Introduction

Green Chemistry

- *Large impact on: industry, research laboratories, education, general public*
- *12 principles of Green Chemistry = design guidelines to provide the framework for sustainable design*

- *1. **Prevention.** It is better to prevent waste than to treat or clean up after a problem.*
- *2. **Atom economy.** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.*
- *3. **Less hazardous chemical synthesis.** When it is possible, synthetic methodologies should be designed to use and generate substances that pose little or no toxicity to human health and the environment.*
- *4. **Designing safer chemicals.** Chemical products should be designed to preserve efficacy of the function while reducing toxicity.*
- *5. **Safer solvents and auxiliaries.** The use of auxiliary substances (solvents, separation agents, …) should be avoided and, when it possible, made innocuous.*
- *6. **Design for energy efficiency.** Energy requirements of chemical processes should be recognized for their environmental impacts and should be minimized. Reactions should be done at ambient temperature and ambient pressure.*

Introduction

Green Chemistry

- *7.* ***Use of renewable feedstocks.*** *A raw material or feedstock should be renewable, when it is technically and economically practicable.*
- *8.* ***Reduce derivatives.*** *Unnecessary derivatization (blocking groups, protecting/deprotecting grows temporary modification of chemical processes) should be minimized or avoided, if possible (any additional step requires additional reagents and can generate waste)*
- *9.* ***Catalysis.*** *Catalytic reagents (as selective as possible) as superior to stoichiometric reagents.*
- *10.* ***Design from degradation.*** *Reaction products will de designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment*
- *11.* ***Real-time analysis for pollution prevention.*** *Analytical methods need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.*
- *12.* ***Inherently safer chemistry for accident prevention.*** *Substances used in a chemical process should be closed to minimize the potential for chemical accidents (explosions, fires, …)*

12 Principles of Green Engineering

The 12 Principles of Green Engineering

Principle 1: Designers need to strive to ensure that all material and energy inputs and outputs are as inherently nonhazardous as possible.

Principle 2: It is better to prevent waste than to treat or clean up waste after it is formed.

Principle 3: Separation and purification operations should be designed to minimize energy consumption and materials use.

Principle 4: Products, processes, and systems should be designed to maximize mass, energy, space, and time efficiency.

Principle 5: Products, processes, and systems should be "output pulled" rather than "input pushed" through the use of energy and materials.

Principle 6: Embedded entropy and complexity must be viewed as an investment when making design choices on recycle, reuse, or beneficial disposition.

Principle 7: Targeted durability, not immortality, should be a design goal.

Principle 8: Design for unnecessary capacity or capability (e.g., "one size fits all") solutions should be considered a design flaw.

Principle 9: Material diversity in multicomponent products should be minimized to promote disassembly and value retention.

Principle 10: Design of products, processes, and systems must include integration and interconnectivity with available energy and materials flows.

Principle 11: Products, processes, and systems should be designed for performance in a commercial "afterlife".

Principle 12: Material and energy inputs should be renewable rather than depleting.

Anastas, P. T.; Zimmerman, J. B. *Environ. Sci. Technol.* **2003**, *37*, 94A–101A

12 Principles of Green Chemistry

1. Prevention

- *Better to prevent the formation of waste rather than to clean it up after the fact.*
- *When large quantities of the starting materials used in a process are lost because of the original design of the process itself then it will inexorably generate waste (undesirable).*
- *E-Factor, or Environmental Impact Factor (introduced in 1992 by Roger Sheldon).*
- *Very important metric in green chemistry*
- ***Quantify the amount of waste generated per kilogram of product (ratio of masses)***
- *Higher E-Factor means more waste*

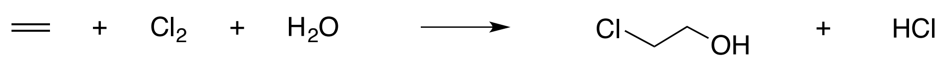
Sheldon, R. A. *Chemtech* **1994**, *24*, 38

12 Principles of Green Chemistry

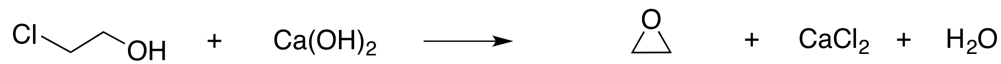
1. Prevention

- *Example: synthesis of ethylene epoxide*
- *Traditional synthesis: 5 kg (HCl, $CaCl_2$, H_2O) of generated waste per kg of ethylene epoxide*

Step 1

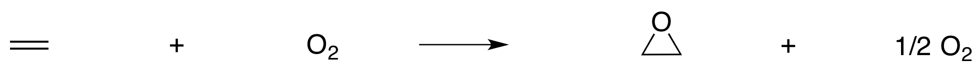


Step 2



E-factor = 5 (over the 2 steps)

- *New method*



E-factor = 0.3

- *New method generating more than 16 times less waste (5/0.3)*

Kilty, P. A.; Sachtler, W. M. H. *Catal. Rev.*, **1974**, *10*, 1

1. Prevention

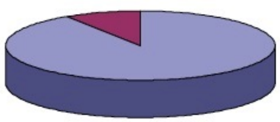
- *E-Factor vs. industry*

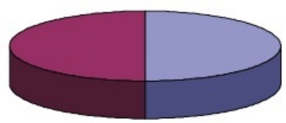
Refineries

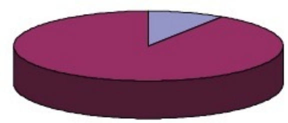
Bulk chemicals

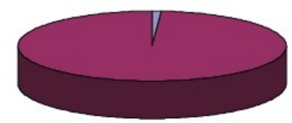
Fine chemicals

Pharmaceutical industry









0.1–10 M (waste)
1–100 (products)

1000–0.1 M (waste)
10–1000 (products)

Industry Segment	Volume (tons/annum)[a]	E Factor (kg waste/kg product)
Bulk Chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5– >50
Pharmaceutical Industry	10–10^3	25– >100

[a] Annual production world-wide or at a single site.

1. Prevention

- *Primary waste in organic synthesis: inorganic salts*
- *Gives an assessment of the"environmental acceptability" of a manufacturing process.*
- *Adopted by many in the chemical industry*
- *E-Factor usually high in the pharmaceutical industry*
- *According to Sheldon's E-Factor, the most polluting industry: pharmaceutical industry (the least polluting one: petrochemical)*

Kilty, P. A.; Sachtler, W. M. H. *Catal. Rev.*, **1974**, *10*, 1

1. Prevention

- *When by-products cannot be avoided, solutions can be found based on innovation*
- *Waste can become raw material (revalorization of by-products)*

Bioethanol

Sugarcane
Sugar beets
Corn
Ligno cellulosic biomass

→ *Energy* + ***Waste*** → ***Energy*** + *Materials* + ***Energy*** ← ***Waste*** + *Energy* ←

Biofuel

Soybean
Palm
Sunflower
Animal fat

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2. Atom economy

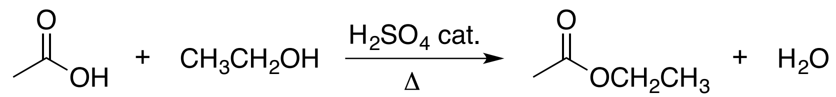
- *Concept of synthetic efficiency*
- *Atom Economy (AE) = Atom Efficiency*
- *AE = theoretical value to assess the efficiency of the reaction*
- *Concept of maximizing the use of raw materials*
- *Final product contains the maximum number of atoms from the reactants*
- *Ideal reaction would incorporate all of the atoms of the reactants.*
- *AE =1 if there no by-product (loss of atoms is low)*
- *AE -> 1 if there is almost no by-product*
- *AE measure: ratio of the molecular weight of the desired product over the molecular weights of all reactants used in the reaction*

$$\mathrm{AE} = \frac{\mathrm{MW\ (Product)}}{\mathrm{MW\ (Reagents)}}$$

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

2. Atom economy

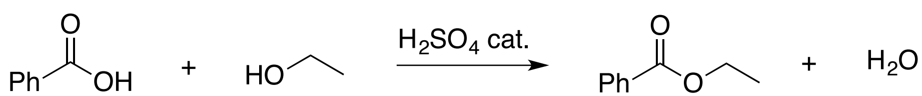
- *Example 1. Esterification of acetic acid with ethanol, water as by-product*



A **B** **P** **Q**

$$AE = \frac{\mathrm{MW}\ (CH_3CO_2CH_2CH_3)}{\mathrm{MW}\ (CH_3CO_2H) + \mathrm{MW}\ (CH_3CH_2OH)} = \frac{72}{90} = 0.80\ (80\%)$$

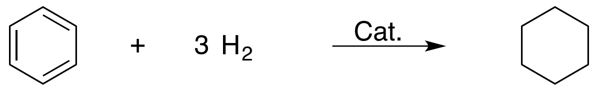
- *Example 2. Esterification of benzoic acid with ethanol, water as by-product*



AE = 0.89 (89%)

2. Atom economy

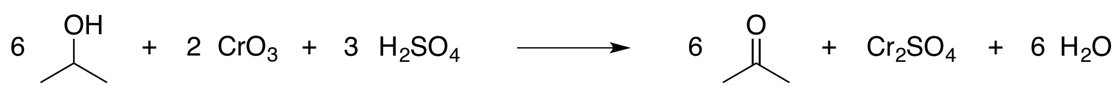
- *Example 3. Catalytic hydrogenation of benzene*



$$AE = \frac{MW\ (C_6H_{12})}{MW\ (C_6H_6) + 3\ MW\ (H_2)} = \frac{84}{78+6} = 1.00\ (100\%)$$

  - *Catalyst not involved in AE!*
  - *-> Catalytic method better than stoichiometric*

- *Example 4. Oxidation of isopropanol with chromium oxide*



$$AE = \frac{6\ MW\ (C_3H_6O)}{2\ MW\ (CrO_3) + 6\ MW\ (C_3H_8O) + 3\ MW\ (H_2SO_4)} = \frac{6*58}{2*100 + 6*60 + 3*98} = 0.41\ (41\%)$$

  - *Low AE!*
  - *Classical method but not very satisfactory*

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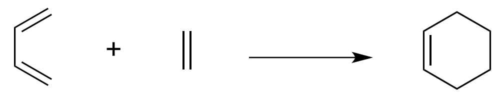
2. Atom economy

- *Example 5. Diels-Alder reaction*



AE = 100%

  - *Completely atom-economical reaction*

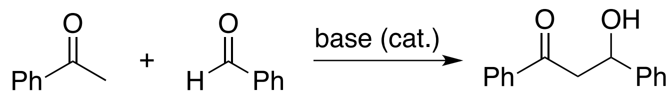
- *Example 6. Oxidation of isopropanol with chromium oxide*

$$\mathrm{AE} = \frac{6\ \mathrm{MW}\ (C_3H_6O)}{2\ \mathrm{MW}\ (CrO_3) + 6\ \mathrm{MW}\ (C_3H_8O) + 3\ \mathrm{MW}\ (H_2SO_4)} = \frac{6*58}{2*100 + 6*60 + 3*98} = 0.41\ (41\%)$$

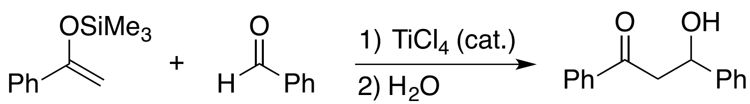
  - *Low AE!*
  - *Classical method but not very satisfactory*

2. Atom economy

- *Example 7. aldol vs. Mukaiyama aldol reaction*



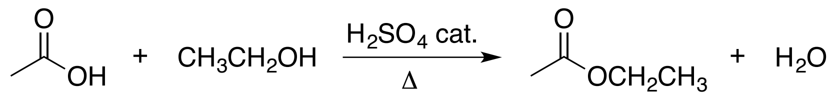
$E_{At} = 1$



$E_{At} = 0.76$

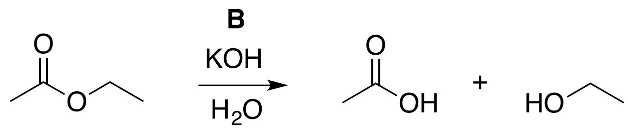
2. Atom economy

- *Carbon economy*



A B P Q

$$E_C = \frac{n_C(P)}{n_C(A) + n_C(B)} = \frac{n_C(CH_3CO_2CH_2CH_3)}{n_C(CH_3CO_2H) + n_C(CH_3CH_2OH)} = \frac{4}{4} = 100\%$$



A P Q

$E_C = 0.5$

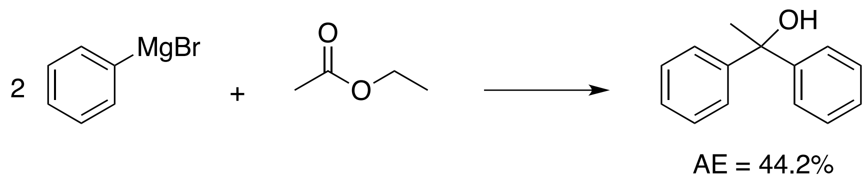
2. Atom economy

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

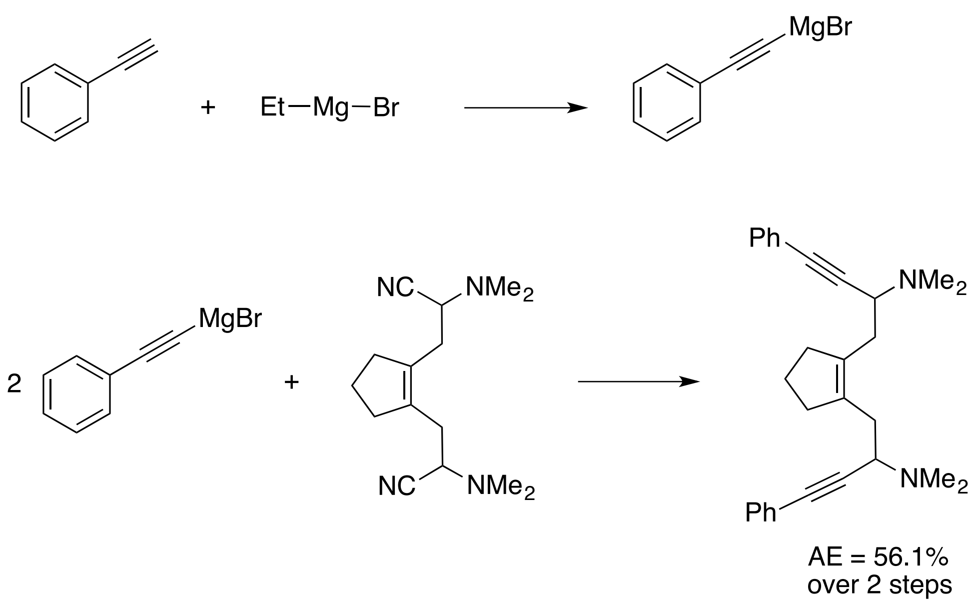
3. Less hazardous chemical synthesis

- *When it is possible, synthetic methodologies should be designed to use and generate substances that pose little or no toxicity to human health and the environment.*

- *Uses of Grignard reagents (very poor AE)*

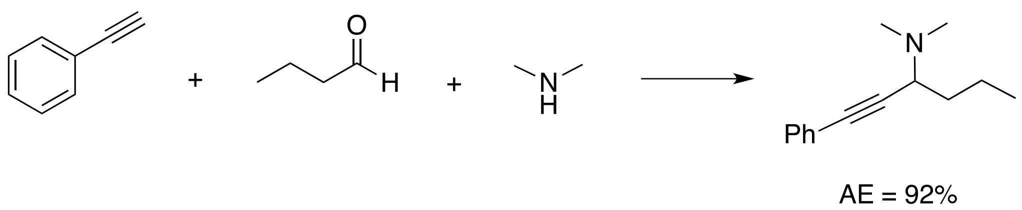


  - *for the synthesis of propargylic amine*

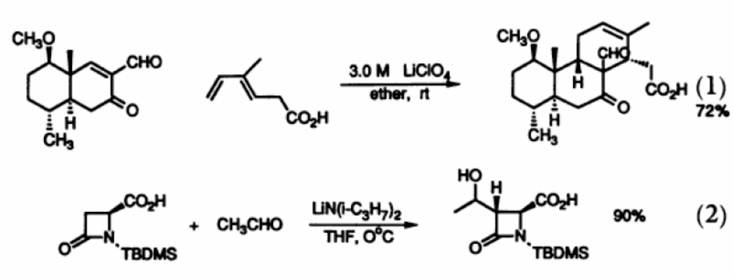


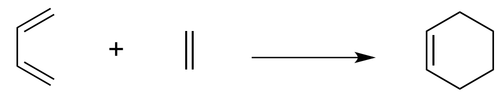
3. Less hazardous chemical synthesis

- *Multicomponent reactions as a valuable alternative (synthesis of propargylic amine)*

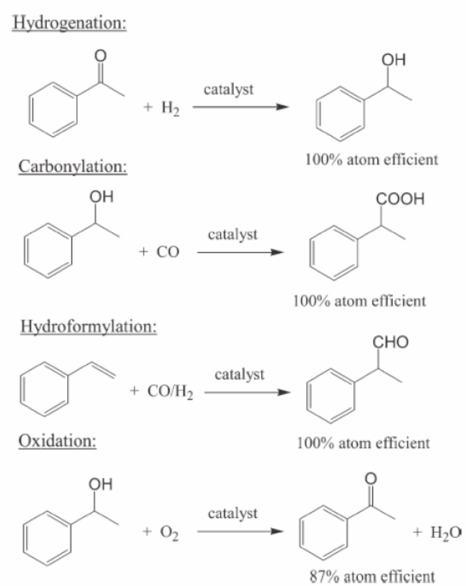


3. Less hazardous chemical synthesis





AE = 100%



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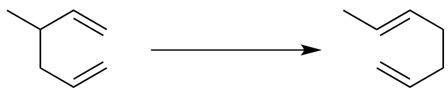
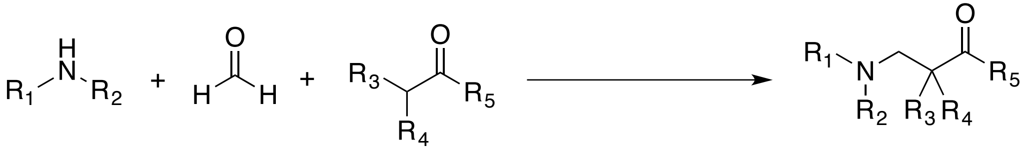
3. Less hazardous chemical synthesis

- *Cope rearrangement*

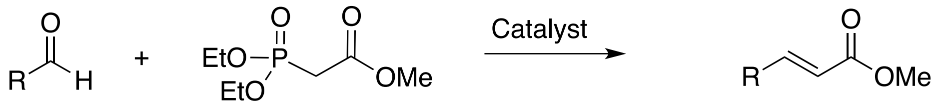


AE = 1 (100%)

- *Mannich reaction (condensation)*

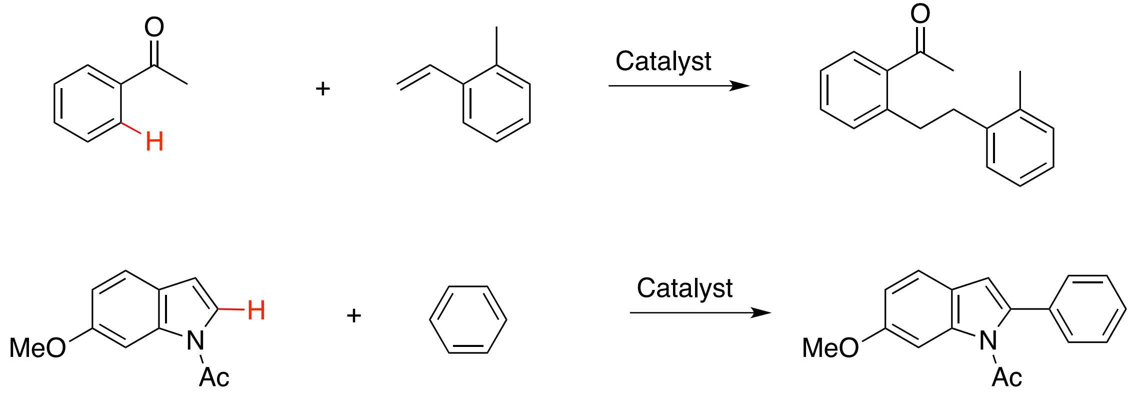


- *Horner-Wadsworth-Emmons reaction (to compare with Wittig reaction)*



3. Less hazardous chemical synthesis

- *More recent approach: C–H activation*

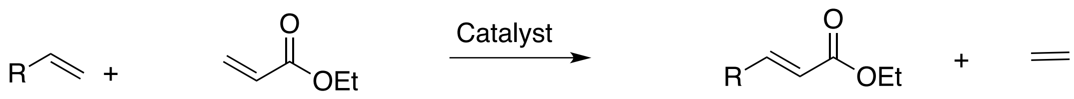


AE = very high

12 Principles of Green Chemistry

3. Less hazardous chemical synthesis

- *More recent approach: metathesis of alkenes*



12 Principles of Green Chemistry

4. Designing safer chemicals

- *Molecular design*
- *Taking into consideration hazard in the design process*
- *Design less toxic chemicals via incorporation of specific design features*

5. Solvents

Green solvents

Selection guide of solvents

- D. Prat article (Sanofi-Aventis Research & Development)

- Safety criteria (flammability)
- Health criteria (exposure, …)
- Environmental criteria

- Score taking into account the 3 criteria

Score combination	Ranking
One score ≥8	Hazardous
Two "red" scores	Hazardous
One score = 7	Problematic
Two "yellow" scores	Problematic
Other	Recommended

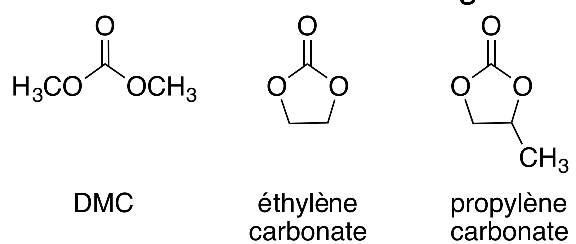
Family	Solvent	BP (°C)	FP (°C)	Worst H3xx[a]	H4xx	Safety score	Health score	Env. score	Ranking by default
Water	Water	100	na	None	None	1	1	1	Recommended
Alcohols	MeOH	65	11	H301	None	4	7	5	Problematic
	EtOH	78	13	H319	None	4	3	3	Recommended
	i-PrOH	82	12	H319	None	4	3	3	Recommended
	n-BuOH	118	29	H318	None	3	4	3	Recommended
	t-BuOH[c]	82	11	H319	None	4	3	3	Recommended
	Benzyl alcohol	206	101	H302	None	1	2	7	Problematic
	Ethylene glycol	198	116	H302	None	1	2	5	Recommended
Ketones	Acetone	56	−18	H319	None	5	3	5	Problematic
	MEK	80	−6	H319	None	5	3	3	Recommended
Halogenated	DCM	40	na	H351	None	1	7	7	Hazardous
	Chloroform	61	na	H351	None	2	7	5	Problematic
	CCl_4	77	na	H351	H420	2	7	10	Hazardous
	DCE	84	13	H350	None	4	10	3	Hazardous
	Chlorobenzene	132	29	H332	H411	3	2	7	Problematic
Aprotic polar	Acetonitrile	82	2	H319	None	4	3	3	Recommended
	DMF	153	58	H360	None	3	9	5	Hazardous
	DMAc	166	70	H360	None	1	9	5	Hazardous
	NMP	202	96	H360	None	1	9	7	Hazardous

Prat 2016GC288

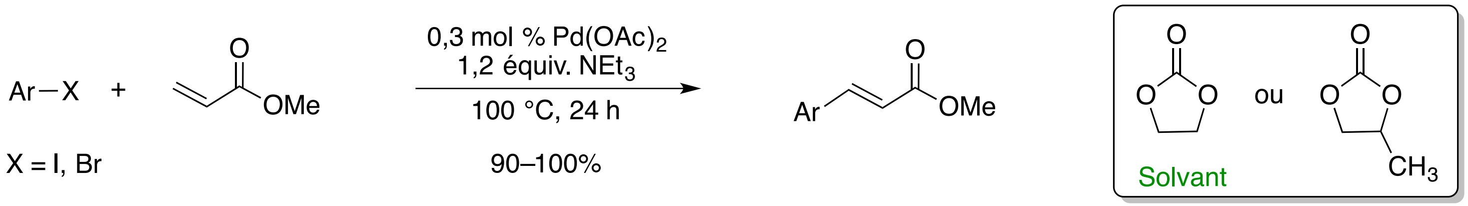
Green solvents

Use of carbonates (cyclic)

- *Reactions of cross-coupling: generally in aprotic and very polar solvents:*
  N,N-dimethylformamide (DMF),
  N-methylpyrrolidone (NMP)
  N,N-dimethylacétamide (DMAc)
- *NMP et DMF : toxic (human health)*
- *Consulter REACH : Registration, Evaluation, Authorisation and restriction of CHemicals (REACH). https://echa.europa.eu/information-on-chemicals/registered-substances (consulted on 27 May 2017).*
- *Alcohols and cyclic carbonates considered as green solvents:*

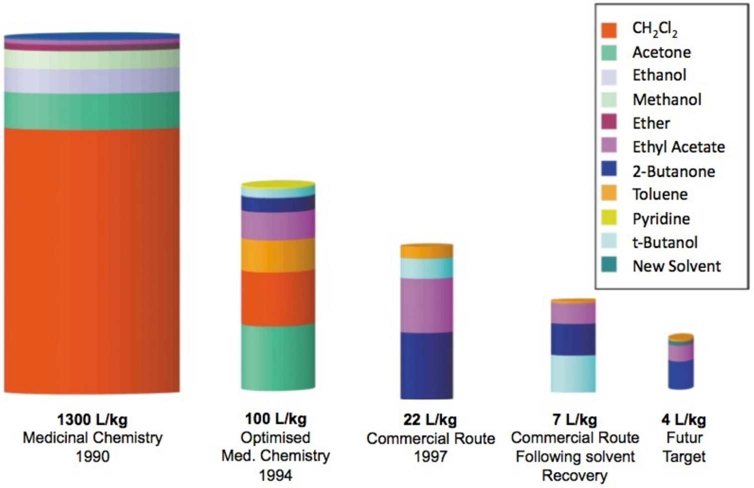


- *Application to the Heck reaction:*



Industrial examples: synthesis of sildenafil citrate

- Solvent balance



✓ Toluène recyclé
✓ Plusieurs étapes dans l'acétate d'éthyle (solvant vert)
✓ Solvants chlorés supprimés
✓ Solvants très volatiles supprimés

« The development of an environmentally benign synthesis of sildenafil citrate (Viagra) and its assessment by Green Chemistry metrics » Dunn, P. J.; Galvin, S.; Hettenbach, K., *Green Chem.* **2004**, *6*, 43–48

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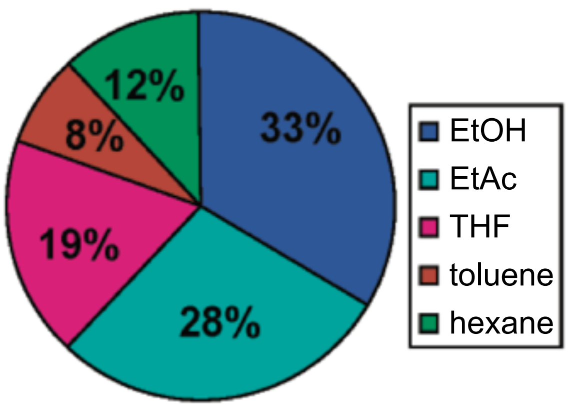
Industrial examples: one-pot reactions

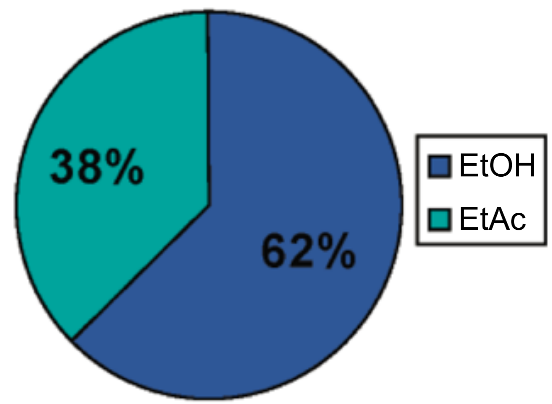
- Impact of solvent use

Sertraline Hydrochloride First Commercial Route



EtOH	34 000 L
EtAc	28 000 L
THF	19 000 L
Toluene	8 000 L
Hexane	12 000 L
Total	**101 400 L**

Sertraline Hydrochloride New Route

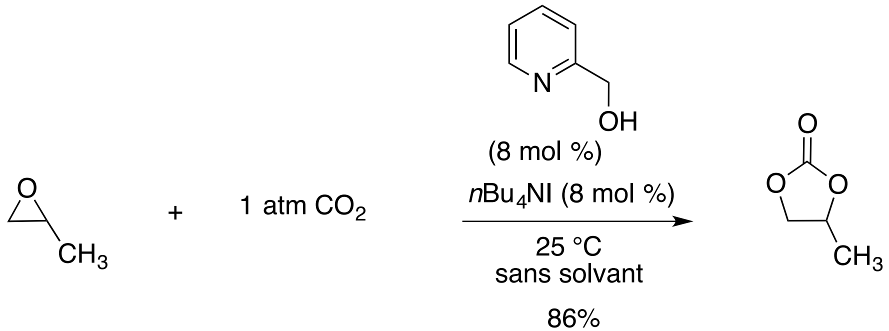


EtOH	15 000 L
EtAc	9 000 L
Total	**24 000 L**

Comparison of solvent utilization (solvents L/1000 kg of sertraline hydrochloride) between the first commercial route and the new route for Zoloft

"A New and Simplified Process for Preparing Two Key Intermediates in the Synthesis of Sertraline Hydrochloride"
Taber, G. P.; Pfisterer, D. M.; Colberg, J. C., *Org. Proc. Res. Dev.* **2004**, *8*, 385–388

Synthesis of a cyclic carbonate



- CO_2 : *non toxic, economic, abundant source of* C_1

- *Advantages of the method: no solvent, use and incorporation of* CO_2 *(1 atm !), no metallic catalyst, recycling of catalyst*

Hirose 2016GC1229

12 Principles of Green Chemistry

6. Energy

- *Concern: depletion of petroleum feedstocks*
- *Increase in energy consumption*
- *Consequence: development of more energy efficient processes and search for renewable energies*

7. Renewable materials

- *Major renewable feedstock: bio-mass*
- *Bio-mass = material available from living organisms*
- *Bio-mass includes wood, crops, agricultural residues, food, …*
- *Examples: cellulose, lignin, starch*
- *Lignin = major waste of the pulp and paper industry*
- *Chitin = abundant natural polymer (exoskeleton from arthropods (crustaceans, …), major byproduct from the seafood industry*

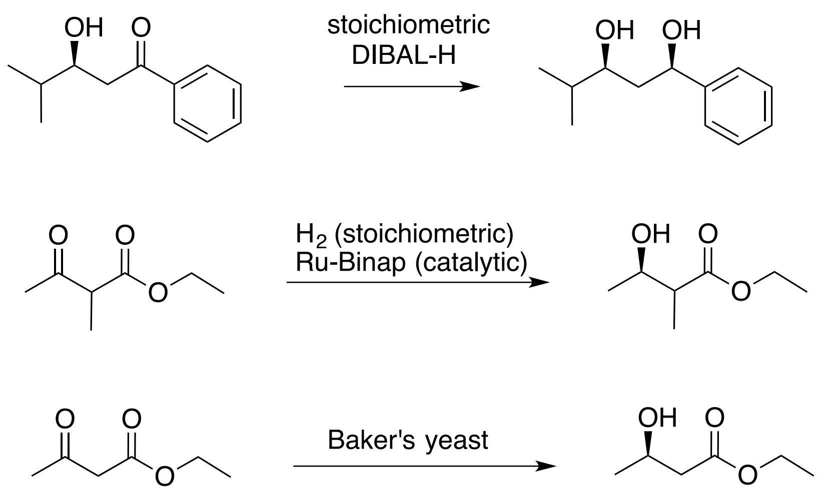
8. Derivatives

- *Concern: preparation of derivatives using covalent bonds = negative*
- *Innovation: use of non-covalent bonds*

12 Principles of Green Chemistry

9. Catalysis

- *Concern: stoichiometric use of reagents*
- *Objective: improve the efficiency of the synthetic toolbox*
- *Catalytic quantities of reagents: efficiency increased (less energy input), more selectivity*
- *Consequences: less energy, less feedstock, less waste*
- *Very good examples: oxidation/reduction reactions*
- *Biocatalysis: enzymes*
- *Reactions with enzymes: chemoselective, regioselective, stereoselective*



12 Principles of Green Chemistry

10. Biodegradation

- *Concern: problem of persistence (from the early stage of industrial development)*
- *Many detergents end up in aqueous waste and nature (foaming water)*
- *Solution: designing biodegradable materials*
- *Biodegradable polymers, …*

11. Analysis

- *Use of analytical chemistry*
- *Real time direct analysis*
- *Live monitoring of chemical transformations*
- *In situ monitoring has a major advantage in terms of green chemistry*
- *Quicker control of the situation*

12. Accident prevention

- *Many chemicals still in use present serious hazards*
- *They should replaced by safer alternatives to prevent accidents wherever possible*