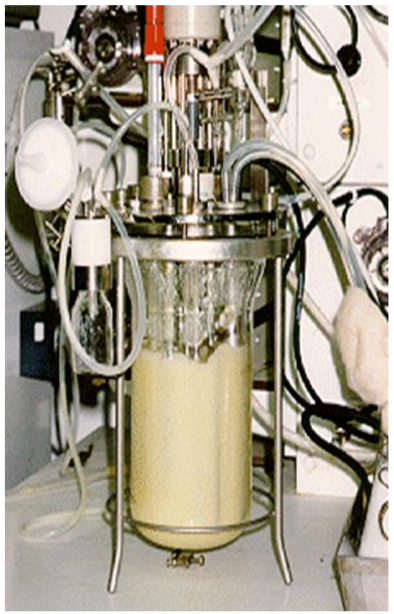
12 Principles of Green Chemistry

7. Use renewable feedstocks: Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.

Renewable resources offer the chemical industry an opportunity to diversify its raw materials base, **but…** '**greenwashing**' (presenting a process or product as greener than it actually is) **should be prevented!!!!**

Bio-based materials are typically classified as being sustainable, simply because of renewability of the resource, yet these resources are often created in a linear production process without sustainable end-of-life options.

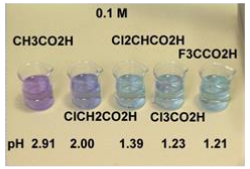
Grain



Bio-refineria

Fuels

Solvent



Bulk chemicals

Plastics

Fibres

Fine chemicals

Oils

From petroleum-base to bio-based

- Raw material one single stream oil refinery industry — ethylene, propylene, butane, benzene, toluene, xylenes, and methanol— high volume available
- chemicals are obtained with limited or not transformation.
- Structure of the polymers optimize for performance (i.e. flexibility, strength, toughness, etc)
- Optimized technological platform for many years where multiple products share investment and infrastructure costs without customized production requirements

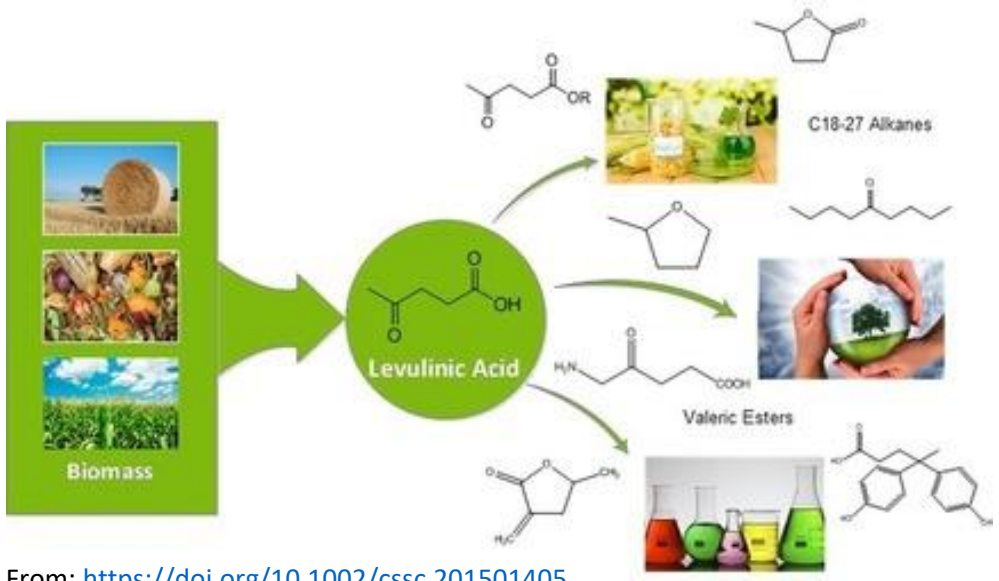
- Multiple raw materials with not required availability
- Need of relatively complex innovative chemical transformations / multistep to produce high quality chemicals from renewable feedstocks in an efficient manner.
- structure–property relationships can be appropriately matched to the specific and unique requirements of each biodegradable application. **Trade-Off between Performance and biodegradability**
- Required fast development
- New infrastructures (biorefineries)

Catal. Sci. Technol., 2014,**4**, 1174-1196
https://doi.org/10.1039/C3CY01058A

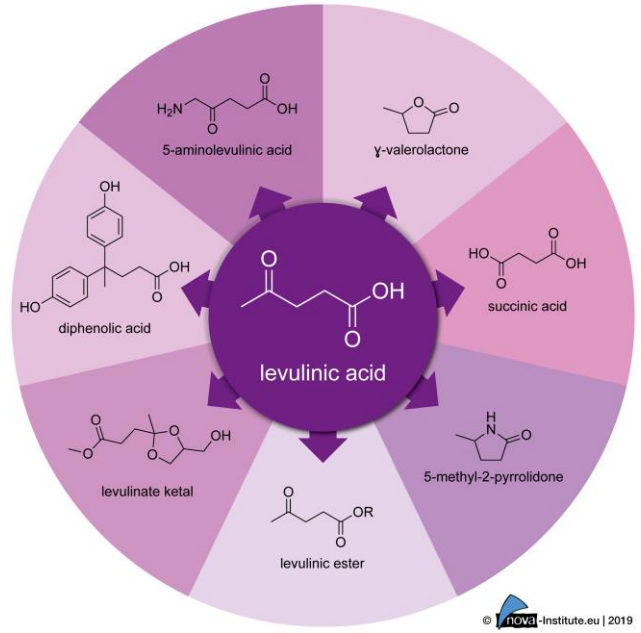
12 Principles of Green Chemistry

7. Use renewable feedstocks: Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.

- **Biofine** (now DPS Biometrics, Inc.) developed a process to convert the **waste cellulose in paper mill sludge, municipal solid waste, unrecyclable wastepaper, waste wood, and agricultural residues into levulinic acid (LA).**
- LA can be used as a building block for chemicals in many useful materials, including pharmaceuticals, food additives and plastics.
- LA made from waste cellulose reduces the use of fossil fuels and reduces the overall cost of LA from $4–6 per pound to as little as $0.32 per pound.
- In 2015, **GF Biochemical** opened a **10,000MT capacity plant to produce LA from biomass on an industrial scale**



From: https://doi.org/10.1002/cssc.201501405

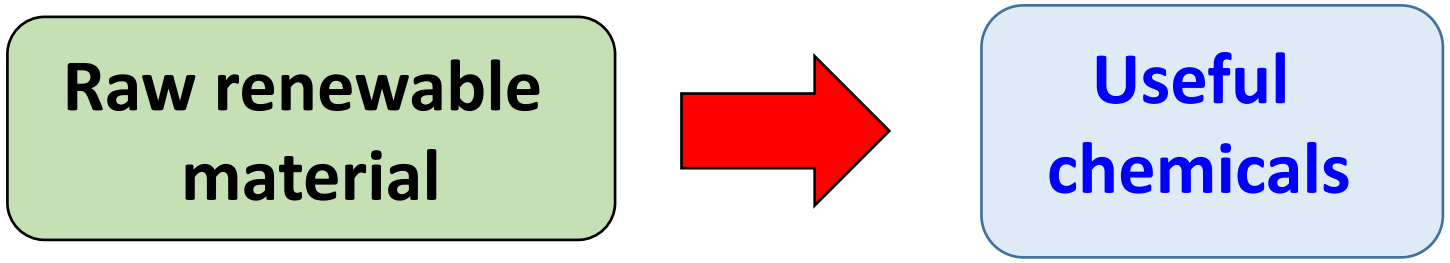


https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-1999-small-business-award
https://cen.acs.org/articles/94/i2/One-Companys-Big-Plans-Levulinic.html

http://www.gfbiochemicals.com

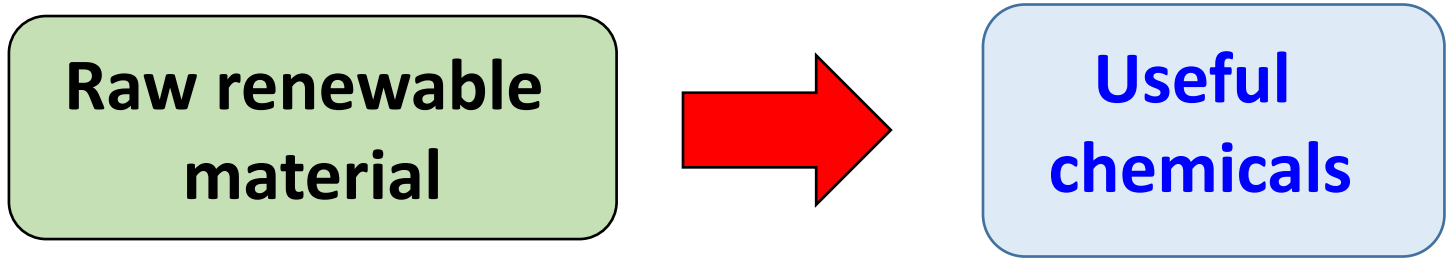
12 Principles of Green Chemistry

7. Use renewable feedstocks: Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.



Renewable raw materials have the potential to provide a wide range of chemicals arguably as comprehensive as those provided by the petrochemical industry

Which are the best raw materials?

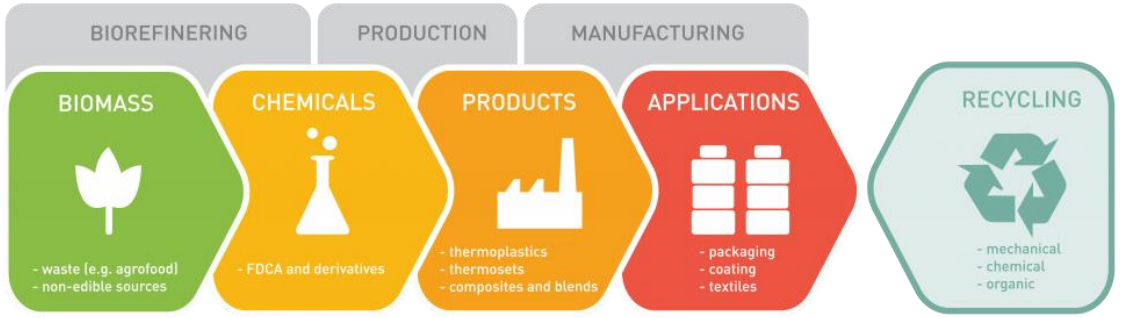


- ❑ Source
- ❑ Nature
- ❑ How to obtain them
- ❑ availability
- ❑ Cost

Which are the best raw materials?

Raw renewable material → **Useful monomers**

- ❑ Source
- ❑ Nature
- ❑ How to obtain them
- ❑ availability
- ❑ Cost



✓ Type of polymer

From petroleum-base to bio-based

Feedstocks in a biorefinery will largely **involve different processes and reaction types** to those involved in a petrochemical refinery

- ❑ feedstocks are gaseous or liquid hydrocarbons that are oxidized at elevated temperatures, in the vapor or liquid phase, under solvent-free conditions
- ❑ Low functionalization and oxidation degree
- ❑ reaction types: oxidation, hydroformylation, carbonylation, hydrogenation, hydrocyanation, oligomerization
- ❑ Distillation, crystallizations

- ➢ solid, water soluble carbohydrates
- ➢ Oxygenated feedstocks
- ➢ derivatives are oxygen-containing carbohydrates requiring a series of reaction steps such as, e.g. hydrolysis, dehydration/alkylation, hydrodeoxygenation (HDO), Hydrogenation etc.
- ➢ cascade or one-pot tandem catalytic reaction processes are preferred
- ➢ separation and purification can be an issue

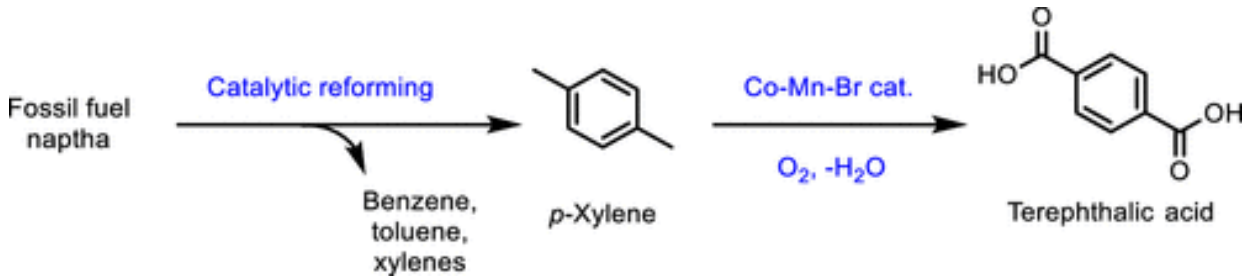
Greening the Synthesis of Biorenewable Fuels and Chemicals by Stoichiometric Reagentless Organic Transformations,
S. Dutta. Ind. Eng. Chem. Res. **2022**, 61, 35, 12884–12904,
https://doi.org/10.1021/acs.iecr.2c02322

From petroleum-base to bio-based

feedstocks in a biorefinery will largely involve different processes and reaction types to those involved in a petrochemical refinery

Useful monomers

- feedstocks are gaseous or liquid hydrocarbons that are oxidized at elevated temperatures, in the vapor or liquid phase, under solvent-free conditions
- Low functionalization and oxidation degree
- reaction types: oxidation, hydroformylation, carbonylation, hydrogenation, hydrocyanation, oligomerization
- Distillations crystallizations

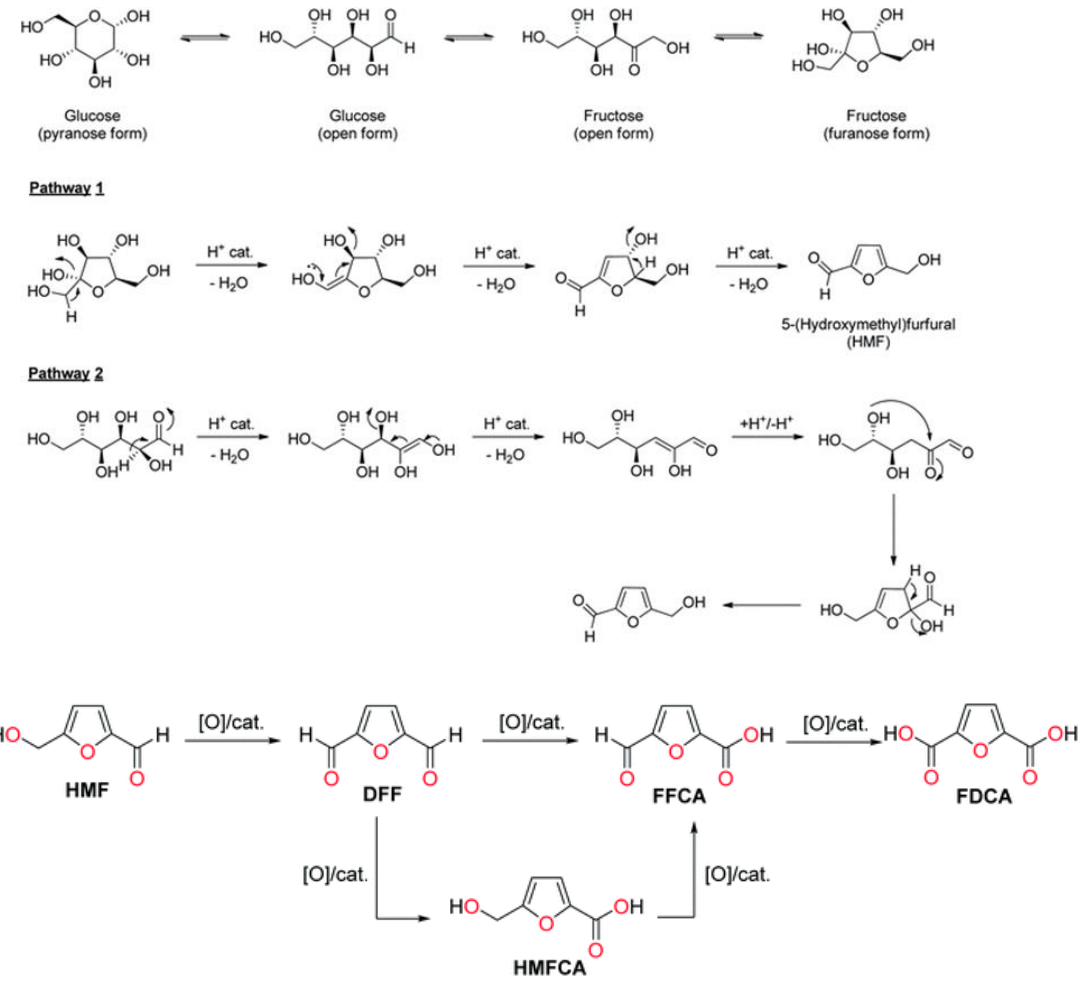


Greening the Synthesis of Biorenewable Fuels and Chemicals by Stoichiometric Reagentless Organic Transformations,
S. Dutta. Ind. Eng. Chem. Res. **2022**, 61, 35, 12884–12904,
https://doi.org/10.1021/acs.iecr.2c02322

From petroleum-base to bio-based

feedstocks in a biorefinery will largely involve different processes and reaction types to those involved in a petrochemical refinery

Useful monomers



- solid, water soluble carbohydrates
- Oxygenated feedstocks
- derivatives are oxygen-containing carbohydrates requiring a series of reaction steps such as, e.g. hydrolysis, dehydration/alkylation, hydrodeoxygenation (HDO),Hydrogenation etc. to be converted into
- cascade or one-pot tandem catalytic reaction processes are preferred
- separation and purification can be an issue

Greening the Synthesis of Biorenewable Fuels and Chemicals by Stoichiometric Reagentless Organic Transformations,
S. Dutta. Ind. Eng. Chem. Res. **2022**, 61, 35, 12884–12904,
https://doi.org/10.1021/acs.iecr.2c02322

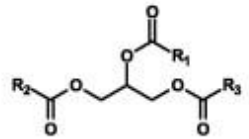
What source of renewable raw material?

Vegetable oils, Soybean oil, castor oil, nahor seed oil, *etc.*

diverse chemistry can be applied on them, leading to a large variety of monomers and polymers

A

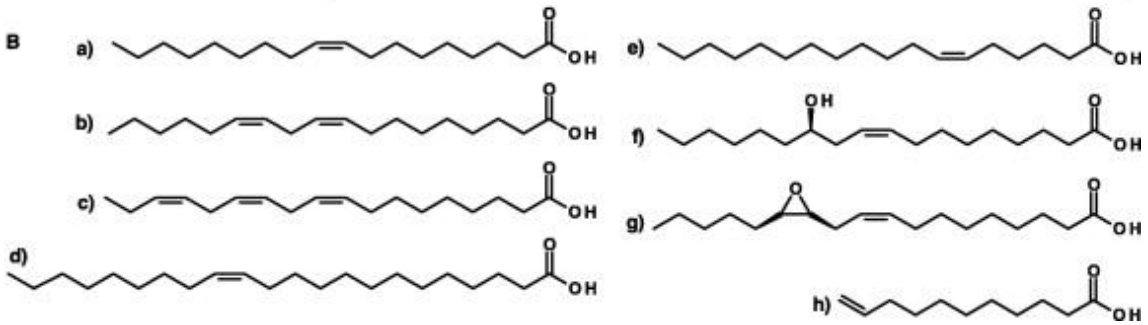
Triglyceride generic structure



R = fatty acid chain

	14:0	14:1	16:0	16:1	17:0	17:1	18:0	18:1	18:2	18:3	20:0	20:1
Canola	0.1	0.0	4.1	0.3	0.1	0.0	1.8	60.9	21.0	8.8	0.7	1.0
Corn	0.1	0.0	10.9	0.2	0.1	0.0	2.0	25.4	59.6	1.2	0.4	0.0
Linseed	0.0	0.0	5.5	0.0	0.0	0.0	3.5	19.1	15.3	56.6	0.0	0.0
Olive	0.0	0.0	13.7	1.2	0.0	0.0	2.5	71.1	10.0	0.6	0.9	0.0
Palm	1.0	0.0	44.4	0.2	0.1	0.0	4.1	39.3	10.0	0.4	0.3	0.0
Soybean	0.1	0.0	11.0	0.1	0.0	0.0	4.0	23.4	53.2	7.8	0.3	0.0
Sunflower	0.0	0.0	6.1	0.0	0.0	0.0	3.9	42.6	46.4	1.0	0.0	0.0
High oleic	0.0	0.0	6.4	0.1	0.0	0.0	3.1	82.6	2.3	3.7	0.2	0.4

B



epoxidation,
oxidation
cross-metathesis

oils → **Oils synthetic monomers**

Oils synthetic monomers → **Polyester, polyamides, polyurethanes, epoxy resins, thiol–ene/fatty acids**

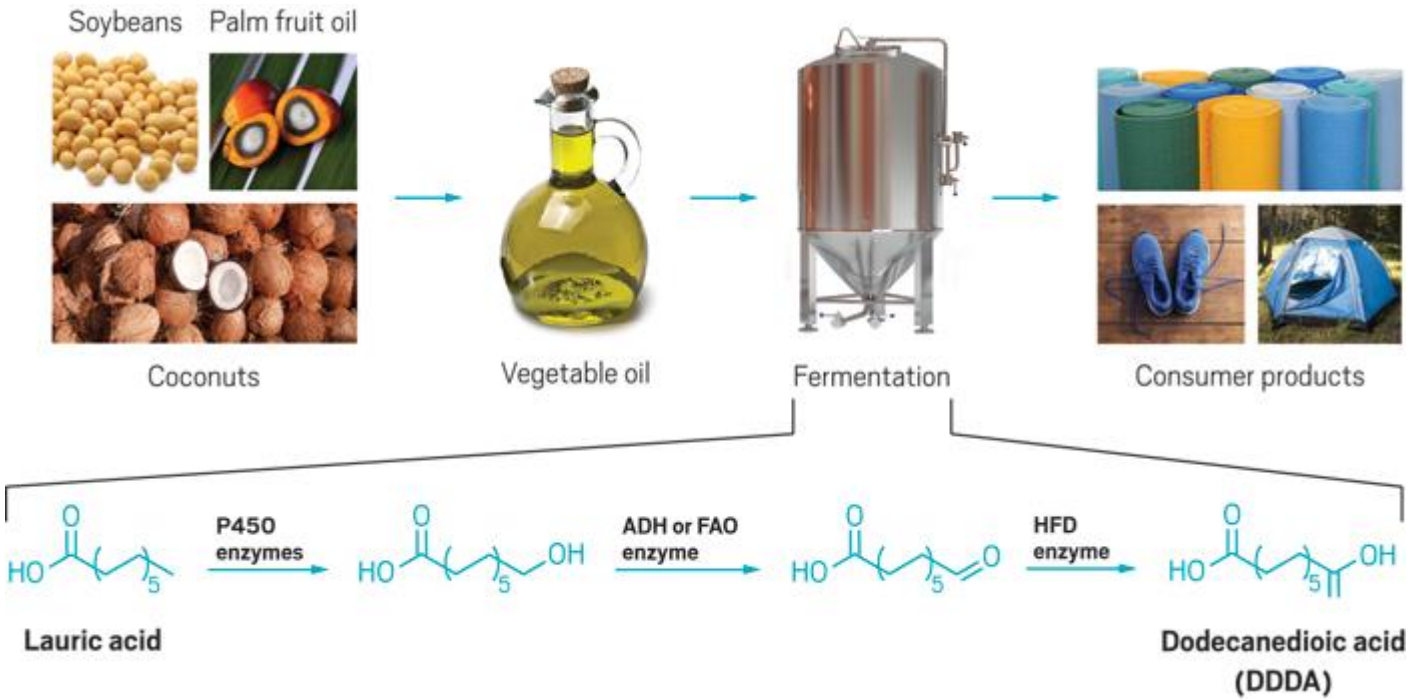
Plant oils: The perfect renewable resource for polymer science?!, L. Montero de Espinosa, M. A.R.Meier, European Polymer J., 2011, 47, 837-852.
, https://doi.org/10.1016/j.eurpolymj.2010.11.020

Fatty Acids and their Derivatives as Renewable Platform Molecules for the Chemical Industry, U. Biermann, U. T. Bornscheuer, I. Feussner, M. A. R. Meier, J. O. Metzger, *Angew. Chem. Int. Ed.* **2021**, *60*, 20144.
https://doi.org/10.1002/anie.202100778

12 Principles of Green Chemistry

7. Use renewable feedstocks: Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.

Verdezyne scientists adapted yeast to develop a three-step enzymatic process for converting lauric acid derived from vegetable oil into diacids such as DDDA, which is used to make nylon and other chemicals that go into manufacturing consumer products



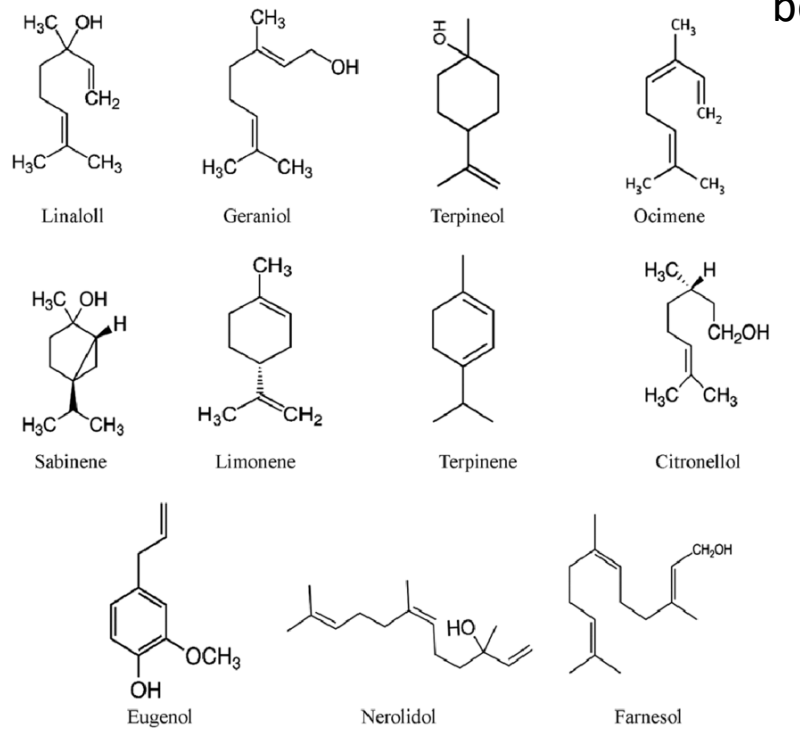
- The optimized yeast uses a three-step enzyme-mediated fermentation process to oxidize lauric acid to DDDA at a rate of better than 140 g/L.
- Verdezyne has demonstrated the technology in a pilot facility and is now building a 9,000-metric-ton-per-year Biolon commercial facility in Malaysia.

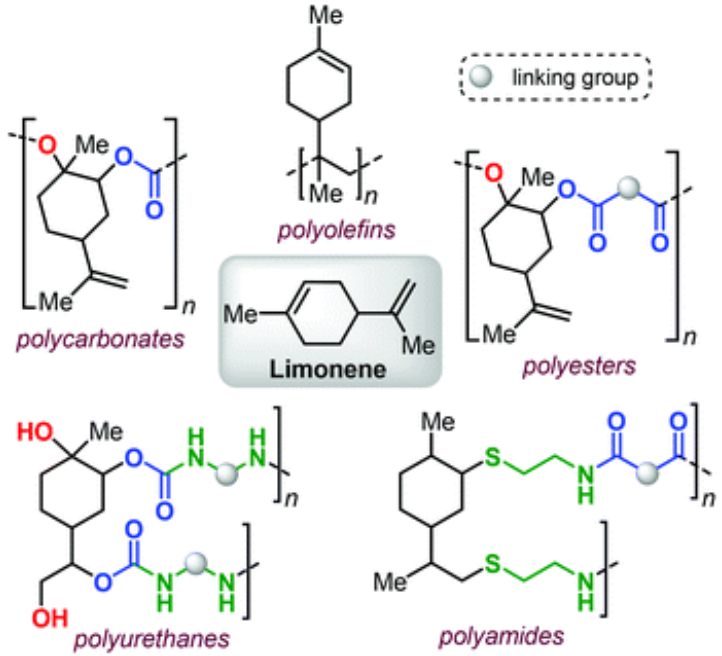
https://cen.acs.org/articles/94/i25/Green-success-stories-2016-Presidential.html

What source of renewable raw material?

Terpenes

Limonene is one of the most abundant terpenes (present in more than 300 plants) and is a prominent waste stream of the citrus industry, with the (*R*)-enantiomer being produced on a scale of over 70 KTA



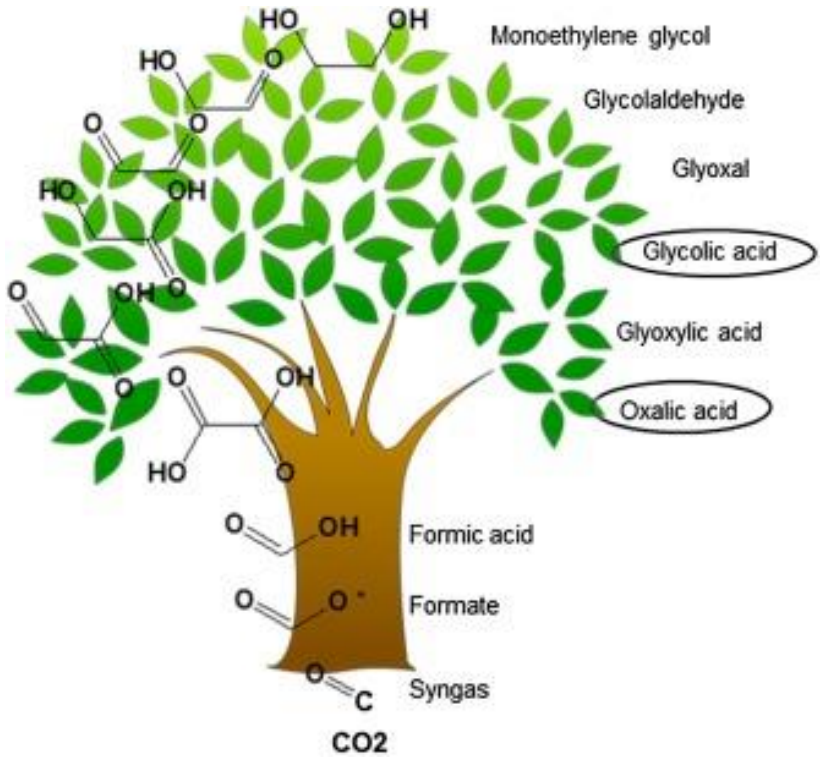


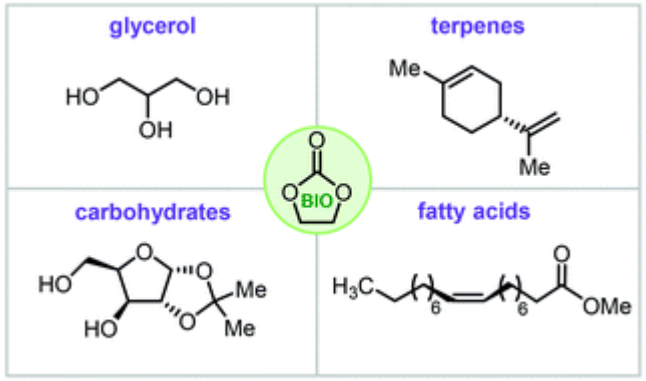
Polymers of Limonene Oxide and Carbon Dioxide: Polycarbonates of the Solar Economy, F. Parrino, A. Fidalgo, L. Palmisano, L. M. Ilharco, M. Pagliaro, R. Ciriminna, *ACS Omega* 2018, 3, 5, 4884–4890, https://doi.org/10.1021/acsomega.8b00644

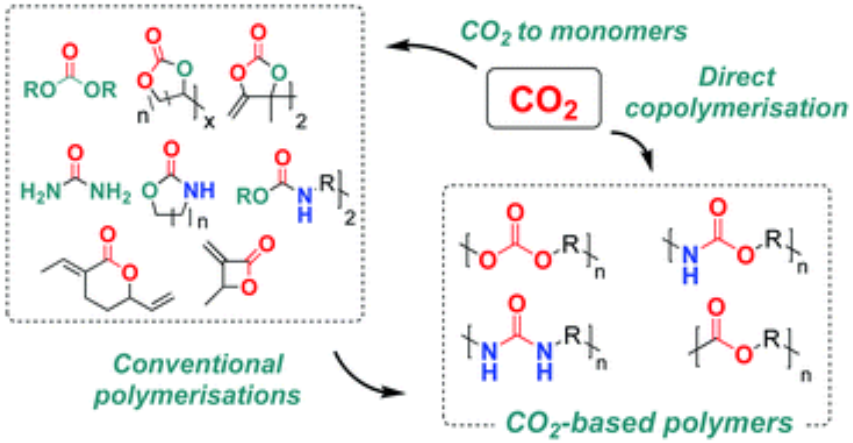
From terpenes to sustainable and functional polymers, F. Della Monica, A. W. Kleij, *Polym. Chem.*, **2020**, 11, 5109-5127 https://doi.org/10.1039/D0PY00817F

What source of renewable raw material?

CO_2







The potential of oxalic – and glycolic acid based polyesters (review). Towards CO2 as a feedstock (Carbon Capture and Utilization – CCU), M. A. Murcia Valderrama, R.-J.. Putten, G.-J. M.Gruter, European Pol. J., 2019, 19, 445-468. https://doi.org/10.1016/j.eurpolymj.2019.07.036

Towards Sustainable Oxalic Acid from CO_2 and Biomass, E. Schuler, M. Demetriou, N. R. Shiju, G.-J. M. Gruter, *ChemSusChem* **2021**, *14*, 3636. https://doi.org/10.1002/cssc.202101272

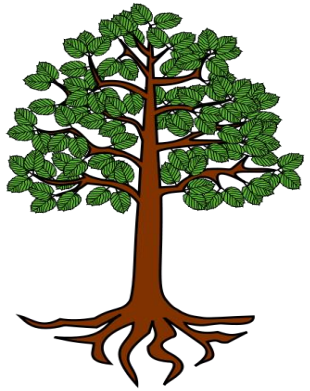
Advances in the use of CO2 as a renewable feedstock for the synthesis of polymers, B. Grignard, S. Gennen, C. Jérôme, A. W. Kleij, C. Detrembleur, *Chem. Soc. Rev.,* **2019**, 48, 4466-4514, https://doi.org/10.1039/C9CS00047J

CO_2-fixation into cyclic and polymeric carbonates: principles and applications, A. J. Kamphuis, F. Picchionia, P. P. Pescarmona**,** *Green Chem.*, **2019**, 21, 406-448, https://doi.org/10.1039/C8GC03086C

Recent progress in the catalytic transformation of carbon dioxide into biosourced organic carbonates, V. Aomchad, À. Cristòfol, F. Della Monica, B. Limburg, V. D'Elia, A. W. Kleij, *Green Chem*., **2021**, 23, 1077-1113 https://doi.org/10.1039/D0GC03824E

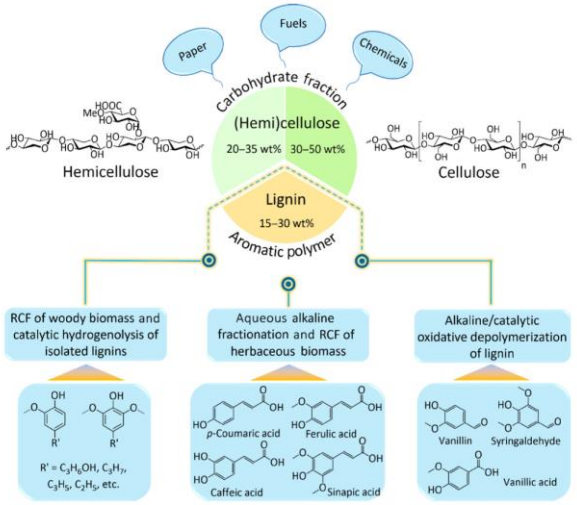
What source of renewable raw material?

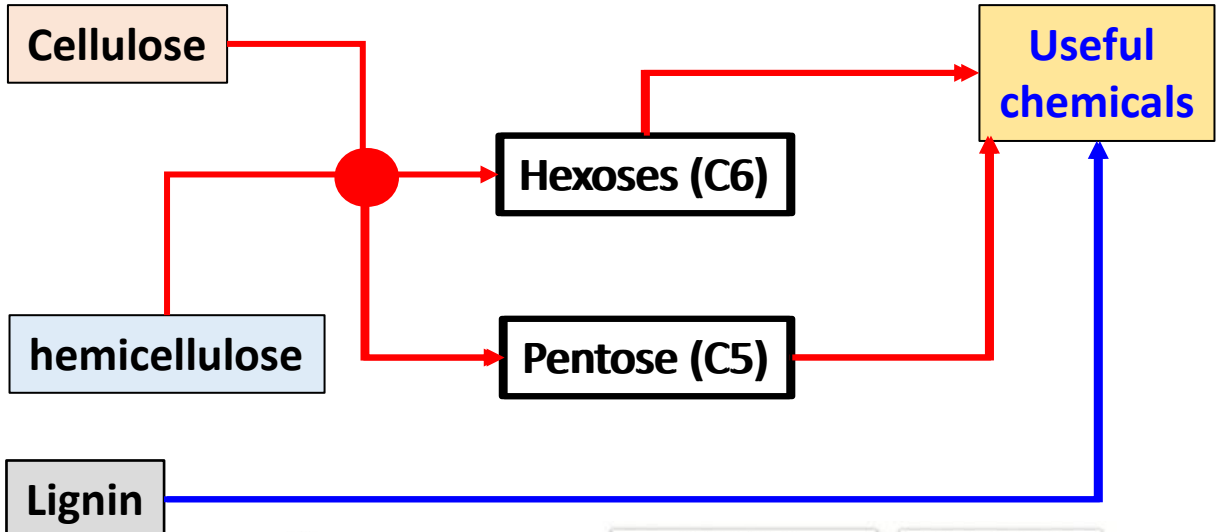
Multi-step conversion of lignocellulosic resources into monomeric compounds

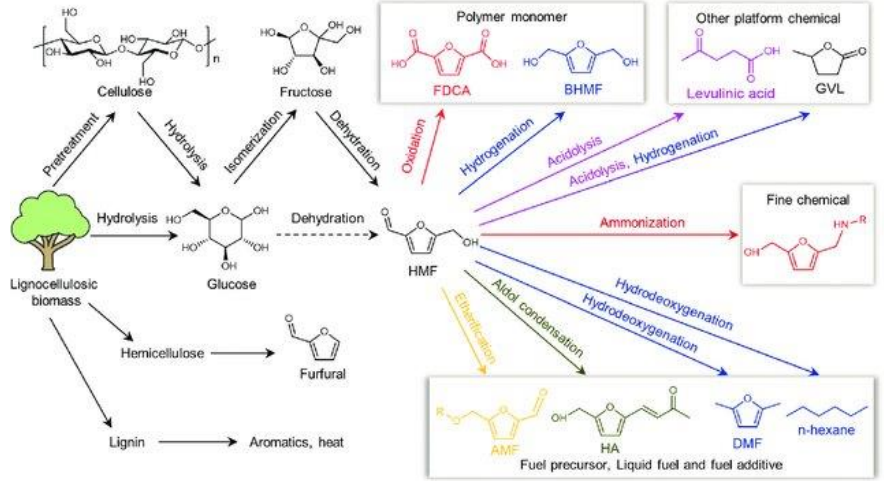


Pre-treatment Step

H_2O –organic solvent
ILs
scF
(catalysis)







Towards Lignin-Derived Chemicals Using Atom-Efficient Catalytic Routes, P. Sudarsanam, D. Ruijten, Y. Liao, T. Renders, S.-F. Koelewijn, B. F. Sels, *Trends in Chemistry*, **2020**, 2, 898
https://doi.org/10.1016/j.trechm.2020.07.011

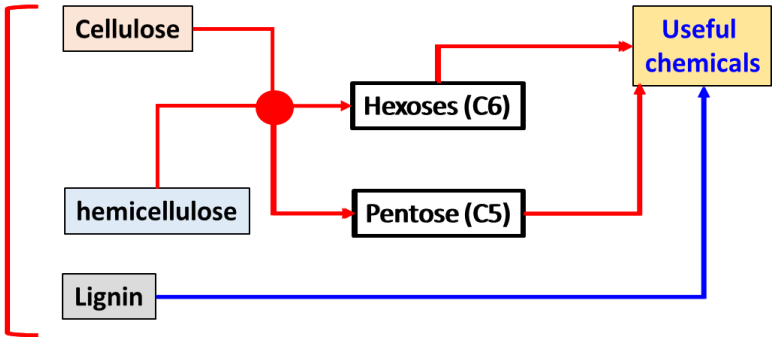
Lignin Biorefinery: New Horizons in Catalytic Hydrodeoxygenation for the Production of Chemicals, A. Kumar, M. Jindal, S.a Maharana, B. Thallada, *Energy Fuels* **2021**, 35, 21, 16965–16994,
https://doi.org/10.1021/acs.energyfuels.1c01651

Biorefinery roadmap based on catalytic production and upgrading 5-hydroxymethylfurfural, *Green Chem.*, **2021**, 23, 119-231

What Type of chemistry ?

Pre-treatment Step

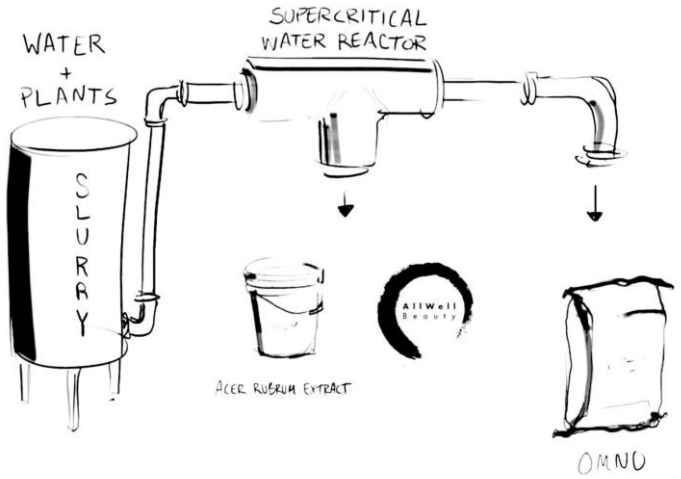
H_2O –organic solvent
ILs
scF
(catalysis)



C → A + B

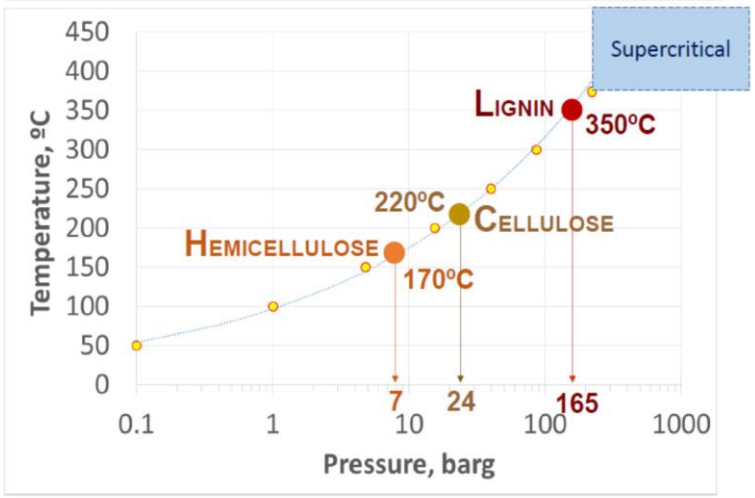
Renmatix™

Renmatix's technological innovation, the use of water-based chemistry, provides a cleaner, faster, and lower-cost method for deconstructing biomass into cellulosic sugars



http://renmatix.com

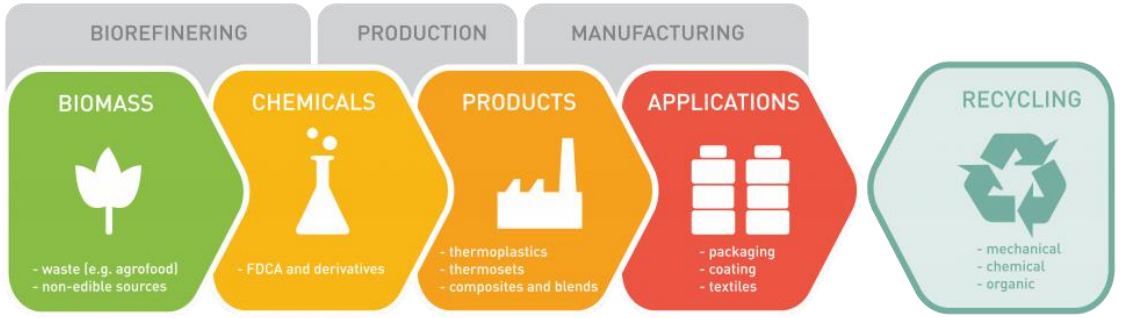
1. **Biomass slurry**
2. **Biomass Components**
   Hemicellulose, cellulose, lignin
3. **Hemi-hydrolysis**
   Solubilize the hemicellulose into a C5 Sugar
4. **Solid/liquid Separation**
   remove the remaining solids from the C5 sugar stream
5. **Cellulose hydrolysis slurry**
   Solids mixed with water to forma slurry
6. **Cellulose hydrolysis**
7. **Pose-hydrolysis**
   Remove the lignin solid from C6 sugar stream



What type of monomers to aim?

Raw renewable material → **Useful Monomers**

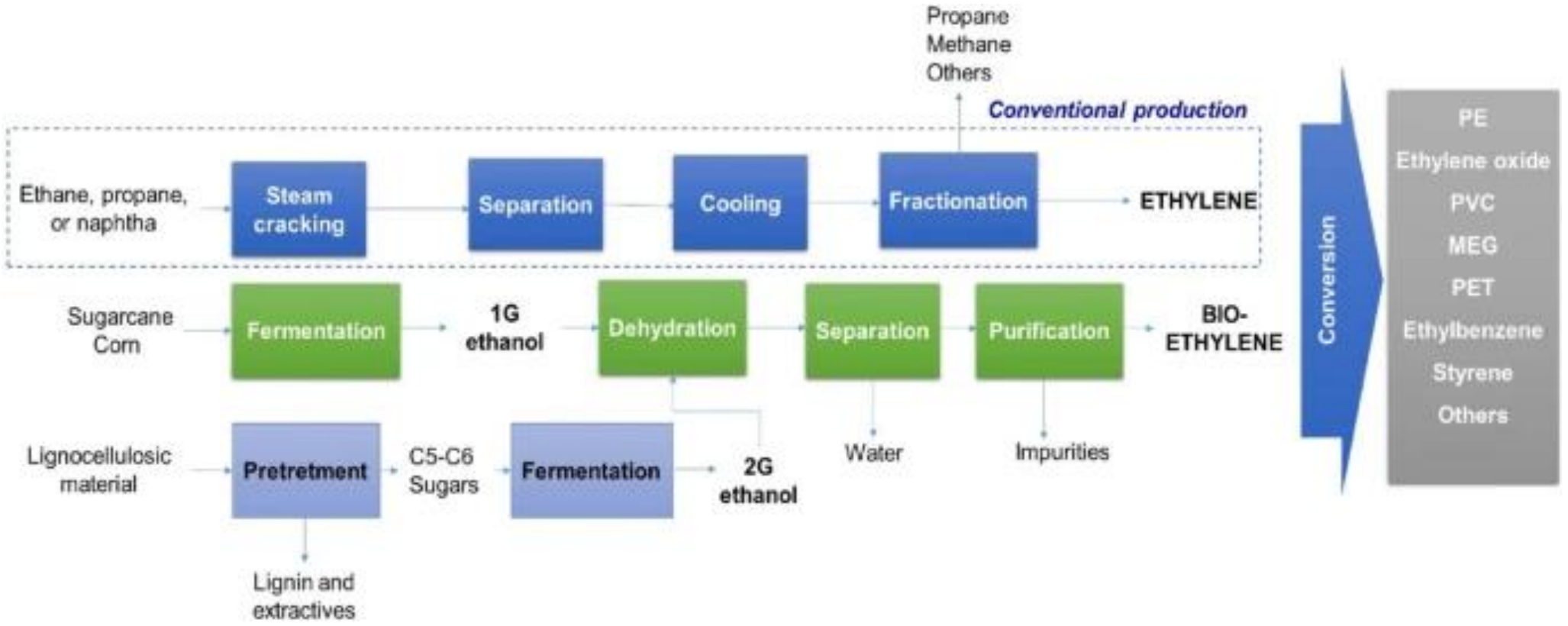
- new/old ones
- Chemical nature
- How to obtain them
- Cost



✓ Type of polymer

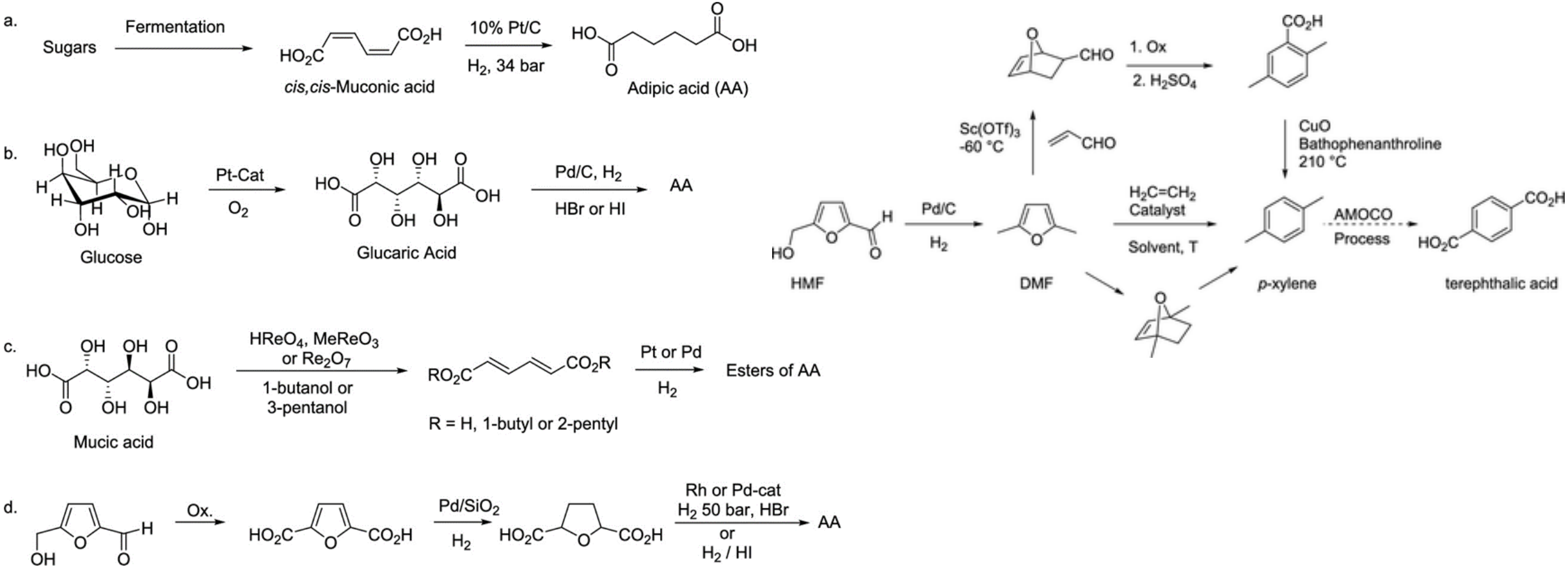
What type of monomers to aim?

Analogous of known petroleum-based monomer **from renewable sources** to replicate their corresponding polymer performances



What type of monomers to aim?

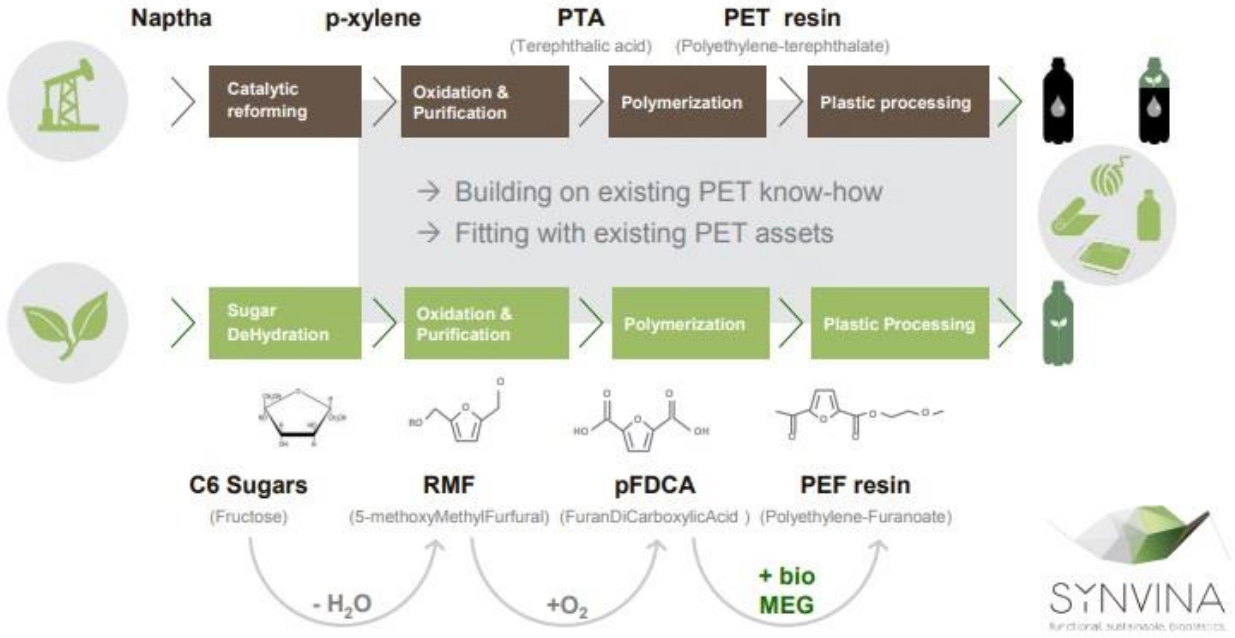
Analogous of known petroleum-based monomer **from renewable sources** to replicate their corresponding polymer performances



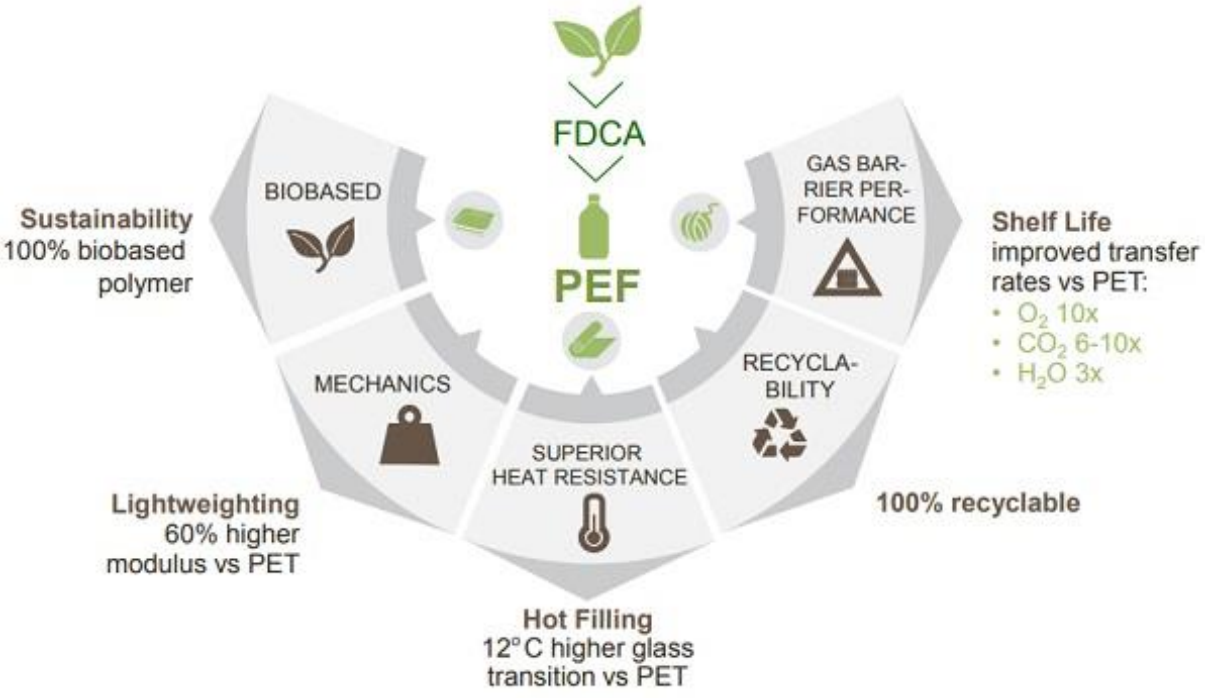
Catalytic Approaches to Monomers for Polymers Based on Renewables,
B. M. Stadler, C. Wulf, T. Werner, S. Tin, J. G. de Vries, *ACS Catal*. **2019**, 9, 9, 8012–8067,
https://doi.org/10.1021/acscatal.9b01665

What type of monomers to aim?

developing **chemically distinct monomer** leading to **new materials** from biofeedstocks with novel properties (e.g., self-healing, thermo-reversible) that are **not currently available** with petroleum-based plastics



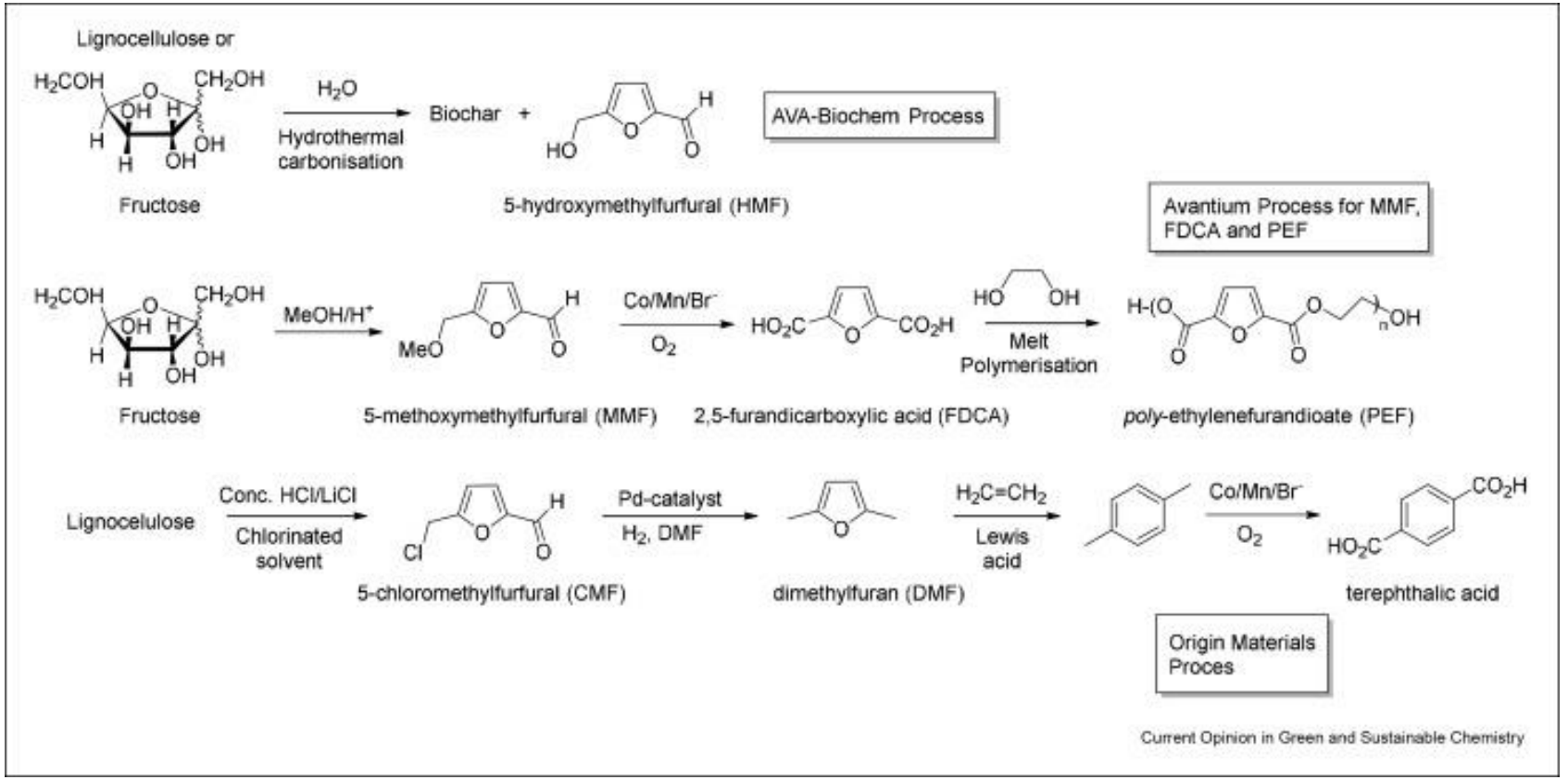
Source: Synvina



PEF versus Existing Packaging Materials
Source: Avantium and BASF

12 Principles of Green Chemistry

7. Use renewable feedstocks: Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.

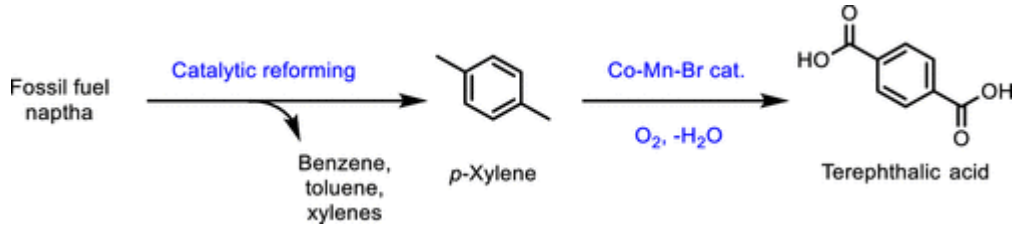


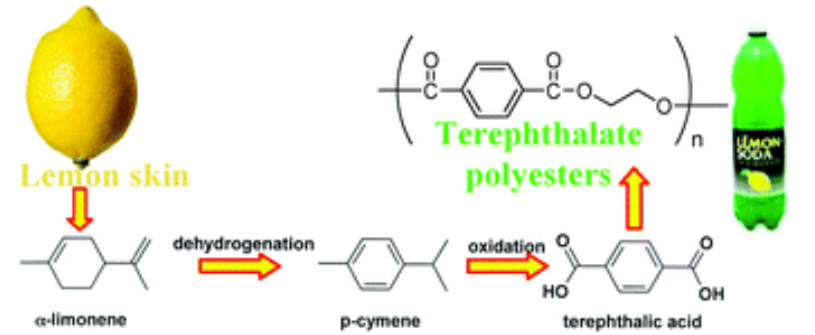
J. G. de Vries, Industrial implementation of chemical biomass conversion, Opinion in Green and Sustainable Chemistry, 2023, 39, 100715, https://doi.org/10.1016/j.cogsc.2022.100715

12 Principles of Green Chemistry

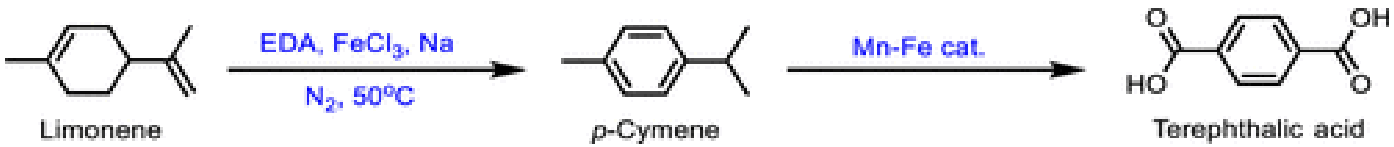
7. Use renewable feedstocks: Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.

Raw renewable material → **Useful monomers**





Terephthalate polyesters such as PET have been prepared from renewable terephthalic acid and proven to be bio-based through radiocarbon analysis

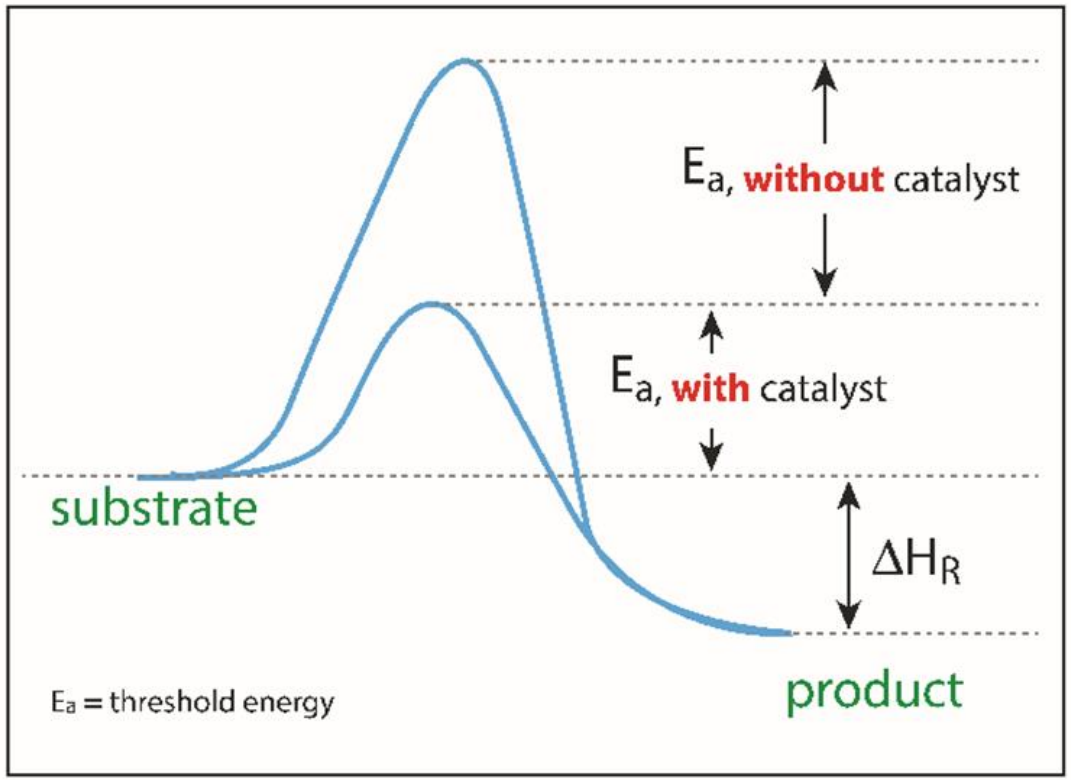


- 45 kilo tons in 2015 and is anticipated to exceed 65 kilo tons by 2023, with estimated gains at above 5%.
- In 2006, global purified terephthalic acid (PTA) demand had exceeded 30 million tonnes.

Green Chem., 2011,13, 2543-2548 https://doi.org/10.1039/C1GC15400A

12 Principles of Green Chemistry

9. Use catalysts, not stoichiometric reagents: Minimize waste by using catalytic reactions. Catalysts are effective in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and carry out a reaction only once.



Ways to prevent waste?

1. Avoid the generation of W.
2. Find alternatives to A & B to improved overall efficiency of a reaction.
3. Incorporate better catalysts to push the reaction to full completion

12 Principles of Green Chemistry

9. Use catalysts, not stoichiometric reagents: Minimize waste by using catalytic reactions. Catalysts are effective in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and carry out a reaction only once.

Nobel Prize for 'green chemistry' **reducing potentially waste through smarter catalyst**

2001: William S. Knowles and **Ryoji Noyori** "**for their work on chirally catalysed hydrogenation reactions**" and the other half to K**. Barry Sharpless** "**for his work on chirally catalysed oxidation reactions**"

2005: Yves Chauvin, Robert H. Grubbs and Richard R. Schrock "**for the development of the metathesis method in organic synthesis**"

2010: Richard F. Heck, Ei-ichi Negishi and Akira Suzuki "**for palladium-catalyzed cross couplings in organic synthesis**"

2021: Benjamin List and **David MacMillan** "**for the development of asymmetric organocatalysis**"

How?

- **Advanced Technology**: Use of cutting-edge technology and instruments,

A + B → C

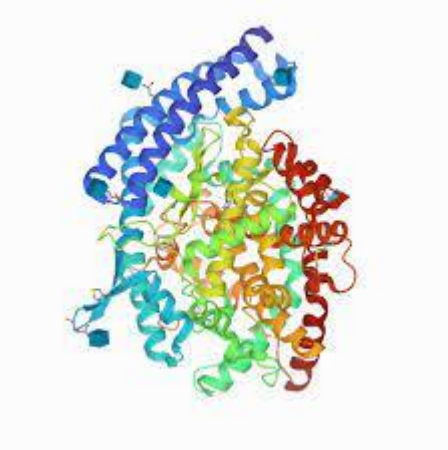
Key enabling technologies (KET)

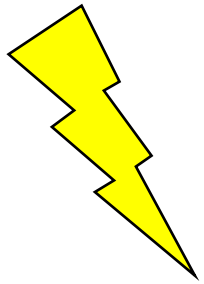
How?

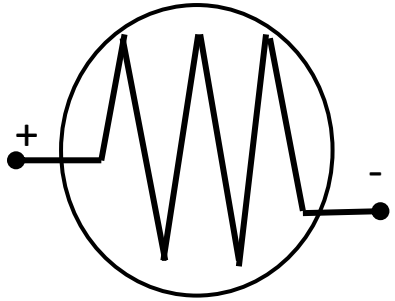
A + B → C

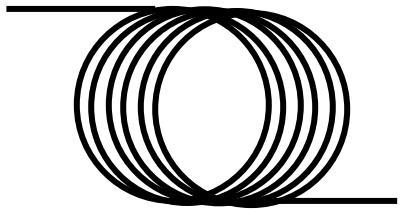
- **Advanced Technology**: Use of cutting-edge technology and instruments,

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**









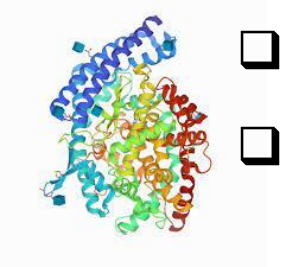
catalytic technologies

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

How?

Raw renewable material → **Useful monomers**

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**



- ❑ Ambient temperature and atmospheric pressure
- ❑ Highly selective process
- ❑ The 'construction' of microorganisms with multiple enzymatic functionalities, especially the direct conversion of carbohydrates
- ❑ **lower feedstock concentration**
- ❑ Genetic engineering and gene sequencing to produce biocatalysts with enhanced catalytic activity, stability

Chemocatalysis	Biocatalysis	
✓ High activity	✓ Mild reaction conditions	
✓ Wide variety of catalysts available	✓ Aqueous solvents	
✓ Robust	✓ Benign oxidants	
	✓ Biodegradable catalysts	
	✓ Low energy costs	
✕ Low selectivity	✕ Slow reactions	
✕ High energy costs	✕ Low substrate concentrations	
	Whole cell	**Enzyme**
✕ High equipment costs	✓ Robust	✓ Highly efficient reactions
	✓ Accepts crude substrate	✓ Easy product recovery
	✓ Endogenous cofactors	✓ High selectivity
✕ High reagent costs	✓ Protein isolation not necessary	✓ High control of reactions ✓ Low contamination
✕ Toxic reagents	✓ Good for bulk chemical production	✓ Good for fine chemical production
✕ Low recyclability	✕ Impure products	✕ Cost of isolated proteins ✕ Cofactor requirements
✕ High waste generation/not atom-economical	✕ Competing metabolic pathways	✕ Low robustness
✕ Environmental pollution	✕ Metabolic burden	✕ Limited reaction conditions
	✕ High equipment costs	**Multiple Enzymes**
	✕ Difficult product purification	✓ Cofactor recycling ✓ Multi-step reactions ✕ Complicated reaction kinetics

Chemo-enzymatic routes towards the synthesis of bio-based monomers and polymers, S. T. Ahmed, N. G.H. Leferink, N. S. Scrutton, *Molecular Catalysis*, **2019**, 467, 95-110. https://doi.org/10.1016/j.mcat.2019.01.036

Recent advances in biotransformation of 5-Hydroxymethylfurfural : challenges and future aspects, K. Saikia, A. K. Rathankumar, P. S. Kumar, S. Varjani, M. Nizar, R. Lenin, J. George, V. K. Vaidyanathan, ***J Chem Technol Biotechnol***, 2021, **DOI:** 10.1002/jctb.6670

Status of Biocatalysis in the Production of 2,5-Furandicarboxylic Acid, D. Troiano, V. Orsat, M.-J. Dumont, *ACS Catal.*, **2020**, 10, 9145. DOI: 10.1021/acscatal.0c02378

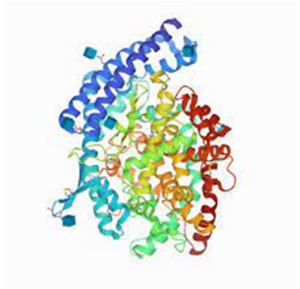
Applications of biotransformations and biocatalysis to complexity generation in organic synthesis
Tomas Hudlicky and Josephine W. Reed, ***Chem. Soc. Rev.***, 2009, **38**, 3117 **DOI:** 10.1039/b901172m

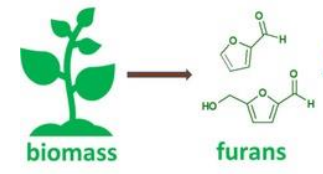
Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

Raw renewable material → **Useful monomers**

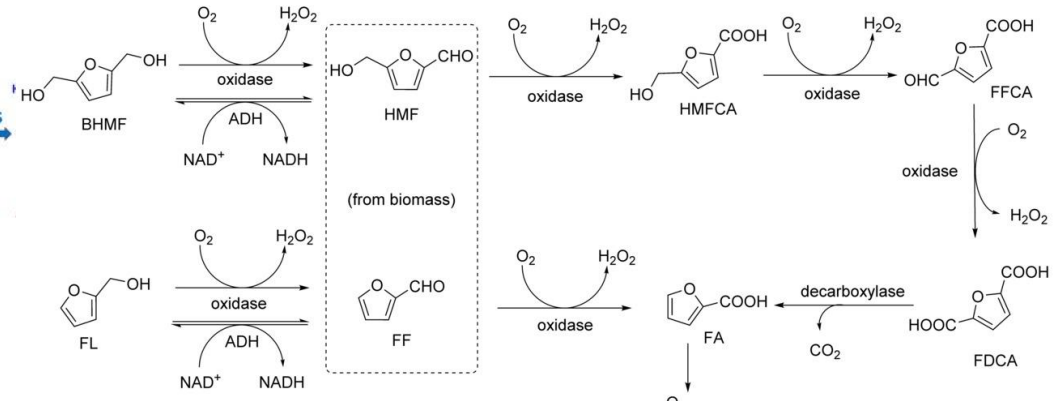
How?

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**





biocatalysis



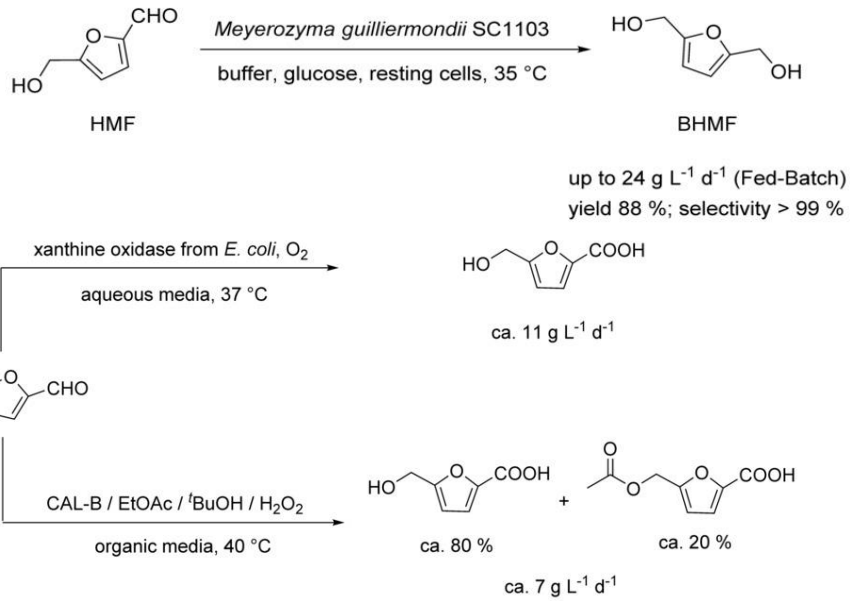


Table 2 HMFCA biosynthesis *via* HMF oxidation by various whole-cell biocatalysts

Origin: strain	HMF (mM)	Cell dosage	Shaker speed (rpm)	Yield (%)	Time (h)	HMFCA (mM)	Ref.
Serratia liquefaciens LF14[a]	300	12 mg mL^{-1}	ND	56	26	168	19
Comamonas testosterone SC1588[a]	160	30 mg mL^{-1}	150	98	36	156.8	20
Pseudomonas putida KT2440[a]	160	25 OD_{600}	200	96.8	12	155	21
Deinococcus wulumuqiensis R12[a]	600	200 mg mL^{-1}	850	90	20	511	22
Pseudomonas aeruginosa PC-1[b]	800	5 mg mL^{-1} (10 OD_{600})	180	90.1	58	721	This study

[a] HMFCA production using resting cells. [b] HMFCA production using growing cells. ND: not determined.

Biocatalytic Valorization of Furans: Opportunities for Inherently Unstable Substra
Domínguez de María, N. Guajardo, ChemSusChem 2017, 10, 4123.
https://doi.org/10.1002/cssc.201701583

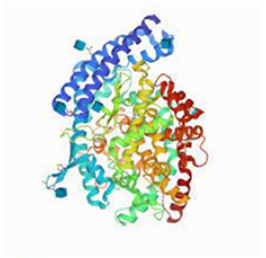
Status of Biocatalysis in the Production of 2,5-Furandicarboxylic Acid, D. Troiano, V. Orsat, M.-J. Dumont, *ACS Catal*., **2020**, 10, 9145. DOI: 10.1021/acscatal.0c02378

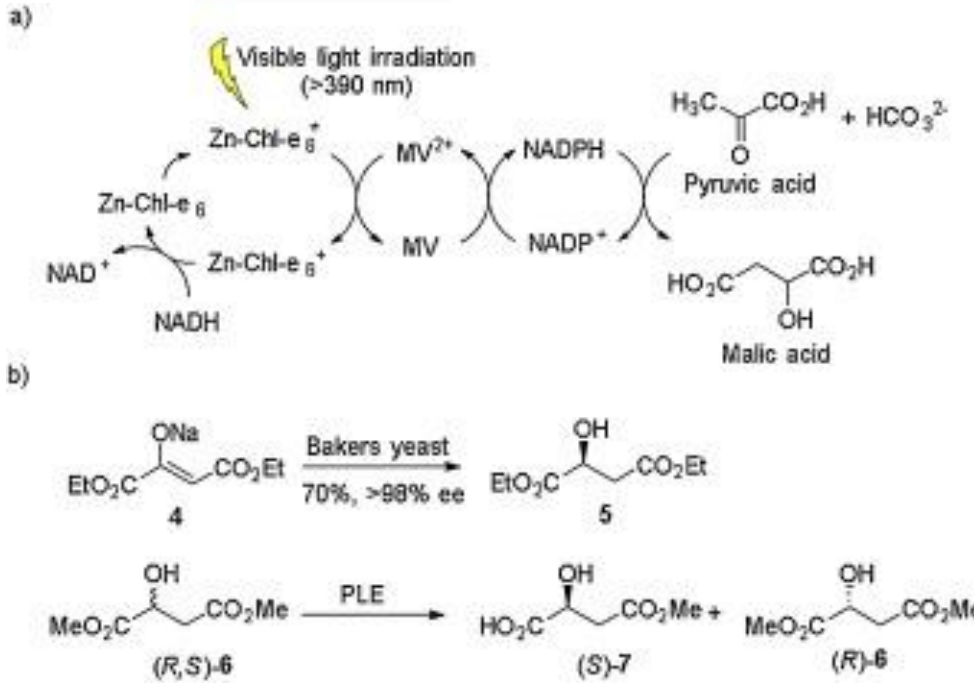
Efficient biotransformation of 5-hydroxymethylfurfural to 5-hydroxymethyl-2-furancarboxylic acid by a new whole-cell biocatalyst Pseudomonas aeruginosa PC-1, X. Pan, S. Wu, D. Yao, L. Liu, L. Zhang, Z. Yao, Y. Pan, S. Chang, B. Li, *React. Chem. Eng*., **2020**, 5, 1397-1404. https://doi.org/10.1039/D0RE00018C

How?

Raw renewable material → Useful monomers

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**





- Biocatalytic and fermentation routes to malic acid. A carbon fixation approach was used to produce malic acid
- photoredox chemo-enzyme by carboxylating pyruvate with hydrogencarbonate using Zn-Chl-e6, ferredoxin-NADP-reductase (FNR), NADPH and malic enzyme (ME) and visible light
- baker's yeast can be used to reduce sodium diethyl oxaloacetate 4 to malate ester 6
- an esterase (PLE) in a resolution to produce enantiopure malate monoester (S)-7
- overexpressing the native pyruvate carboxylase and the relocation of malate dehydrogenase to the cytosol produced 59 g L^{-1} of malic acid

Chemo-enzymatic routes towards the synthesis of bio-based monomers and polymers, S. T. Ahmed, N. G.H. Leferink, N. S. Scrutton, *Molecular Catalysis*, **2019**, 467, 95-110. https://doi.org/10.1016/j.mcat.2019.01.036

Green Chemistry vs. Biocatalysis

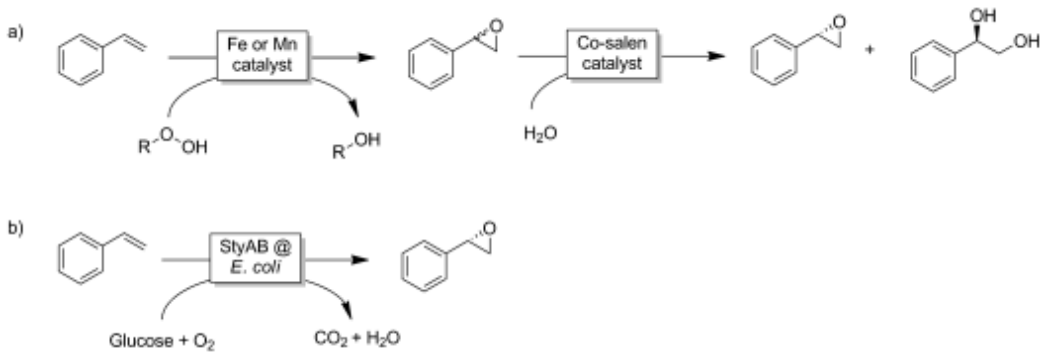
CHEMCATCHEM
MINIREVIEWS

ChemPubSoc Europe

DOI: 10.1002/cctc.201300976

How Green is Biocatalysis? To Calculate is To Know

Yan Ni,[a, b] Dirk Holtmann,[c] and Frank Hollmann*[a]

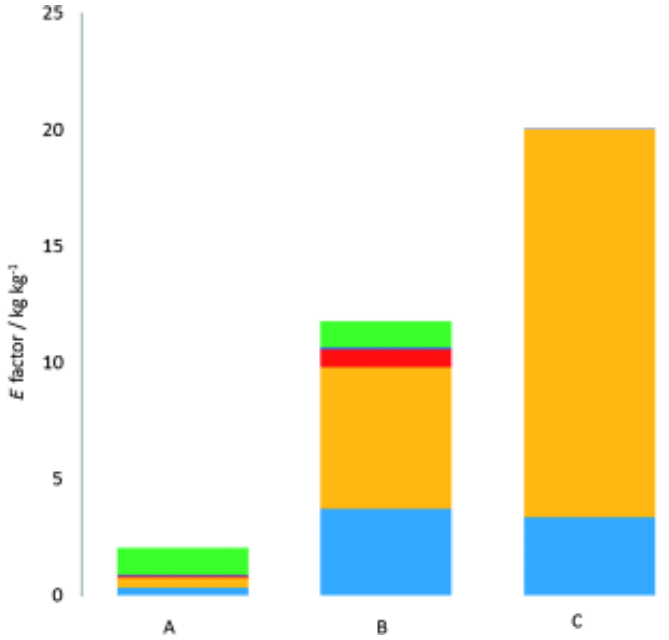


Outlook

Biocatalysis surely bears an enormous potential to make chemical synthesis environmentally more benign. We should, however, be aware of the fact that no chemical process can ever be really green. All chemical transformations consume resources in the form of energy and materials and generate wastes. With that in mind, the term "greener chemistry" appears to be more applicable than just "green chemistry".

It is clear that fulfilling one or a few of the famous 12 Principles of Green Chemistry is not sufficient to be green(er). In our mind, a more quantitative evaluation of the catalytic method-

Ni, Y., Holtmann, D. and Hollmann, F. (2014), How Green is Biocatalysis? To Calculate is To Know.
ChemCatChem, 6: 930-943.
https://doi.org/10.1002/cctc.201300976

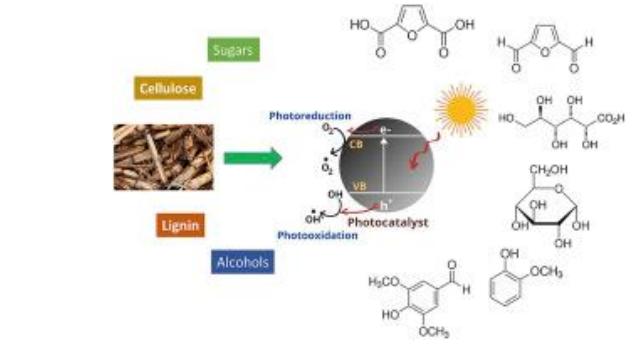


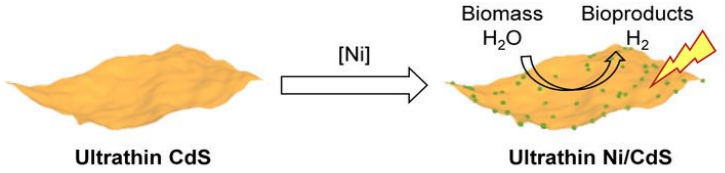
How?

Raw renewable material → **Useful monomers**

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**

- ambient atmospheric pressure and temperature,
- scalable photooxidation procedures with energy-efficient lamps (TL and LED) have been reported
- simple redox reaction (reduction/oxidation) photogenerated radical
- Photocatalytic generated intermediates allow meaningful novel reaction pathways that are unlikely to be achieved in traditional heterogeneous catalysis.
- Valorization of biomass with Co-generation of added-value subproducts





Visible-Light-Driven Valorization of Biomass Intermediates Integrated with H2 Production Catalyzed by Ultrathin Ni/CdS Nanosheets, G. Han , Y.-H. Jin , R. A. Burgess , N. E. Dickenson , X.-M. Cao and Y. Sun , *J. Am. Chem. Soc.*, 2017, 139 , 15584 — 15587

Light-driven transformation of biomass into chemicals using photocatalysts – Vistas and challenges, *Journal of Environmental Management,* **2021**, 284, 111983 https://doi.org/10.1016/j.jenvman.2021.111983

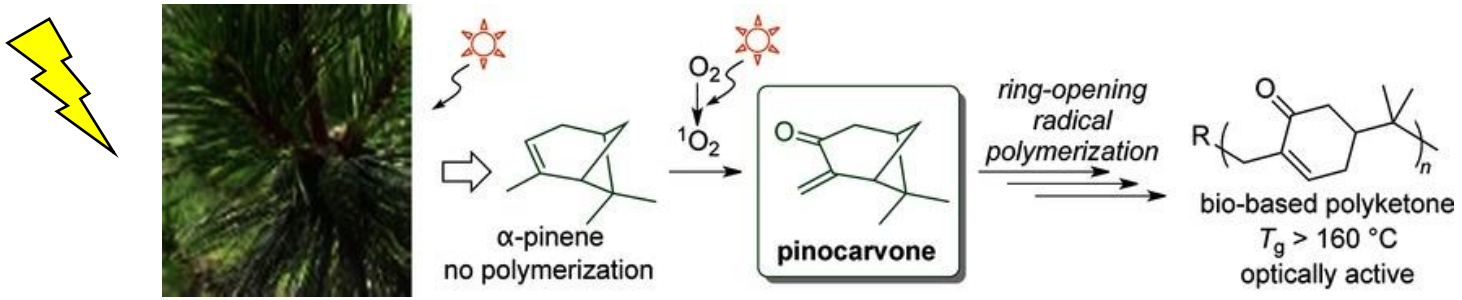
Recent Advances in the Photocatalytic Conversion of Biomass-Derived Furanic Compounds, Chen Li, Jiang Li, Ling Qin, Piaoping Yang, Dionisios G. Vlachos.. ACS Catalysis 2021, 11 (18) , 11336-11359. https://doi.org/10.1021/acscatal.1c02551

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

How?

Raw renewable material → **Useful monomers**

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**



α-pinene was quantitatively converted into pinocarvone (>99 %) by a simple visible-light photooxidation with singlet oxygen, which was produced in the presence of tetraphenylporphyrin as a photosensitizer under mild conditions at room temperature

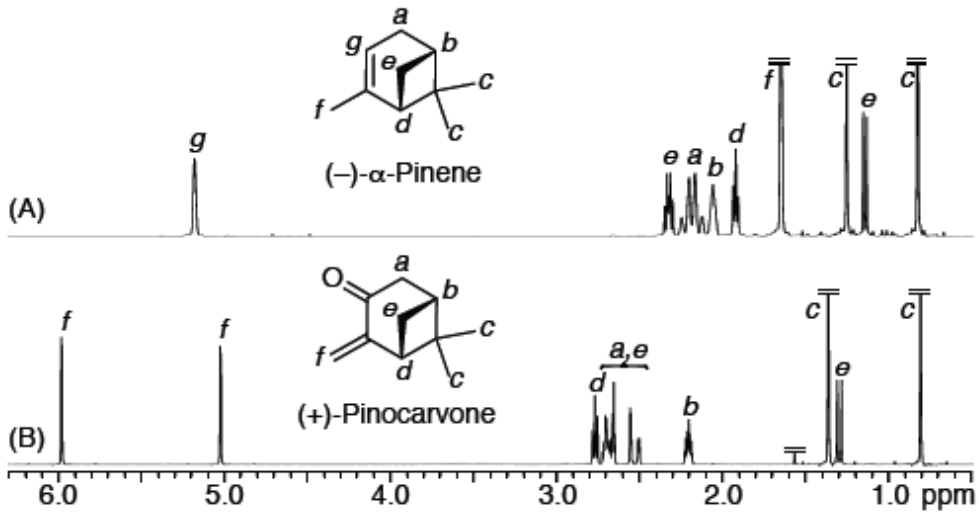


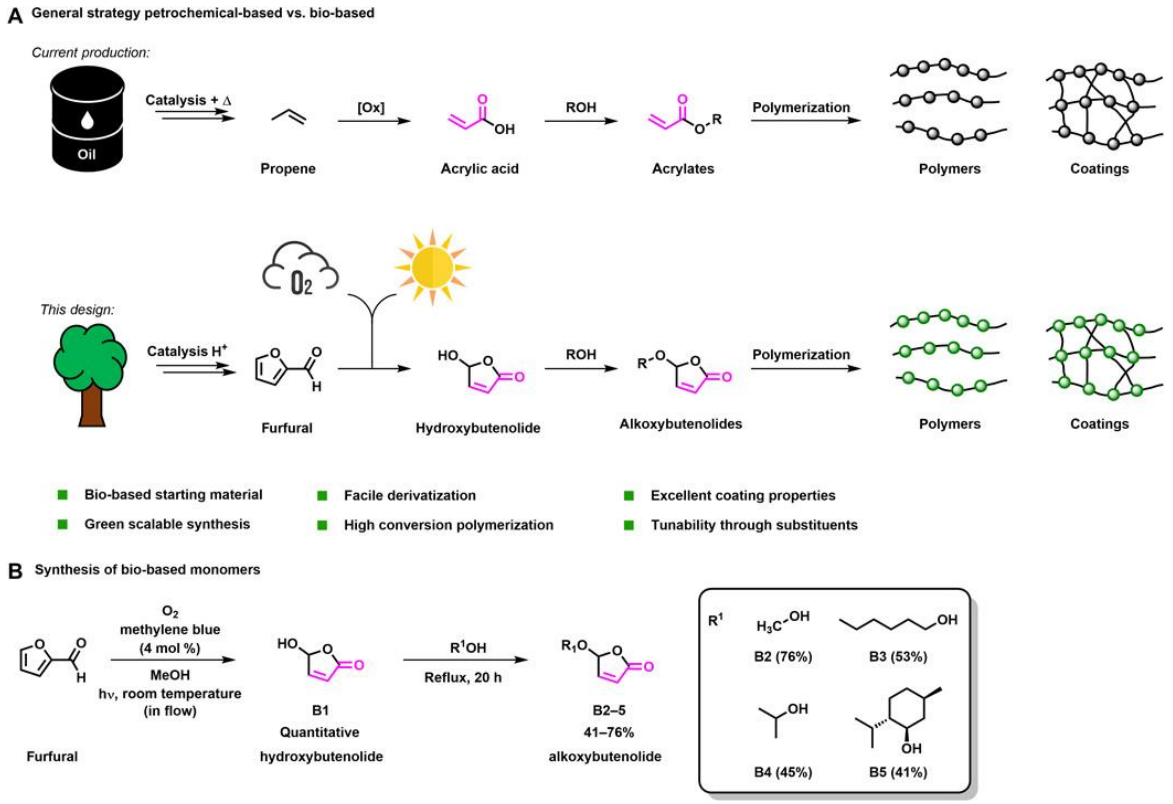
Figure S1. ^{1}H NMR spectra (in $CDCl_3$, r.t.) of (–)-α-pinene (A) and (+)-pinocarvone (B) obtained under visible light photooxidation.

Bio-Based Polyketones by Selective Ring-Opening Radical Polymerization of α-Pinene-Derived Pinocarvone, H. Miyaji, K. Satoh, M. Kamigaito, Angew. Chem. Int. Ed. 2016, 55, 1372. https://doi.org/10.1002/anie.201509379

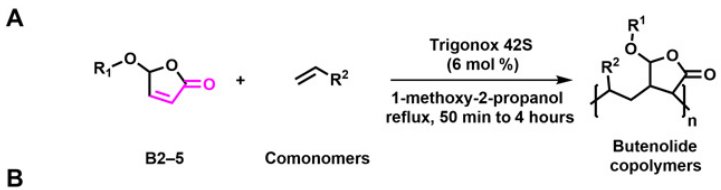
How?

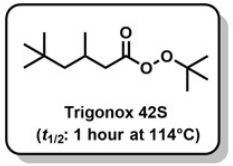
Raw renewable material → **Useful monomers**

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**



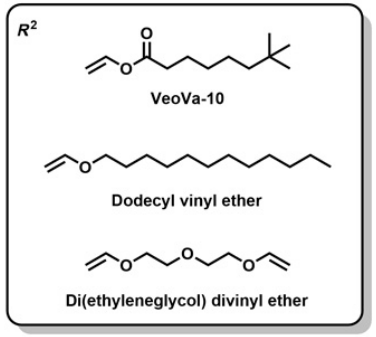
University of Groningen and AkzoNobel, developed a process that allows to turn biomass into a high-quality coating using light, oxygen and UV light.





B

	Monomer	Conversion (co)polymerization (%) Homo-polymerization	VeoVa-10	Dodecyl vinyl ether	Di(ethyleneglycol) divinyl ether
B2		53	99	95	69[a]
B3		51	92	>99	>99
B4		37	96	>99	91[a]
B5		30	92	>99	>99

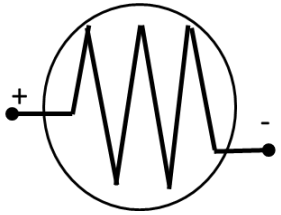


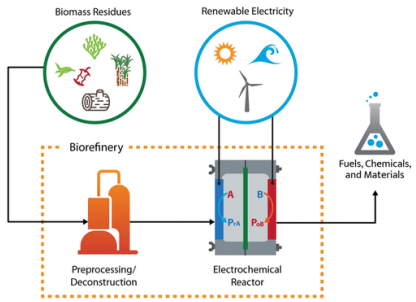
A coating from nature, J. G. H. Hermens, T. Freese, K. J. van den Berg, R. van Gemert, Ben L. Feringa, *Science Advances*, **2020**, 6, 10.1126/sciadv.abe0026.

How?

Raw renewable material → Useful monomers

Biocatalysis **Photocatalysis** **Electrocatalysis** **Flow Chemistry**





- operate directly on aqueous feedstocks,
- generation of oxidative or reducing equivalents without external (wasteful, possibly toxic) reagents,
- operability near ambient conditions,
- smaller (possibly highly distributed) scale intermittent processing with diminished reliance on heat recovery
- a wide variety of reactive intermediates *in situ* (free radicals, ionic radicals, carbocations, carbanions), yielding different products or selectivity distributions than may be achieved within typically accessible temperatures and pressures

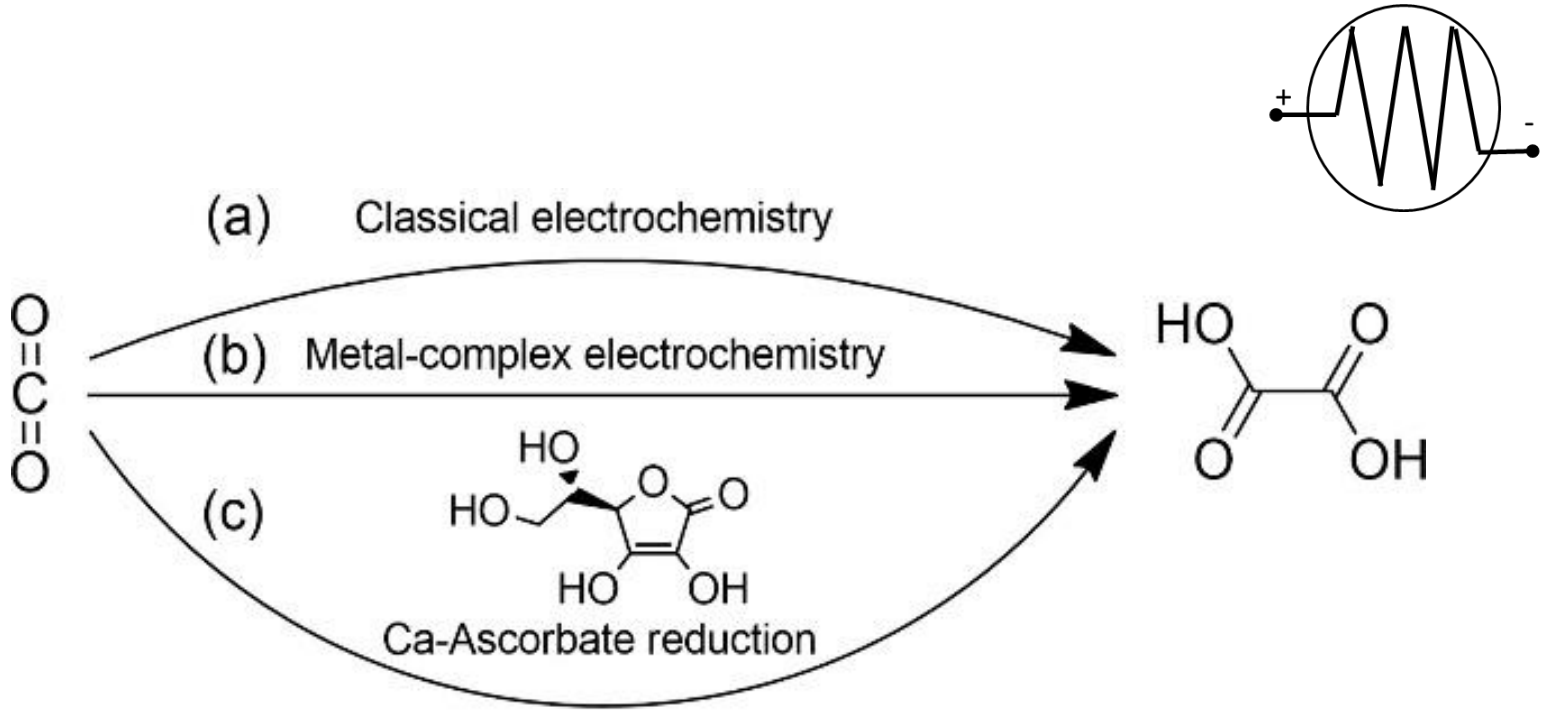
Advances in Electrochemical Modification Strategies of 5-Hydroxymethylfurfural, O. Simoska, Z. Rhodes, S. Weliwatte, J. R. Cabrera-Pardo, E. M. Gaffney, K. Lim, S. D. Minteer, *ChemSusChem* **2021**, *14*, 1674. https://doi/10.1002/cssc.202100139

Electrochemical Routes for the Valorization of Biomass-Derived Feedstocks: From Chemistry to Application, F. W. S. Lucas, R. G. Grim, , S.A. Tacey, C. A. Downes, J. Hasse, A. M. Roman, C. A. Farberow, J. A. Schaidle, A. Holewinski, *ACS Energy Lett*. **2021**, 6, 4, 1205–1270, https://doi.org/10.1021/acsenergylett.0c02692

How?

Raw renewable material → Useful monomers

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**

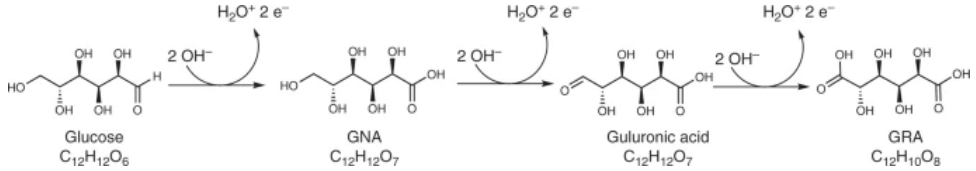


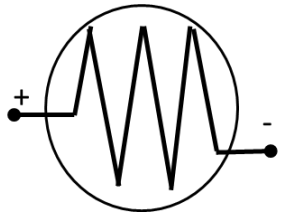
Towards Sustainable Oxalic Acid from CO_2 and Biomass, E. Schuler, M. Demetriou, N. R. Shiju, G.-J. M. Gruter, *ChemSusChem* **2021**, *14*, 3636. https://doi.org/10.1002/cssc.202101272

How?

Raw renewable material → **Useful monomers**

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**





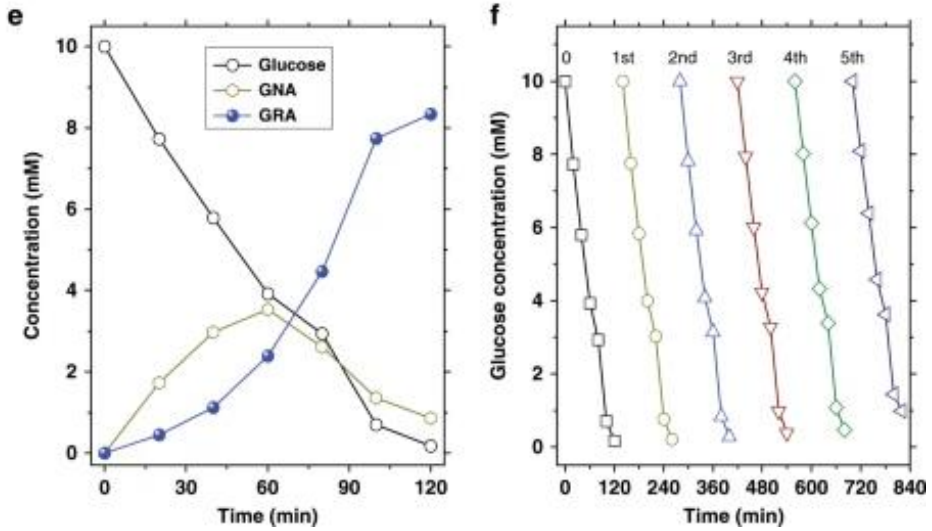


Table 3. Record Performance[a] for Production of Major Compounds from the Electrochemical Valorization of Carbohydrates

entry	polyols	products	Y% (X%)[b]	FE (%)	electrochemical parameters[c]	ref
1	xylose	xylonic acid	>92 (52)	>80	+0.4 V[d] in 0.1 M NaOH on Pd_3Au_7/C (ECSA: 33 m^2 g_{metal}^{-1})	163
2	xylose	xylitol	>90 (>90)	>80	10 mA cm^{-2}, −1.10 V[@-3] (−0.44 V[@-1]) in 0.1 M Na_2SO_4 on $MoFe_{3-x}Pt_x$	144
3	xylose	δ-valerolactone	U.D. (U.D.)	18	TPE in an undivided cell with Pb (cathode) at −1.80 V[@-2] (−1.54 V[@-1]) and RuO_x–TiO_2 DSA (anode), in 1.0 M HCl	160
4	galactose	galactonic acid	93 (87)	U.D.	+1.50 V[@-3] (+2.46 V[@-1]) in 0.1 M NaOH on Au	147
5	glucose	gluconic acid	>84 (69)	>60	+0.40 V[d] in 0.1 M NaOH on Pd_3Au_7/C (ECSA: 33 m^2 g_{metal}^{-1})	163
6	glucose	glucaric acid	>71 (>91)	>73	18–90 mA cm^{-2}(TOF: 0.03–0.16 s^{-1}), +1.3 V[@-1] in 1 M KOH on $NiFe_2O_4$	146
7	mannose	mannonic acid	50 (80)	U.D.	+1.5 V[@-3] (+2.46 V[@-1]) in 0.1 M NaOH on Au	148
8	gluconic acid	arabinose	cathodic: 90–98; anodic: 47–94 (U.D.)	cathodic: 5–39; anodic: 83–88	LPE on graphite, 1.1 mA in 0.2 M Na-acetate/acetic acid buffer + 0.05 M $FeCl_3$ (cathodic mediator)	164
9	glucose	sorbitol (cathodic) and gluconic acid (anodic)	cathodic: 100 (22); anodic: 100 (22)	cathodic: 100; anodic: 100	DPE in an undivided packed-bed flow reactor with Raney Ni (cathode) and graphite (anode), 250 mA in 0.4 M $CaBr_2$ (pH 5–7) at 60 °C	157

[a]Record performance for production of a specific compound was chosen based on highest faradaic efficiency (FE) to the primary product, followed by yield. Only products with yields higher than 20% are shown. [b]Yield [Y%] (conversion [X%]). U.D. = unavailable data; [c]Reference electrodes: [@-1]reversible hydrogen electrode (RHE), [@-2]Ag/AgCl$_{(sat.\ KCl)}$, [@-3]saturated calomel electrode (SCE). TPE = tandem paired electrolysis; LPE = linear paired electrolysis; DPE = divergent paired electrolysis; DSA = dimensionally stable anode. [d]Cell voltage with HER on Pt as the coupled cathodic reaction.

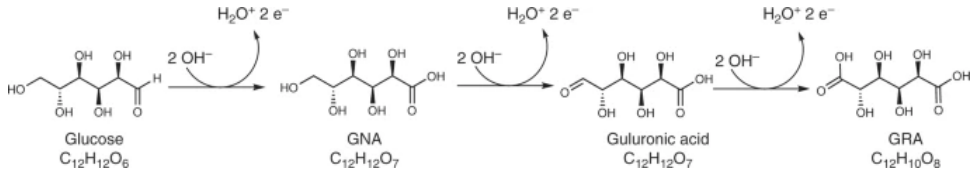
Liu, WJ., Xu, Z., Zhao, D. et al. **Efficient electrochemical production of glucaric acid and H2 via glucose electrolysis**. Nat Commun 11, 265 (2020). https://doi.org/10.1038/s41467-019-14157-3

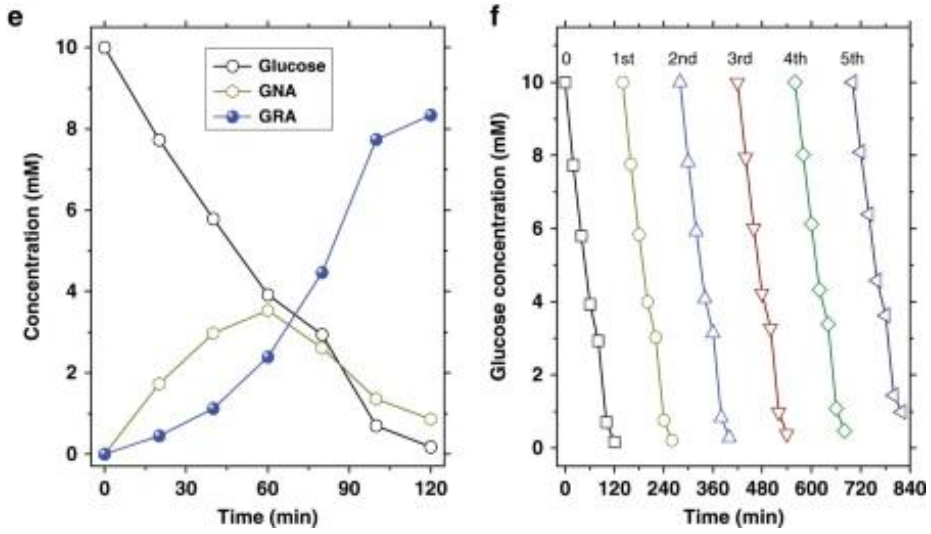
Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

How?

Raw renewable material → **Useful monomers**

Biocatalysis

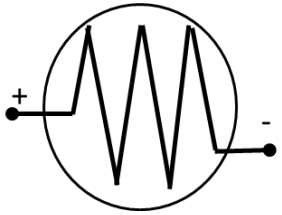




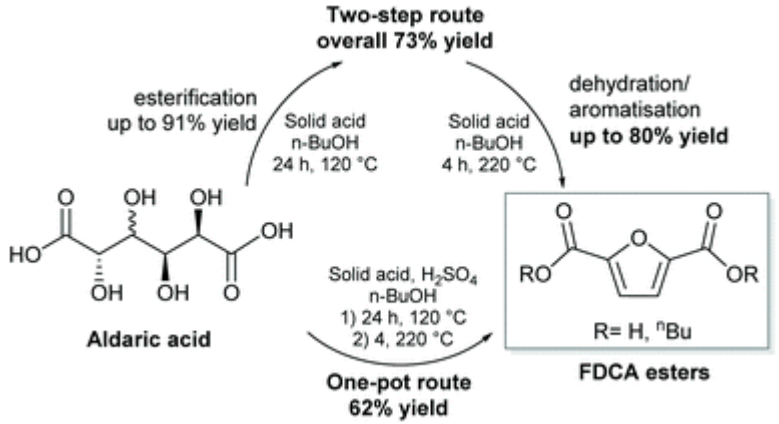
Liu, WJ., Xu, Z., Zhao, D. et al. **Efficient electrochemical production of glucaric acid and H2 via glucose electrolysis**. Nat Commun 11, 265 (2020). https://doi.org/10.1038/s41467-019-14157-3

Photocatalysis

Electrocatalysis



Flow Chemistry

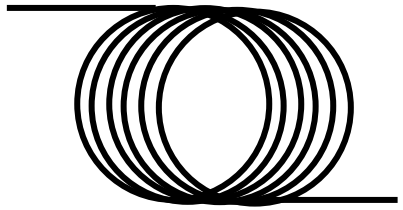


A unique pathway to platform chemicals: aldaric acids as stable intermediates for the synthesis of furandicarboxylic acid esters, N. van Strien, S. Rautiainen, M. Asikainen, D. A. Thomas, J. Linnekoski, K. Niemelä, A. Harlin, *Green Chem*., **2020**, 22, 8271-8277. https://doi.org/10.1039/D0GC02293D

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

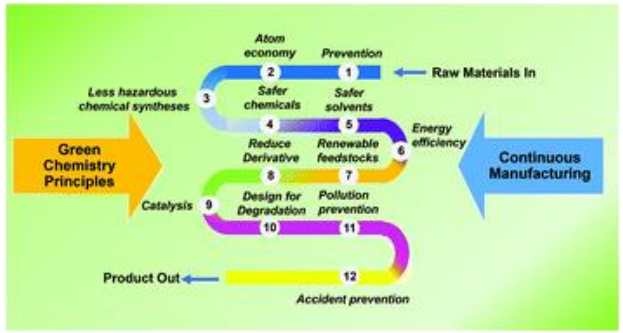
How?

Raw renewable material → **Useful monomers**

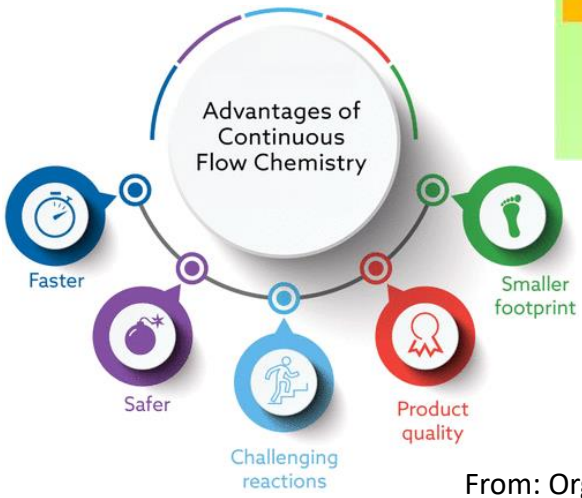


Biocatalysis **Photocatalysis** **Electrocatalysis** **Flow Chemistry**

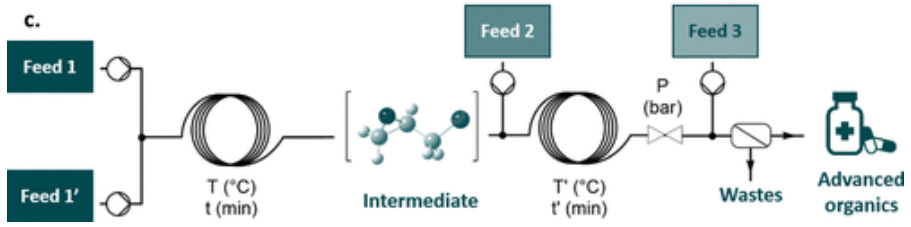
- ❑ Fast heat transfer systems with high surface/volume ratio (very rapid heating and cooling rates), simpler reactors design and construction
- ❑ flow scalability (without the need for re-optimization) systems in parallel (numbering up, scaling out) culminating in attaining the production-scale quantities
- ❑ multi-disciplinary approach in conjunction with electro-, photo-, and MW usage as well as the synthesis of robust catalysts in flow
- ❑ Telescopic reactions



Green Chem., 2019,21, 3481-3498



From: Org. Process Res. Dev. 2020, 24, 10, 1802–1813
https://doi.org/10.1021/acs.oprd.9b00524



Catalytic Transformation of Biomass Derivatives to Value-Added Chemicals and Fuels in Continuous Flow Microreactors, A. Hommes, H. J. Heeres, J. Yue, *ChemCatChem* **2019**, 11, 4671. https://doi.org/10.1002/cctc.201900807

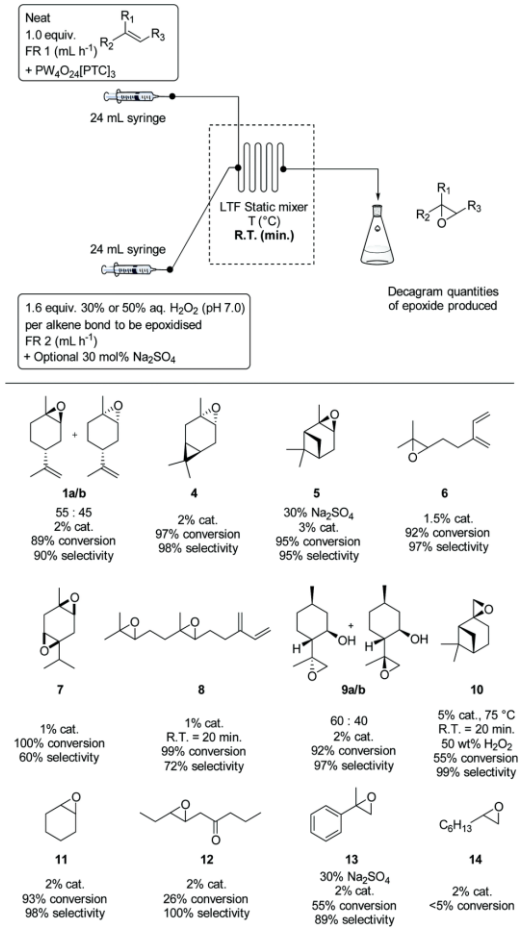
Continuous Flow Upgrading of Selected C2–C6 Platform Chemicals Derived from Biomass, R. Gérardy, D. P. Debecker, J. Estager, P. Luis, J.C. M. Monbaliu, Chem. Rev. **2020**, 120, 15, 7219–7347. https://doi.org/10.1021/acs.chemrev.9b00846

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

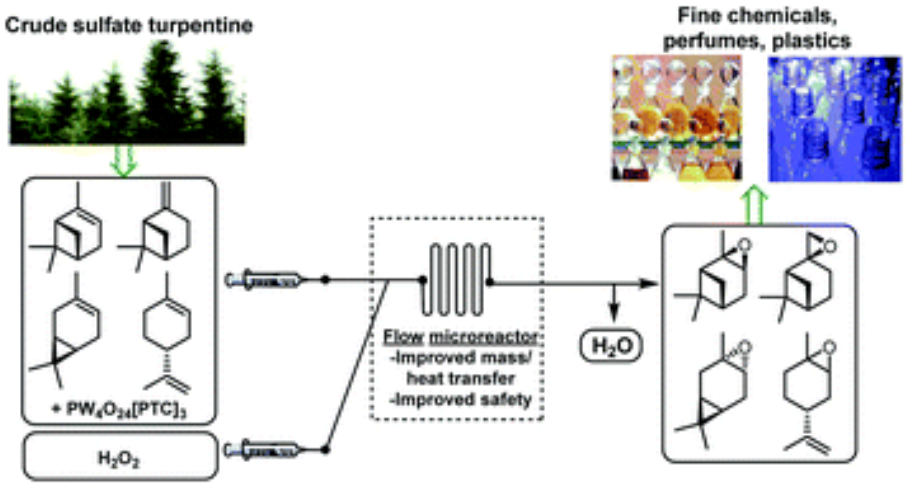
How?

Raw renewable material → **Useful monomers**

Biocatalysis

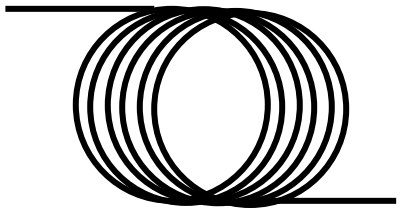


Photocatalysis



Electrocatalysis

Flow Chemistry



improved safety profile

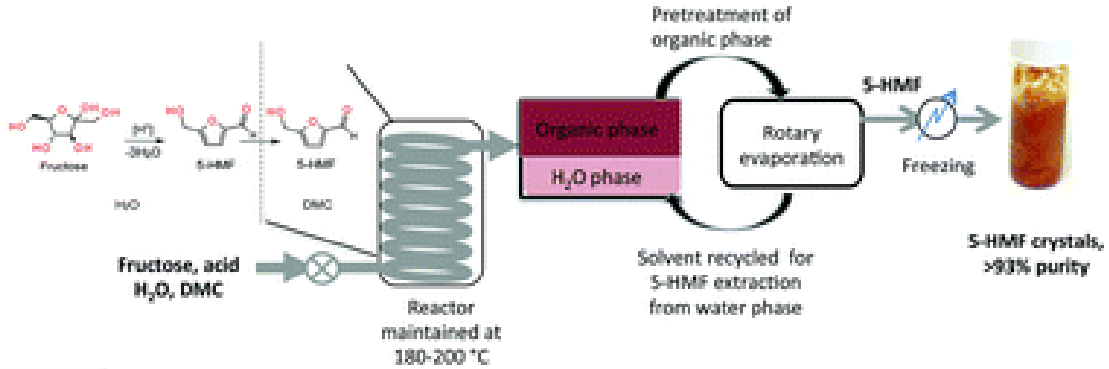
better suited for large-scale manufacturing of epoxides than biphasic batch epoxidation conditions that suffer from potentially dangerous thermal runaways caused by inefficient mixing and poor temperature control.

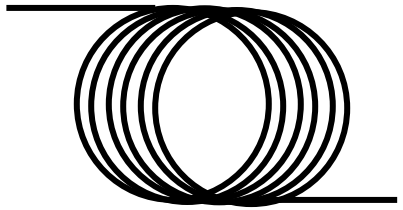
Sustainable catalytic epoxidation of biorenewable terpene feedstocks using H2O2 as an oxidant in flow microreactors, J. D. Tibbetts, W.B. Cunningham, M. Vezzoli, P. Plucinskic, S. D. Bull, *Green Chem.*, **2021**, 23, 5449-5455. https://doi.org/10.1039/D1GC01734A

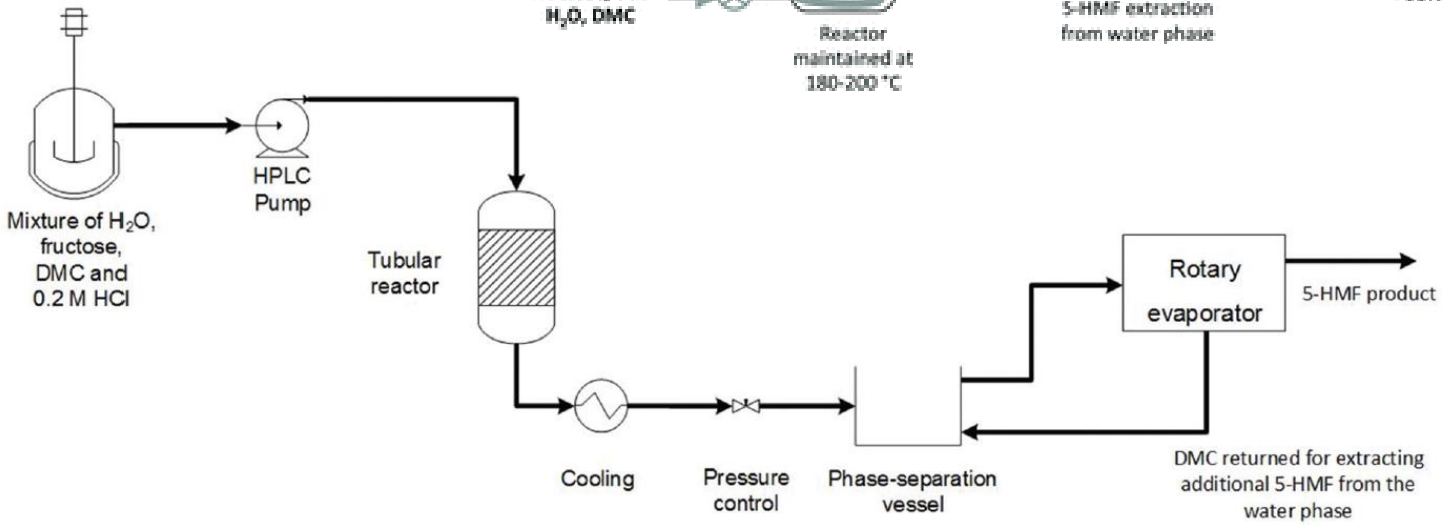
How?

Raw renewable material → **Useful monomers**

Biocatalysis **Photocatalysis** **Electrocatalysis** **Flow Chemistry**







520 g L^{-1} water in 1 : 4 water/DMC system at 200 °C and 2 mL min^{-1} flow rate in a **2.3 mL stainless steel tube** reactor led to 96.4% conversion of fructose and 5-HMF yield of 75%, and selectivity of 89.4 and 74% in DMC and water phase, respectively, but with productivity increasing to **31 g h^{-1}**

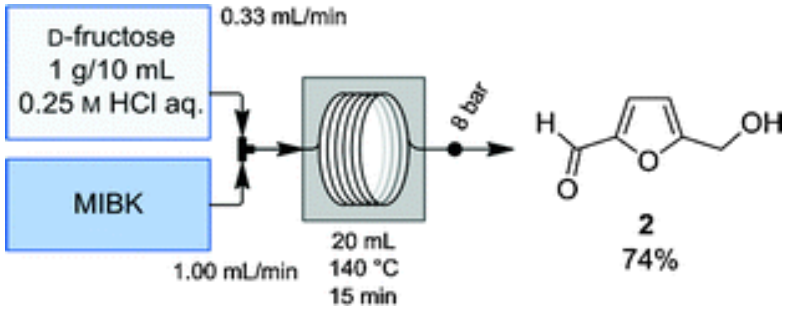
Highly efficient dehydration of carbohydrates to 5-(chloromethyl)furfural (CMF), 5-(hydroxymethyl)furfural (HMF) and levulinic acid by biphasic continuous flow processing, M. Brasholz, K. von Känel, C. H. Hornung, S. Saubern, J. Tsanaktsidis, *Green Chem.*, **2011**, 13, 1114-1117 https://doi.org/10.1039/C1GC15107J

How?

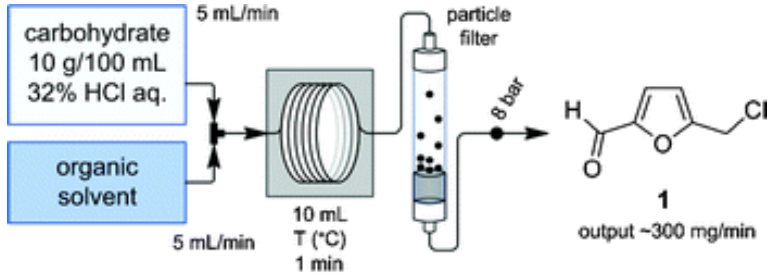
Raw renewable material → **Useful monomers**

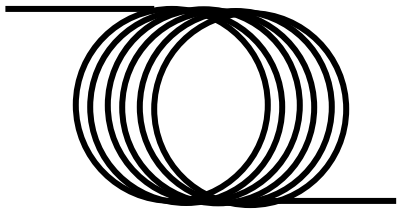
Biocatalysis **Photocatalysis** **Electrocatalysis** **Flow Chemistry**

inexpensive reagent systems, in short reaction times and with simple work-up procedures.



the biphasic continuous flow protocol for the conversion of d-fructose into HMF proceeds with high isolated yield, in a reaction time of only 15 min

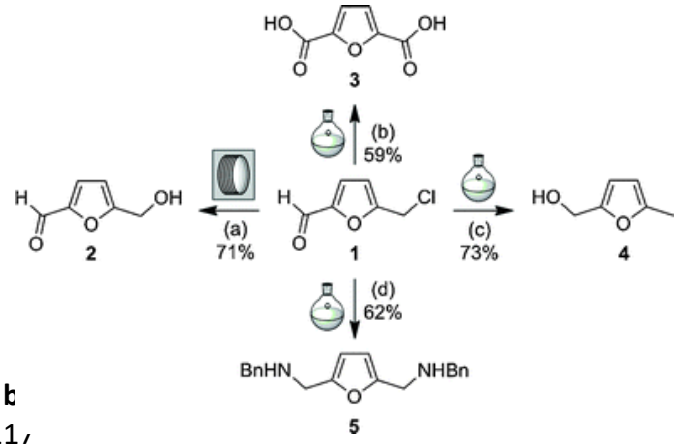




D-fructose (10 g) $\xrightarrow[CH_2Cl_2]{100\ °C}$ CMF **1** (6.32 g) 79%

sucrose (10 g) $\xrightarrow[DCE]{130\ °C}$ CMF **1** (5.13 g) 61%

reaction time of 60 s is sufficient to produce **1** with 80% isolated yield from d-fructose and 60% yield from sucrose.



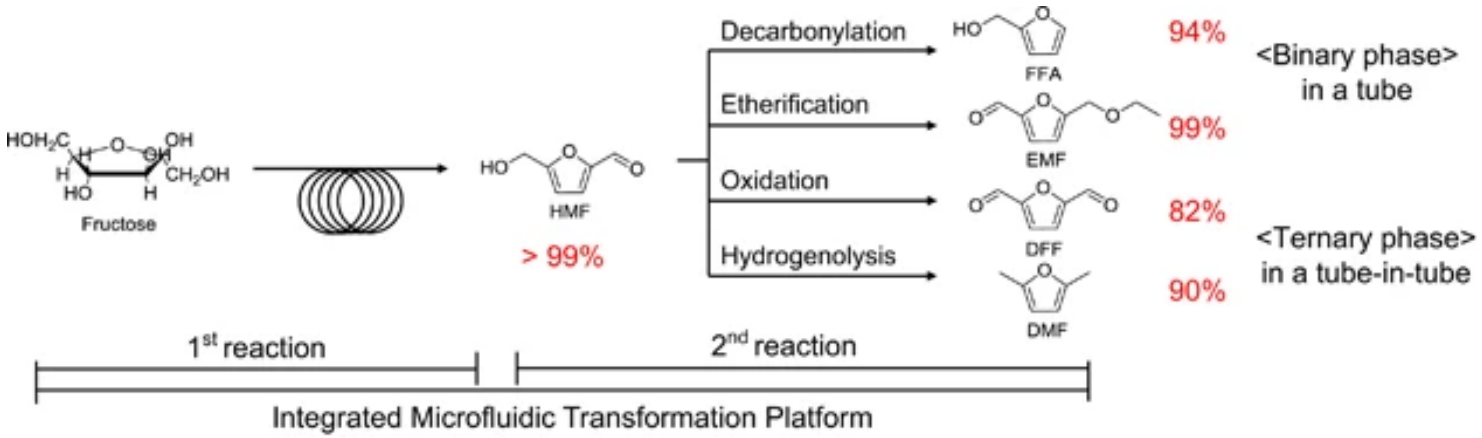
Highly efficient dehydration of carbohydrates to 5-(chloromethyl)furfural (CMF), 5-(hydroxymethyl)furfural (HMF) and levulinic acid b biphasic continuous flow processing, M. Brasholz, K. von Känel, C. H. Hornung, S. Saubern, J. Tsanaktsidis, *Green Chem.*, **2011**, 13, 1114-111, https://doi.org/10.1039/C1GC15107J

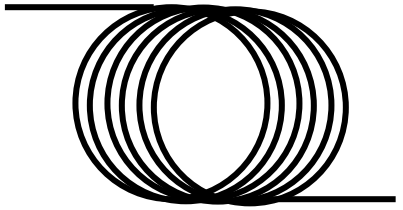
How?

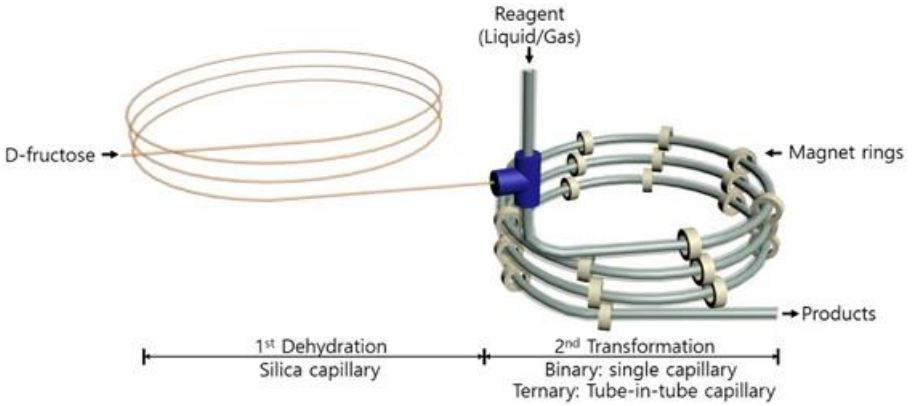
Raw renewable material → **Useful monomers**

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**

fructose biomass into heterocyclic furan derivatives via in situ utilization of HMF by a sequential two-step heterogeneous catalytic process







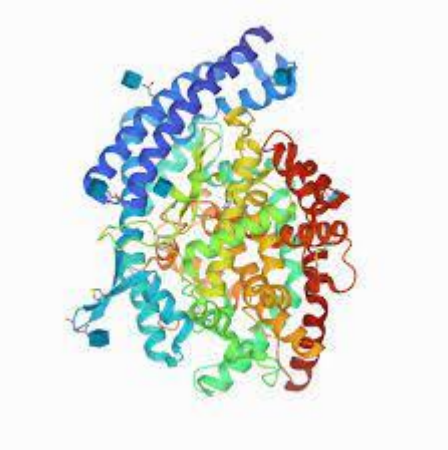
superior performance of the direct biomass conversion compared with batch reactions because of the precise control of the reaction temperatures and times in a time-,cost- and labor-saving manner with no catalyst recycle and no tedious separation–extraction step.

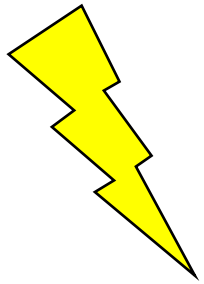
One-flow syntheses of diverse heterocyclic furan chemicals directly from fructose via tandem transformation platform, Jeong, GY., Singh, A., Sharma, S. et al. NPG Asia Mater 7, e173 (2015). https://doi.org/10.1038/am.2015.21

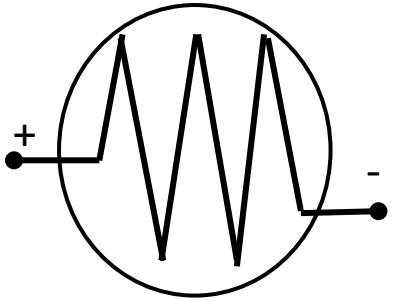
Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

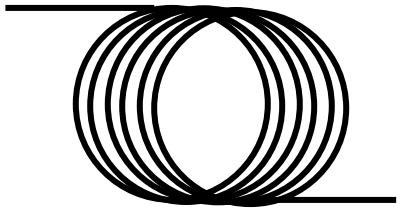
Raw renewable material → **Useful monomers**

Biocatalysis | **Photocatalysis** | **Electrocatalysis** | **Flow Chemistry**







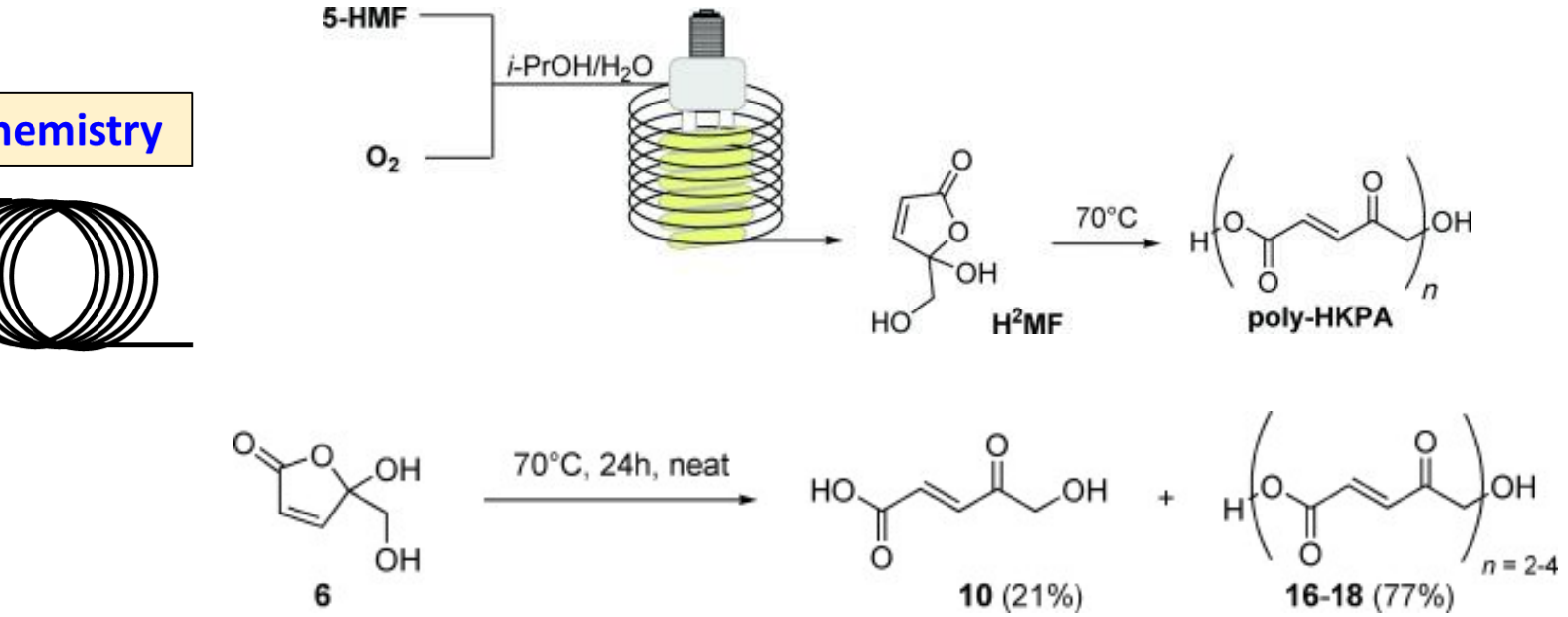


Synergetic combination of two or more KET

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

Raw renewable material → **Useful monomers**

Photocatalysis **Flow Chemistry**



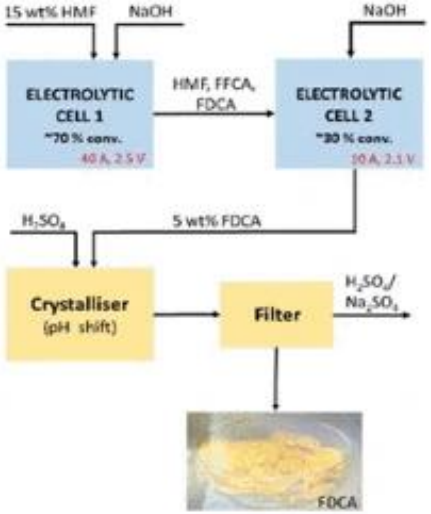
The selective, high yielding, singlet-oxygen-mediated oxidation of 5-hydroxymethylfurfural (5-HMF) is performed in continuous-flow mode using rose Bengal as photosensitizer.
The resulting butenolide (H^2MF) is shown to be a valuable bio-based polyester precursor and the procedure proved to be scalable and applicable to related bio-based furfurals.

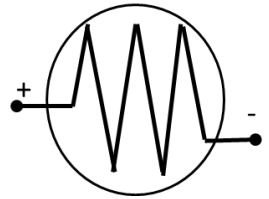
Singlet-Oxygen Oxidation of 5-Hydroxymethylfurfural in Continuous Flow, T. S. A. Heugebaert, C. V. Stevens, C. Oliver Kappe, *ChemSusChem*, 2014, 8, 1648-1651. https://doi.org/10.1002/cssc.201403182

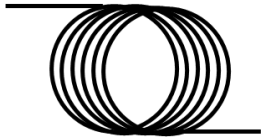
Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

Raw renewable material → **Useful monomers**

Electrocatalysis **Flow Chemistry**







FDCA productivity was approximately 30 g h^{-1}, with an STY of approximately 0.08 mol m−1 s−1. The average faradaic efficiency was approximately 84 % with a FDCA yield of approximately 70 %.

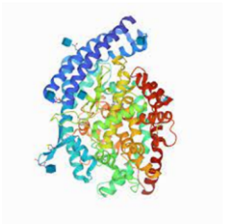
continuous electrochemical FDCA production with integrated product separation system was reported by Latsuzbaia et al.
The production unit comprised an Electro Syn Cell from Electrocell employing NiOOH as anode with surface area of 800 cm^2 and a separation unit with a pH-shift crystallization technique.

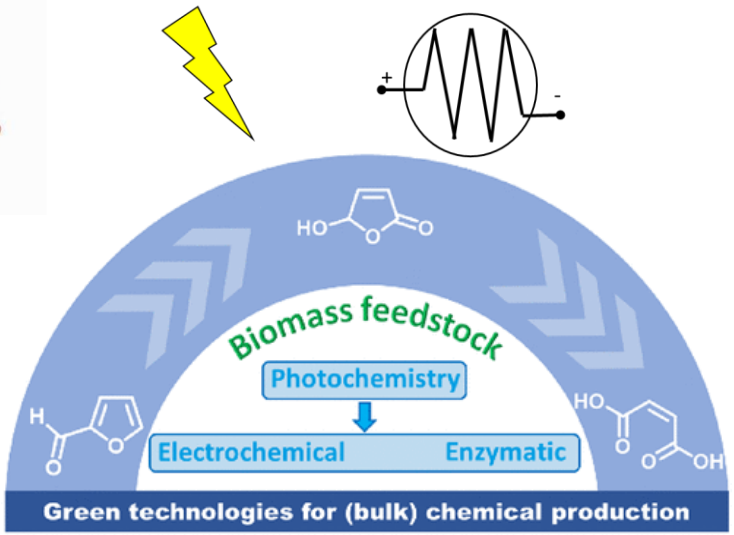
Continuous electrochemical oxidation of biomass derived 5-(hydroxymethyl)furfural into 2,5-furandicarboxylic acid, R. Latsuzbaia, R. Bisselink, A. Anastasopol, H. Van der Meer, R. Van Heck, M. S. Yagüe, M. Zijlstra, M. Roelands, M. Crockatt, E. Goetheer, *J. Appl. Electrochem*. **2018**, 48, 611–626. https://doi.org/10.1007/s10800-018-1157-7

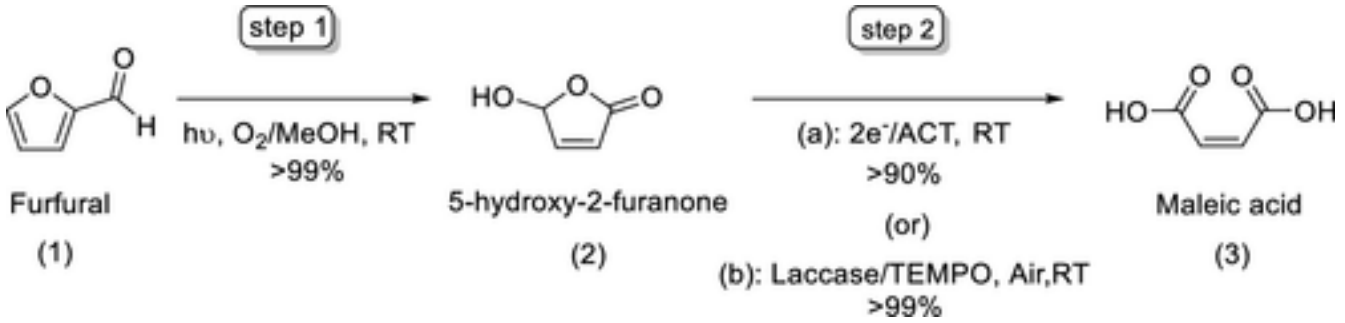
Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

Raw renewable material → **Useful monomers**

Biocatalysis **Photocatalysis** **Electrocatalysis**

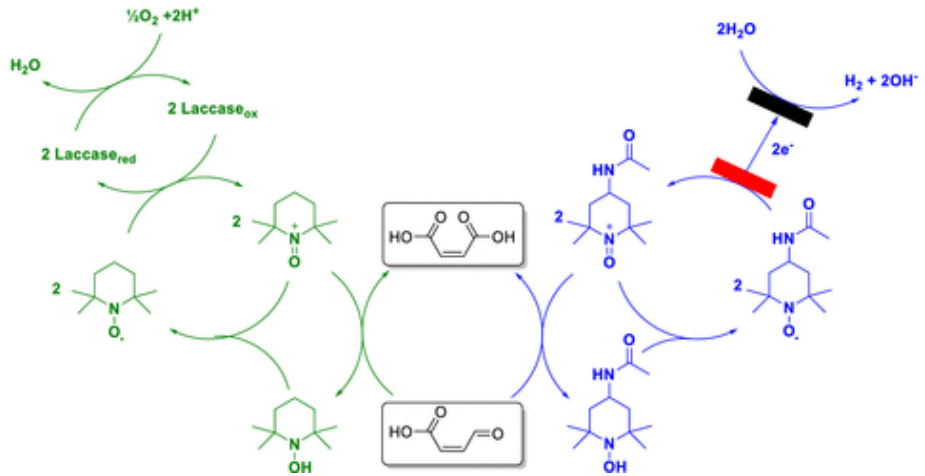






integration of photocatalytic conversion of furfural to 2, followed by oxidation via either an electrochemical or enzymatic approach, to produce maleic acid is an attractive, greener strategy enabling the large-scale production of bulk chemicals such as maleic acid at lower cost from biomass compared to current fossil-based feedstocks and production.

Enzymatic oxidation



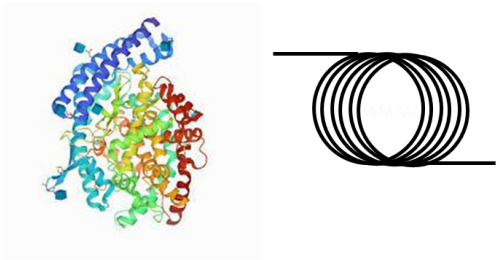
Electrocatalytic oxidation

Selective Production of Maleic Acid from Furfural via a Cascade Approach Combining Photochemistry and Electro- or Biochemistry, S. Thiyagarajan, D. Franciolus, R. J. M. Bisselink, Tom A. Ewing, C. G. Boeriu, J. van Haveren, *ACS Sustainable Chem. Eng*. **2020**, 8, 29, 10626–10632
https://doi.org/10.1021/acssuschemeng.0c02833

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

Raw renewable material → **Useful monomers**

Biocatalysis **Flow Chemistry**

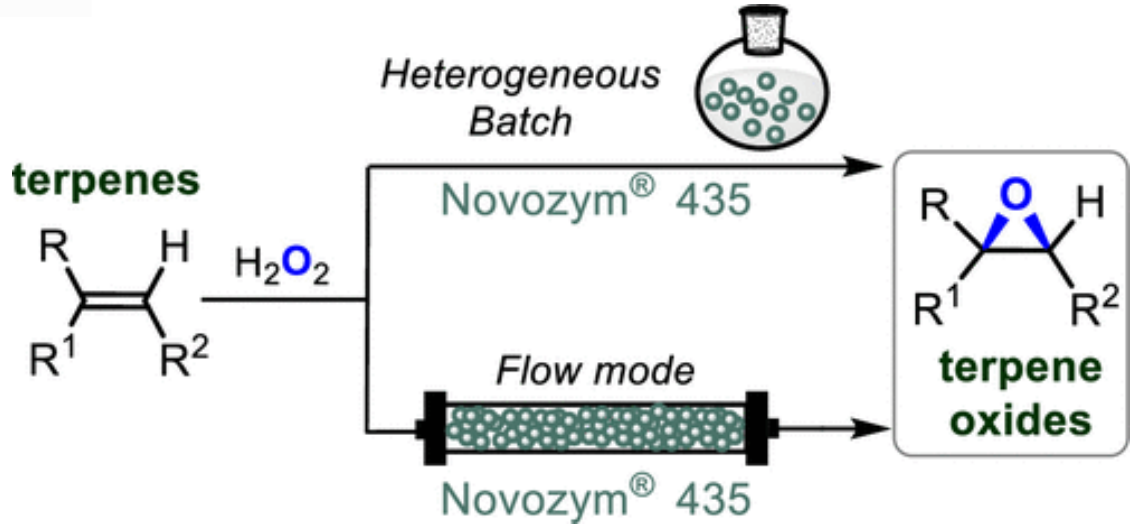


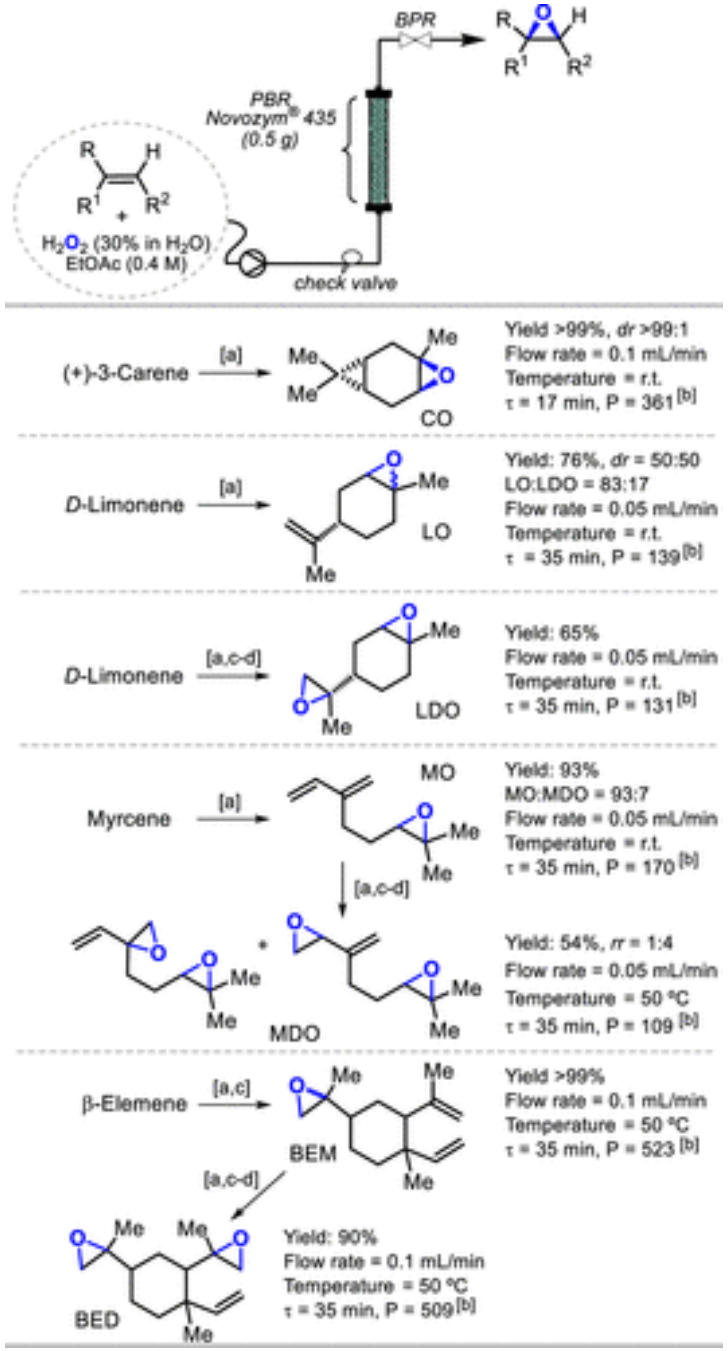
improved safety and environmental profile

biobased polymer epoxidation avoiding the use of toxic reagents and minimizing the formation of byproducts

mild reaction conditions

lower environmental impact





Synthesis of Biorenewable Terpene Monomers Using Enzymatic Epoxidation under Heterogeneous Batch and Continuous Flow Conditions

A. Brandolese, D. H. Lamparelli, M.l A. Pericàs, A. W. Kleij

ACS Sustainable Chem. Eng., 2023, **11**, 4885

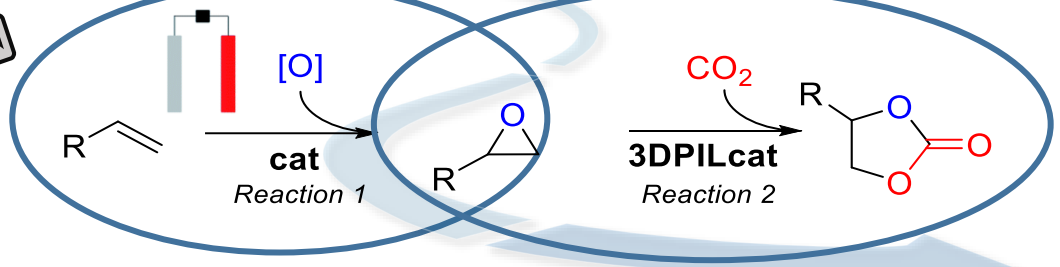
https://doi.org/10.1021/acssuschemeng.3c00370

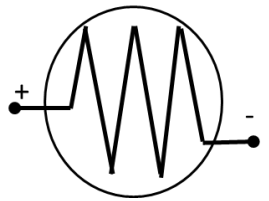
Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

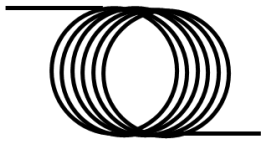
Raw renewable material → **Useful monomers**

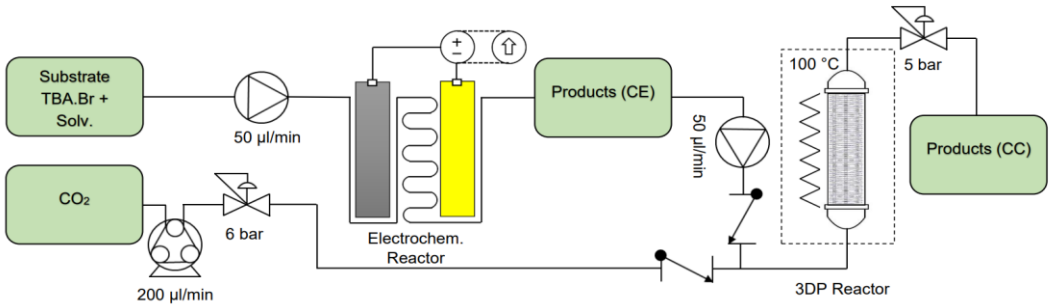
Electrocatalysis | **Flow Chemistry**

Multi-step syntheses









- ✓ Continous flow production
- ✓ Integration of process
- ✓ Valorization of raw materials

Green Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

Check for updates

Multi-step oxidative carboxylation of olefins with carbon dioxide by combining electrochemical and 3D-printed flow reactors†

Cite this: *Green Chem.*, 2023, **25**, 9934

Diego Iglesias,[a] Cristopher Tinajero,[a] Simone Marchetti,[a,b] Ignazio Roppolo,[b] Marcileia Zanatta *[a] and Victor Sans *[a]

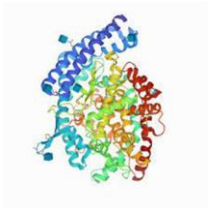
Average yield (CC)
80 % for 20h

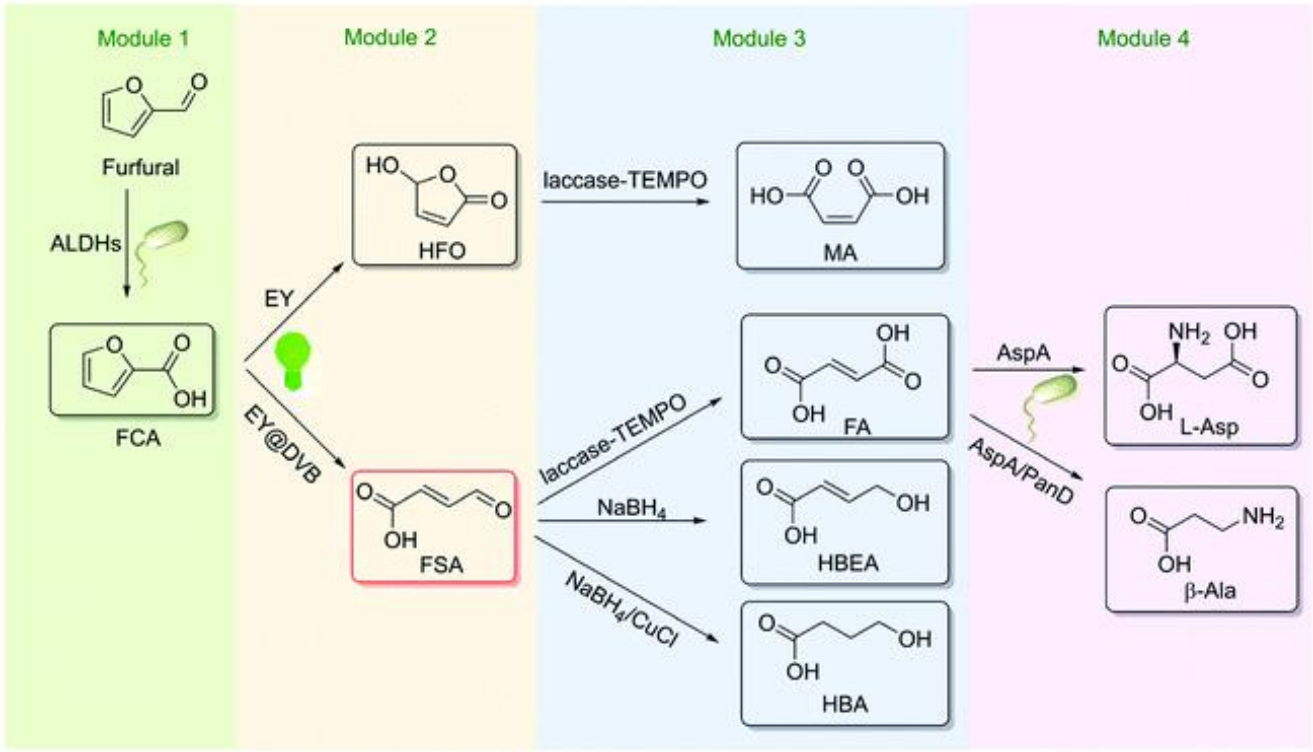
Green Chem., **2023**,25, 9934-9940, https://doi.org/10.1039/D3GC03360K

Grupo de Química Sostenible y Supramolecular
UNIVERSITAT JAUME·I

Raw renewable material → **Useful monomers**

Biocatalysis **Photocatalysis**





multi-step cascades integrating biocatalysis with **organo-, base- and photocatalysis** in a **plug-and-play fashion** were constructed for the controllable synthesis of **eight C4 chemicals** from furfural.

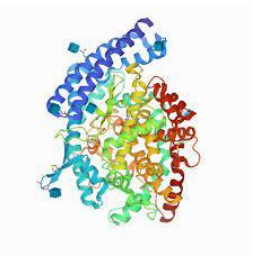
A plug-and-play chemobiocatalytic route for the one-pot controllable synthesis of biobased C4 chemicals from furfural, Y.-M. Huang, G.-H. Lu, M.-H. Zong, W.-J. Cuib, N. Li, ***Green Chem.***, 2021, Advance Article, https://doi.org/10.1039/D1GC03001A

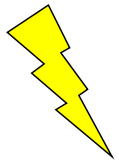
How?

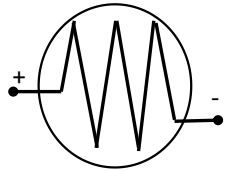
❑ **Advanced Technology**: Use of cutting-edge technology and instruments

Biocatalysis **Photocatalysis** **Electrocatalysis** **Flow Chemistry**

A + B → C







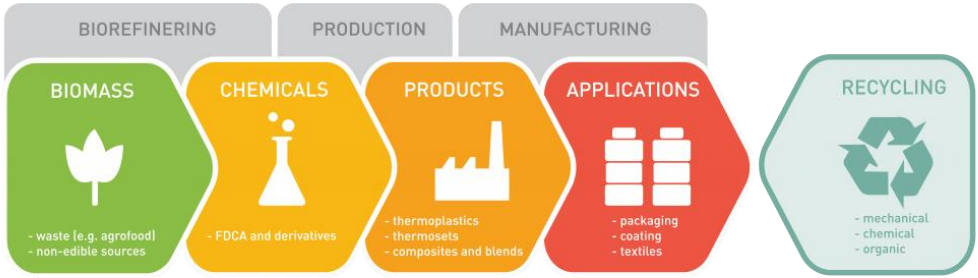
Key enabling technologies (KET)

Renewable raw materials have the potential to provide a wide range of monomers arguably as comprehensive as those provided by the petrochemical industry

Raw renewable material → **Useful monomers**

advocate collaborative development to translate those knowledge, methods, and insights into the other parts of the value chain.

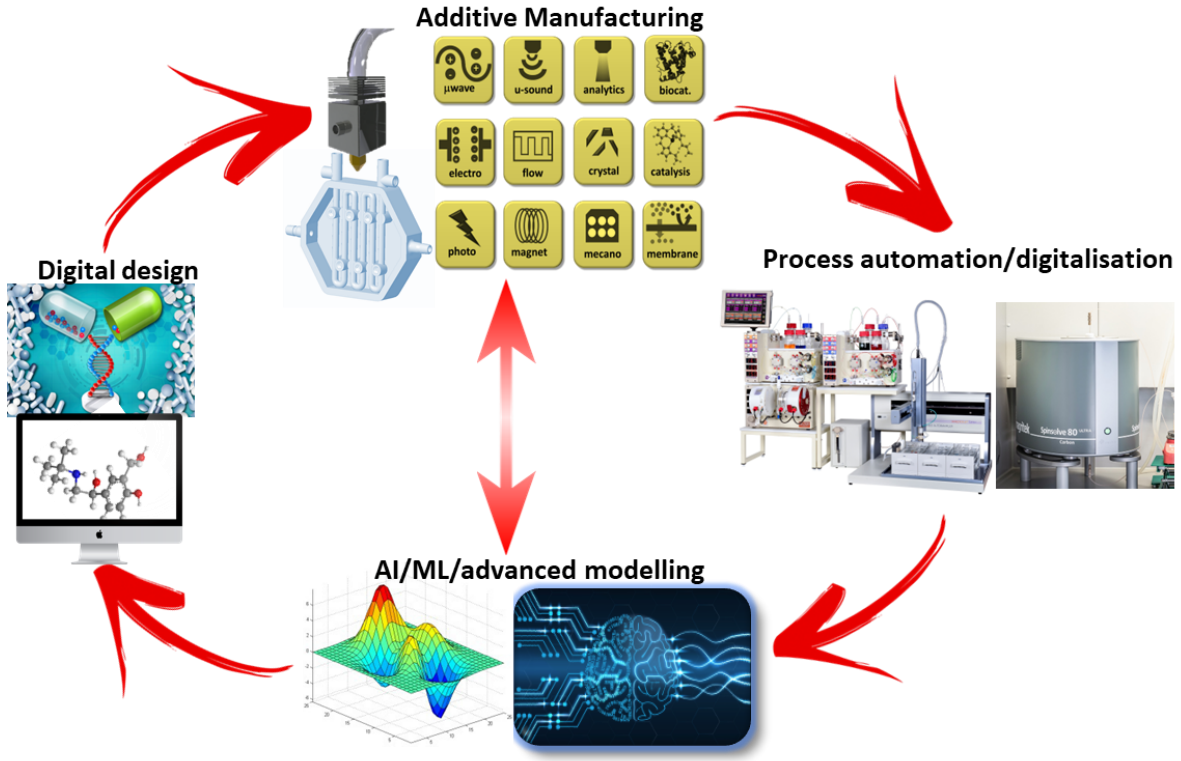
https://doi.org/10.1016/j.cogsc.2020.100367



What is the fashion trend in organic Chemist?

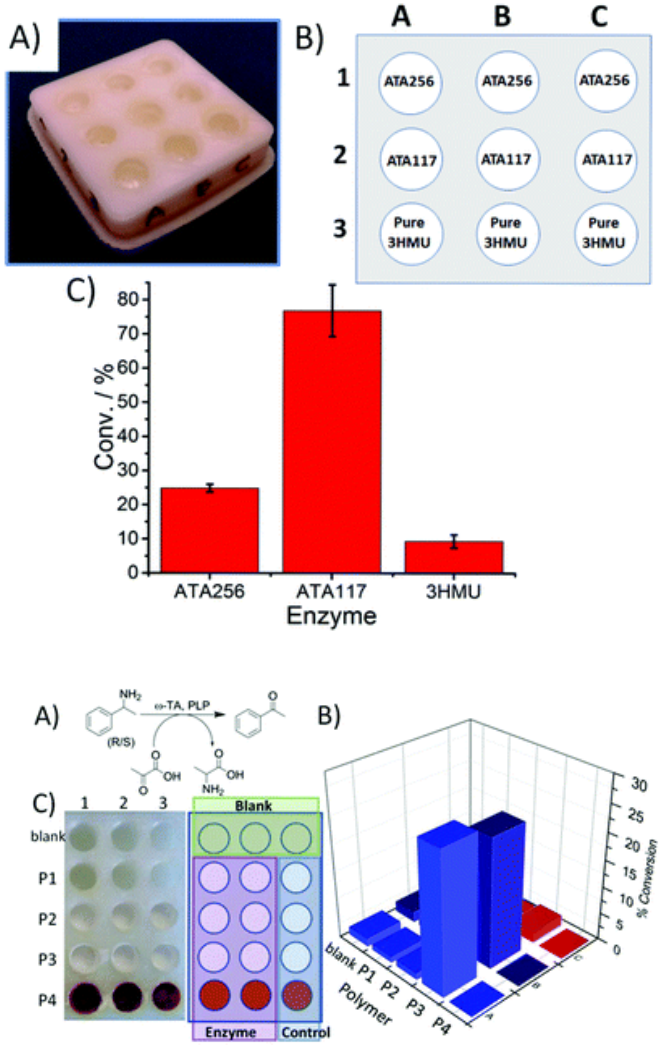
The reactions might stay the same, but nowadays a lot of effort is put into moving from simpler to more complex reactions

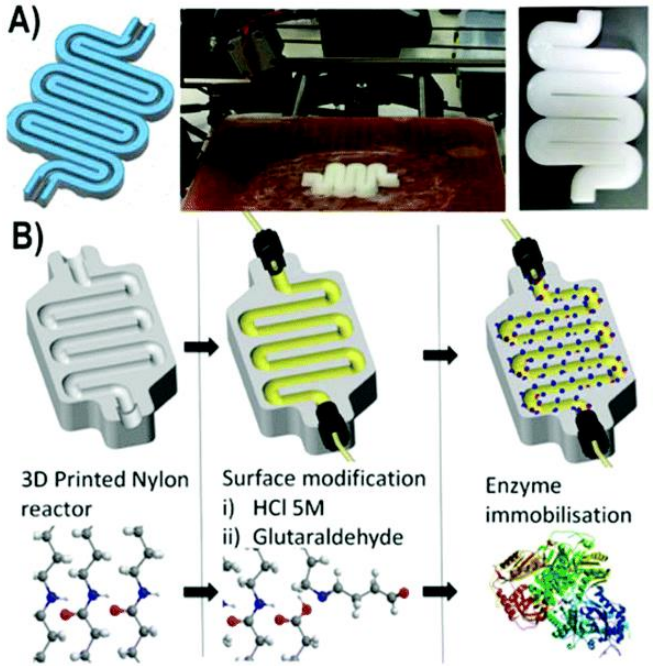
❑ **Advanced Technology**: Use of cutting-edge technology and instruments, the digitalisation of the manufacturing process

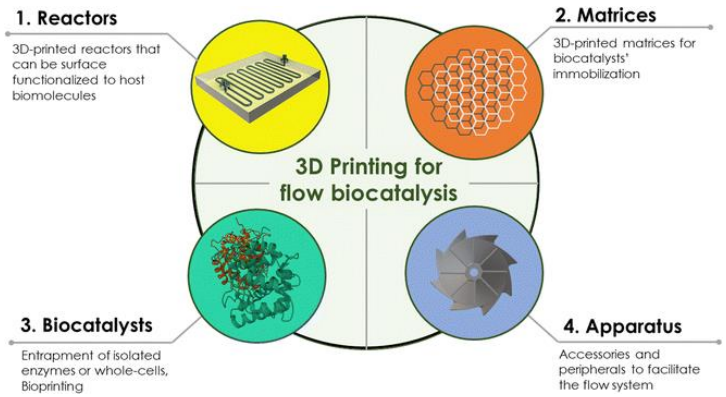


- ❑ integration of multiple enabling technologies
- ❑ reduce heat and mass
- ❑ optimised mixing
- ❑ add functionality to the reactors
- ❑ freedom of design inherent to 3DP.
- ❑ safer and efficient processes with integrated capabilities
- ❑ a simple and cost-effective fashion.

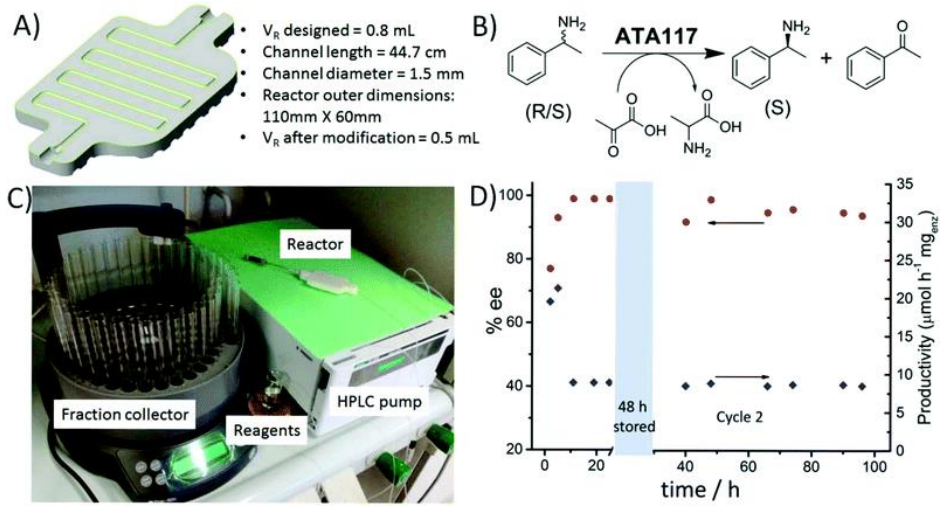
3D printing for Integration







3D printing for flow biocatalysis
E. Gkantzou, M. Weinhartbc, S. Kara
RSC Sustain., 2023, 1, 1672-1685
https://doi.org/10.1039/D3SU00155E

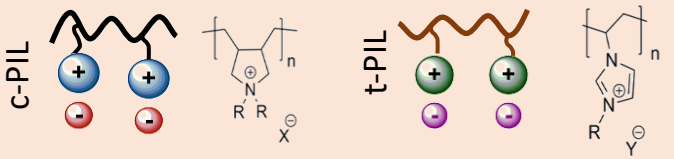


Tuneable 3D printed bioreactors for transaminations under continuous-flow
Green Chem., 2017,**19**, 5345-5349
https://doi.org/10.1039/C7GC02421E

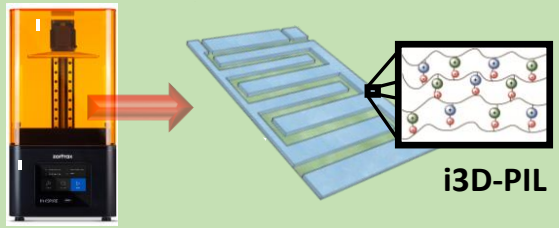
3D printing for Integration

Towards highly efficient continuous-flow catalytic carbon dioxide cycloadditions with additively manufactured reactors

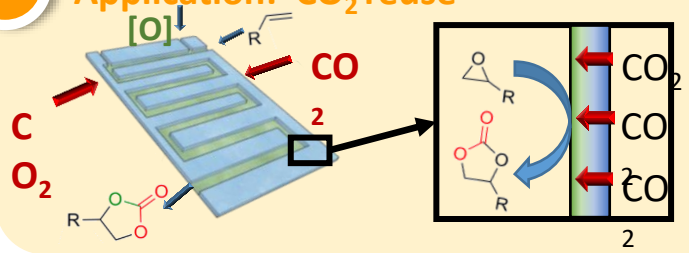
T1 **Material preparation and optimization**

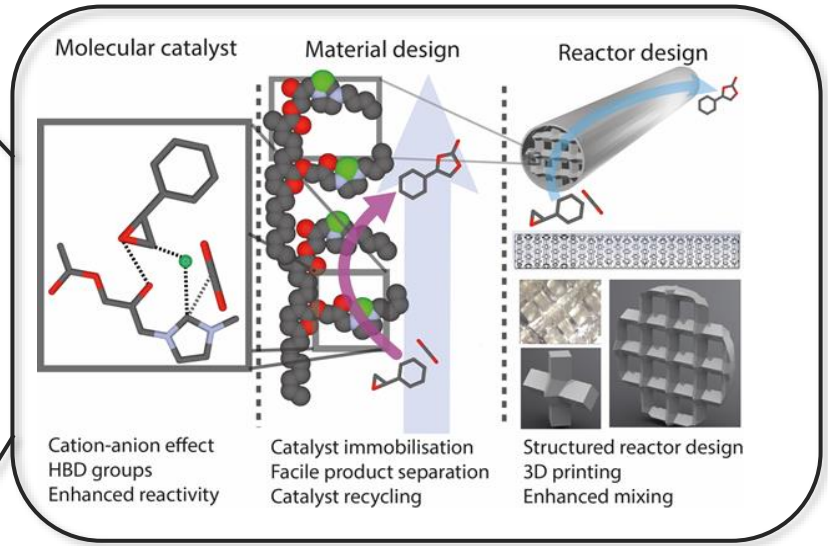


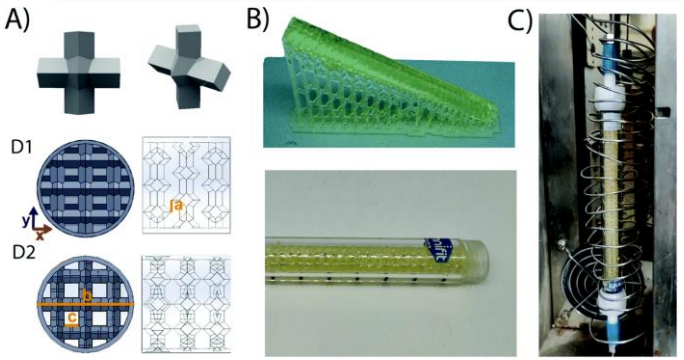
T2 **Design of 3DP reactor**

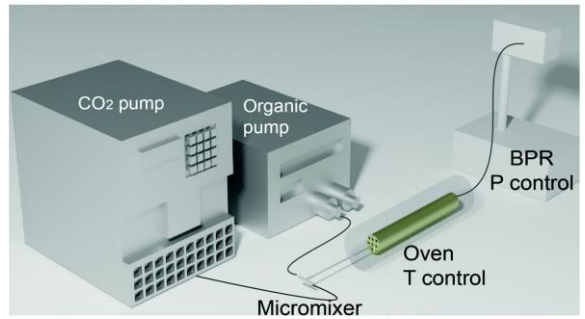


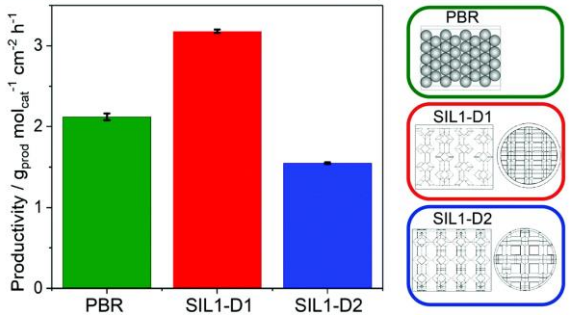
T3 **Application: CO_2 reuse**

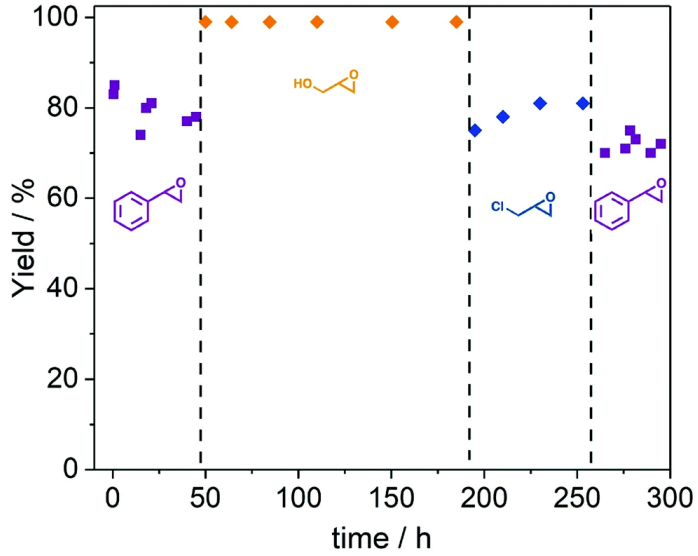












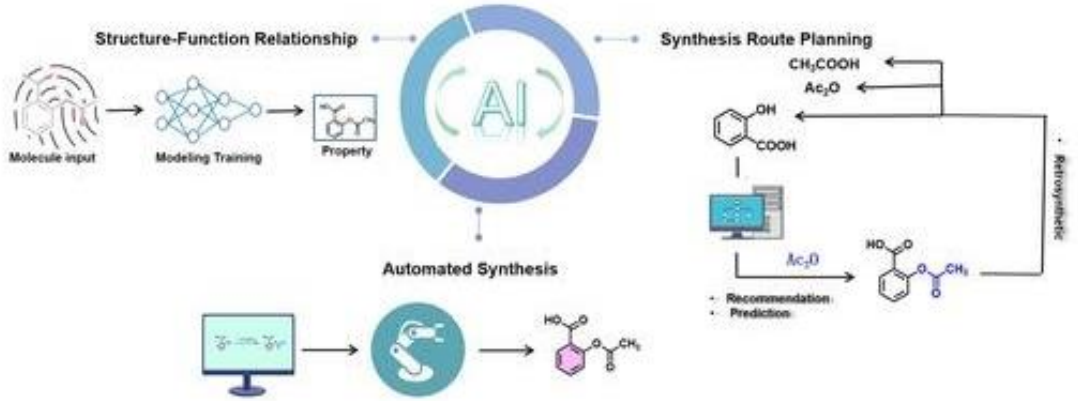
Green Chem., 2022, **24**, 3300-3308, https://doi.org/10.1039/D1GC04593H

What is the fashion trend in organic Chemist?

The reactions might stay the same, but nowadays a lot of effort is put into moving from simpler to more complex reactions

A + B → C

- **Digital / AI Chemistry**: Integration of AI tools to design predict/optimize synthesis, understand mechanisms at a molecular level, and process optimization



AI for Structure-Function Relationship Analysis
- Molecular Property Prediction
- Molecular Design

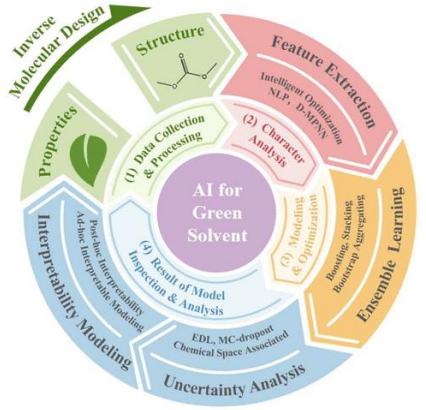
AI for Synthetic Route Planning
- Retrosynthetic Planning
- Forward Reaction Prediction

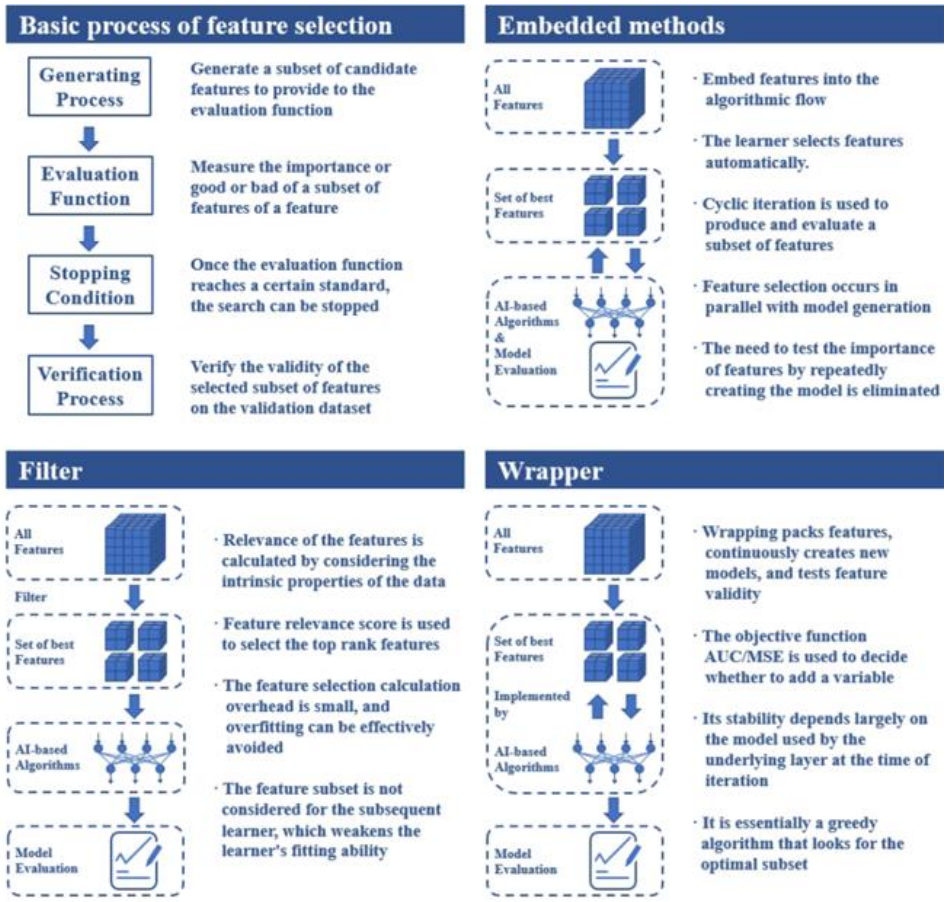
AI for Automated Synthesis
- Robotic Lab Platform
- Automated Synthesis

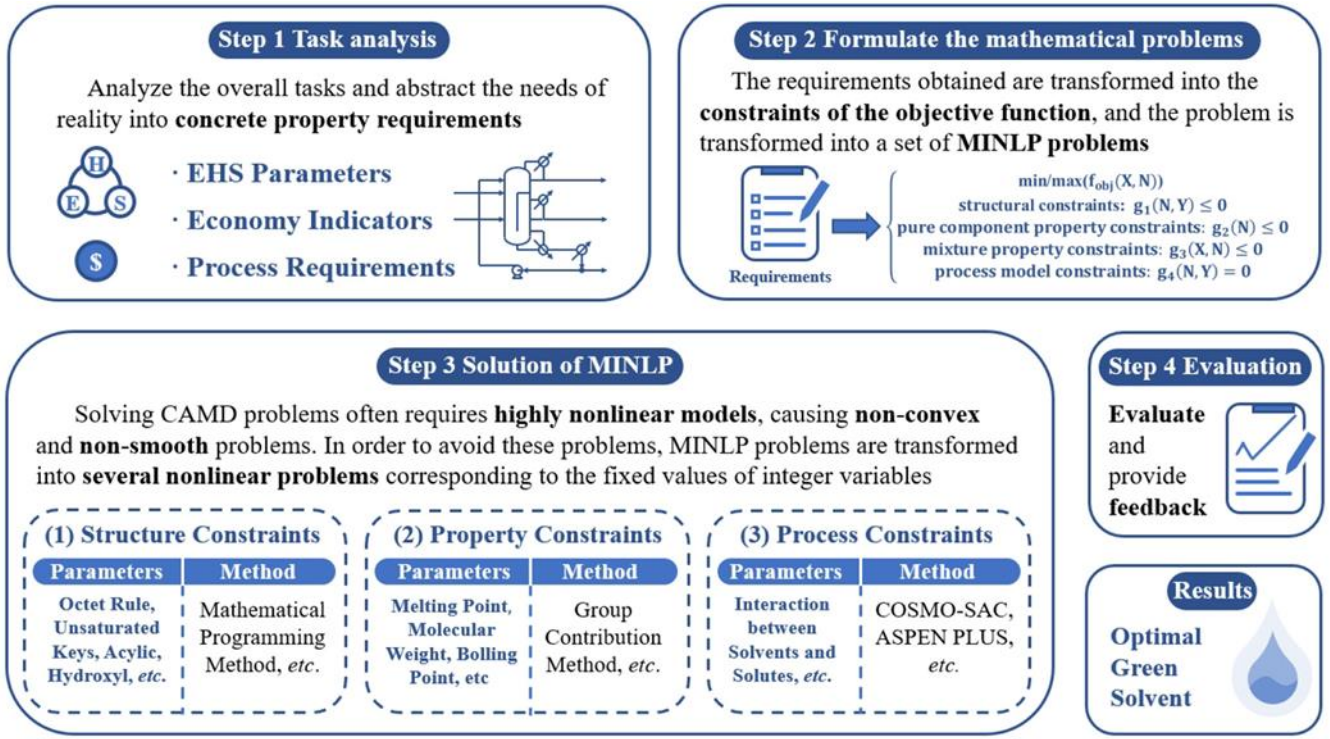
Processes 2023, 11(2), 330; https://doi.org/10.3390/pr11020330
Chem. Rev. 2023, 123, 13, 8736–8780, https://doi.org/10.1021/acs.chemrev.3c00189

Artificial Intelligence Assisted Green Solvent Development

AI-based and data-driven research paradigm is growing to explore the correspondence between the properties and structures of the solvent components.
The integration intensifications of green solvent design with AI as a promising approach



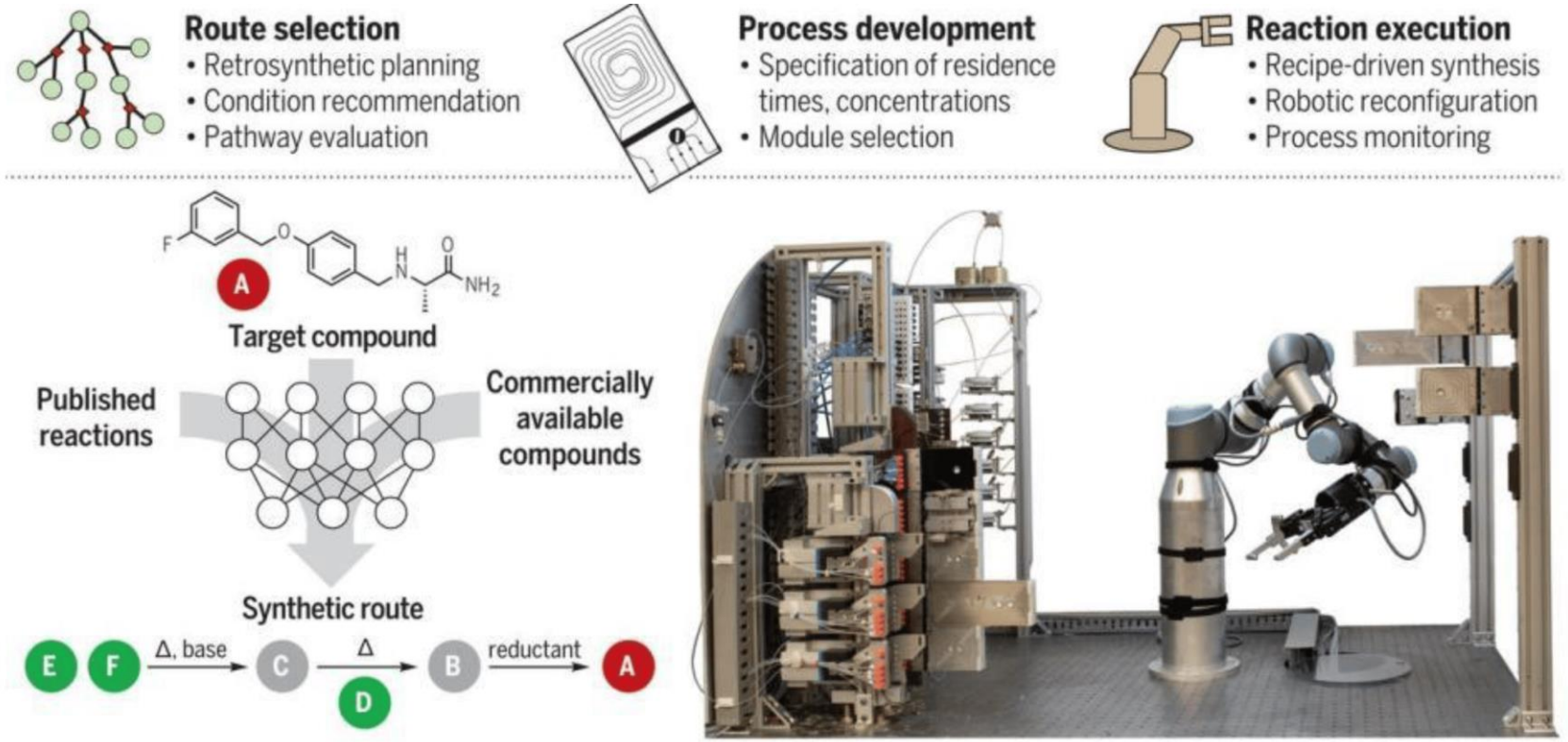




A Systematic Review on Intensifications of Artificial Intelligence Assisted Green Solvent Development
H. Wen, S. Nan, D. Wu, Q. Sun, Y. Tong, J. Zhang, S. Jin, W. Shen
Ind. Eng. Chem. Res. 2023, 62, 48, 20473–20491
https://doi.org/10.1021/acs.iecr.3c02305

Automated Synthesis

The ideal automated synthesis platform would be capable of planning its own synthetic routes and executing them under conditions that facilitate scale-up to production goals.

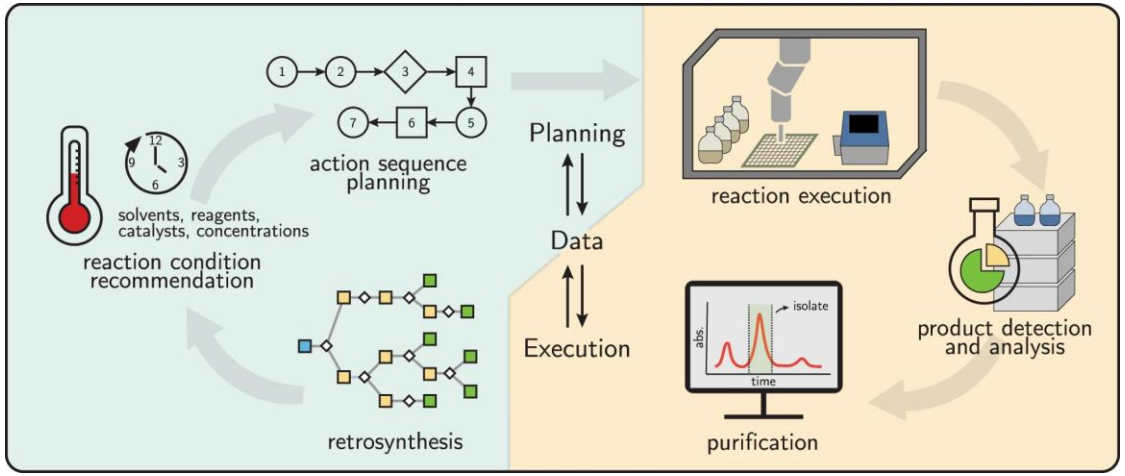


targets required a total of eight particular retrosynthetic routes and nine specific process configurations.

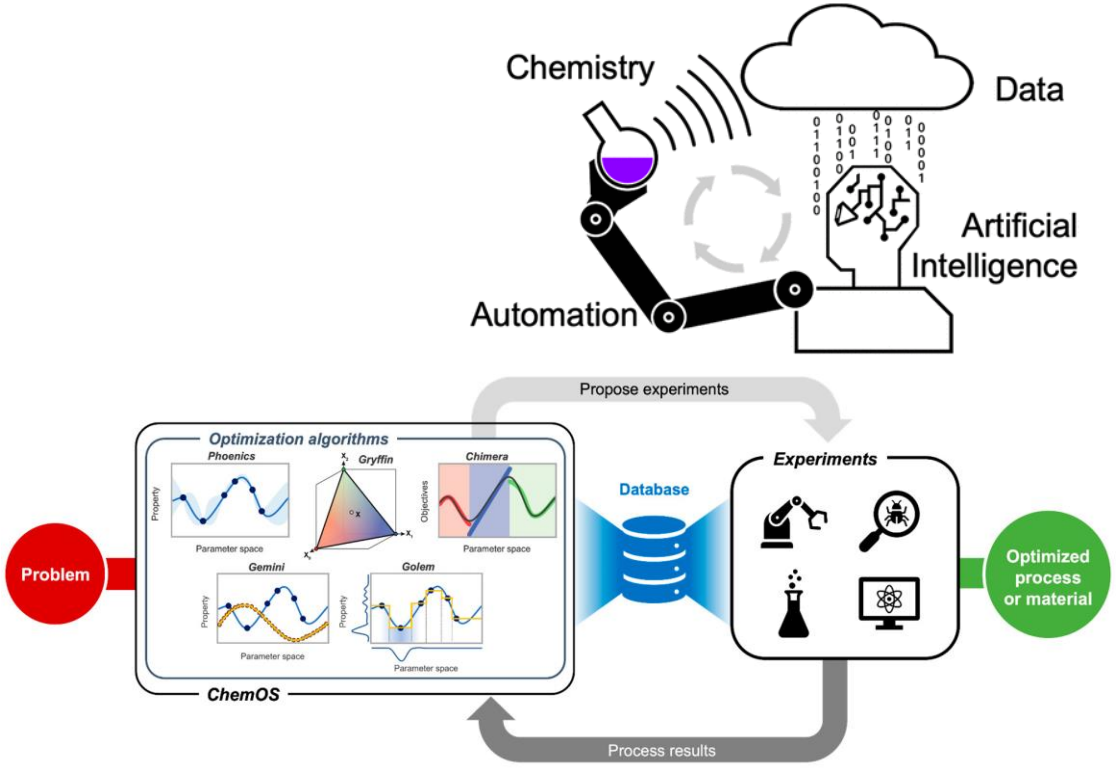
A robotic platform for flow synthesis of organic compounds informed by AI planning. Science 2019, 365, 557–565. DOI: 10.1126/science.aax1566

Automated Synthesis

Platforms capable of performing chemical reactions in an automated or semi-automated manner, where the physical operations of a chemist are replaced by robotics and the planning by data-driven algorithms,



Gao, W., Raghavan, P. & Coley, C.W.
Autonomous platforms for data-driven organic synthesis.
Nat Commun 13, 1075 (2022). https://doi.org/10.1038/s41467-022-2873



Autonomous Chemical Experiments: Challenges and Perspectives on Establishing a Self-Driving Lab
Martin Seifrid, Robert Pollice, Andrés Aguilar-Granda, Zamyla Morgan Chan, Kazuhiro Hotta, Cher Tian Ser, Jenya Vestfrid, Tony C. Wu, and Alán Aspuru-Guzik
Chem. Res. 2022, 55, 17, 2454–2466
https://doi.org/10.1021/acs.accounts.2c00220

You are the new generation of….

Molecular Designers

D-Carbonize Workshop & Kick-off

Organic Chemistry

Eduardo García-Verdugo

cepeda@uji.es

www.quimicasostenible.uji.es
www.miqs.uji.es

Supramolecular and Sustainable Chemistry Group