POLITECNICO DI MILANO

School of Industrial and Information Engineering

Course 096125 (095857)

Introduction to Green and Sustainable Chemistry





Green Metrics: Selection of Sustainable Synthetic Route.

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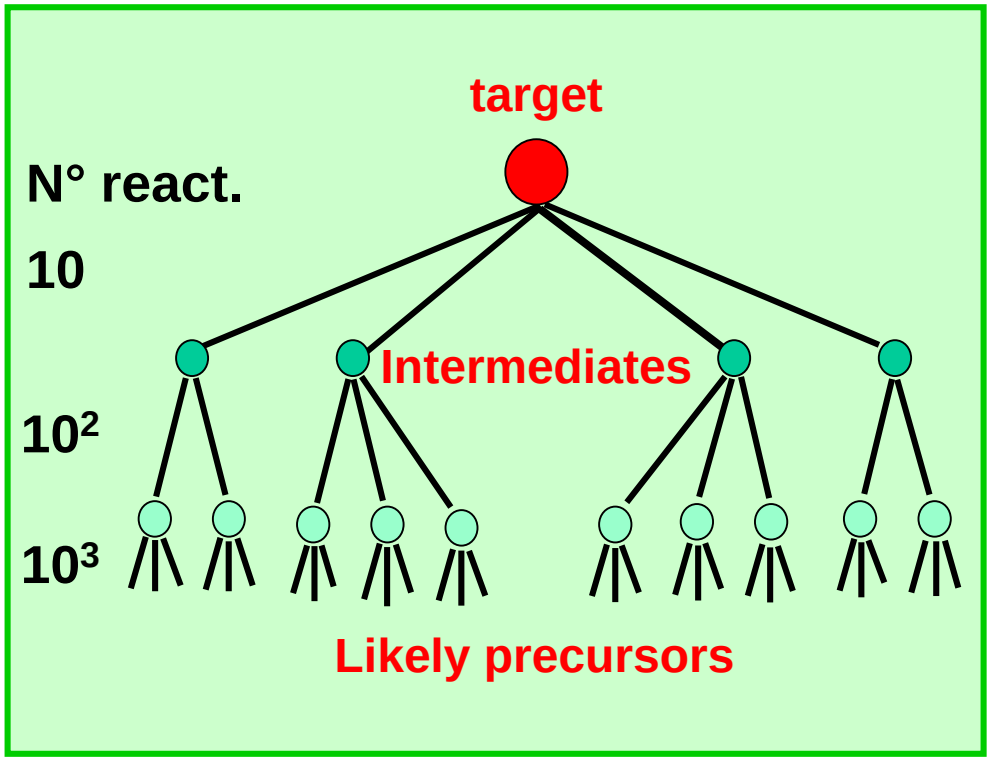
https://iscamapweb.chem.polimi.it/citterio/education/course-topics/

Complexity of Chemical Space and of Research Steps.

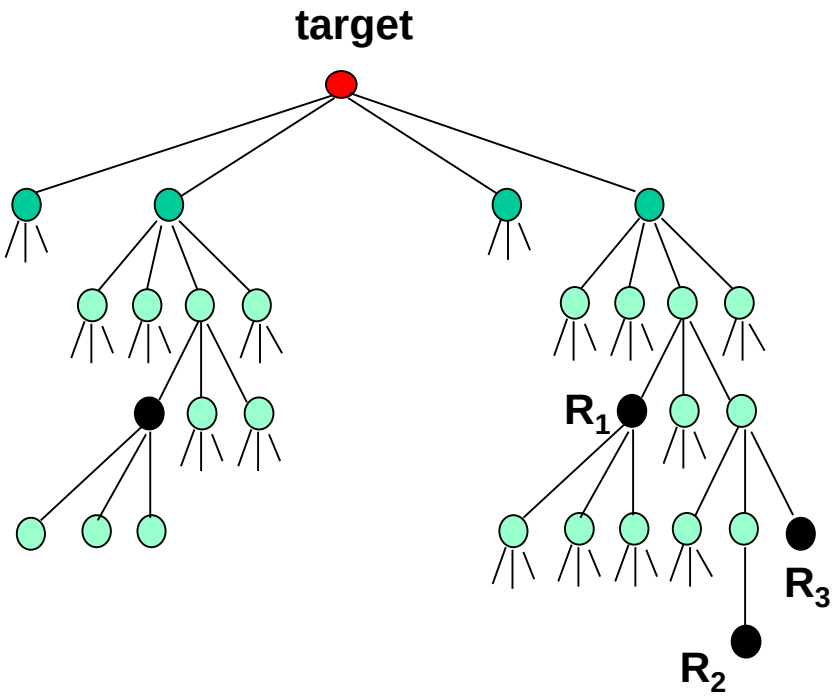
Compounds	15 millions
Known Reactions	several millions

Hypothetic Organic Compd. with PM < 700 and C, H, N, O: 10^{36}



Design and Planning of a Valid Synthesis.

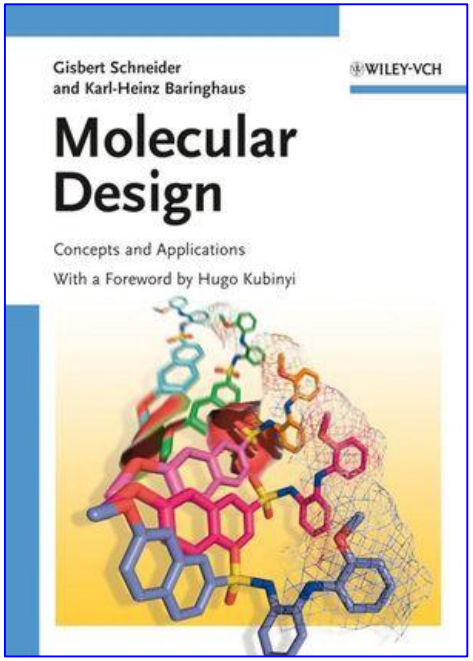
Foundation: step retrosynthesis



- low cost Raw Materials and reliable “producers” (>2)
- parameters: atom efficiency
  - High yield and selectivity (catalysis)
  - efficient reactions with high productivity
  - Minimal environmental impact
- compact approach to the synthesis (limited number of steps, low number of steps, continuous processes), plant reliability and intrinsic safety (c-GMP), internal or consolidated technologies, product family – known or strategic reactions.

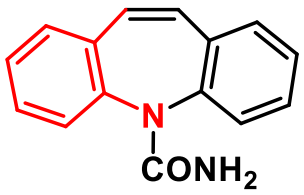
Software Aids to Molecular Design.

- Recognition of synthetic precursors
- Analysis and evaluation of strategic bonds
- Comparison known reactions and products through similarity research
- Proposal of best precursors
- Entry to databases of raw materials
- Entry to databases of MSDS and of fugitive reactions
- 3D Molecular Designs | Molecular Modeling
- Molecular Simulation (evaluation of unknown parameters)
- Preliminary evaluation of costs (raw materials, ecology, etc.)



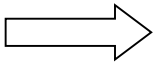
Similarity Research.

Recognition of structural analogies between the target final molecule and available chemicals (analysis by substructures)

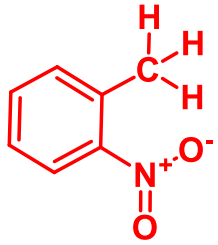


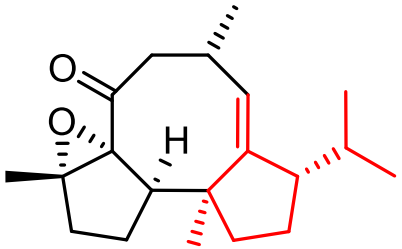
5H-Dibenzo[b,f]azepine-5-carboxamide

Product Catalog



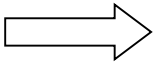
1 kg, 98%, $C_7H_7NO_2$



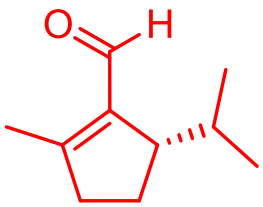


(+) 7,8-epoxy-2-basmen-6-one

Chiron Catalog

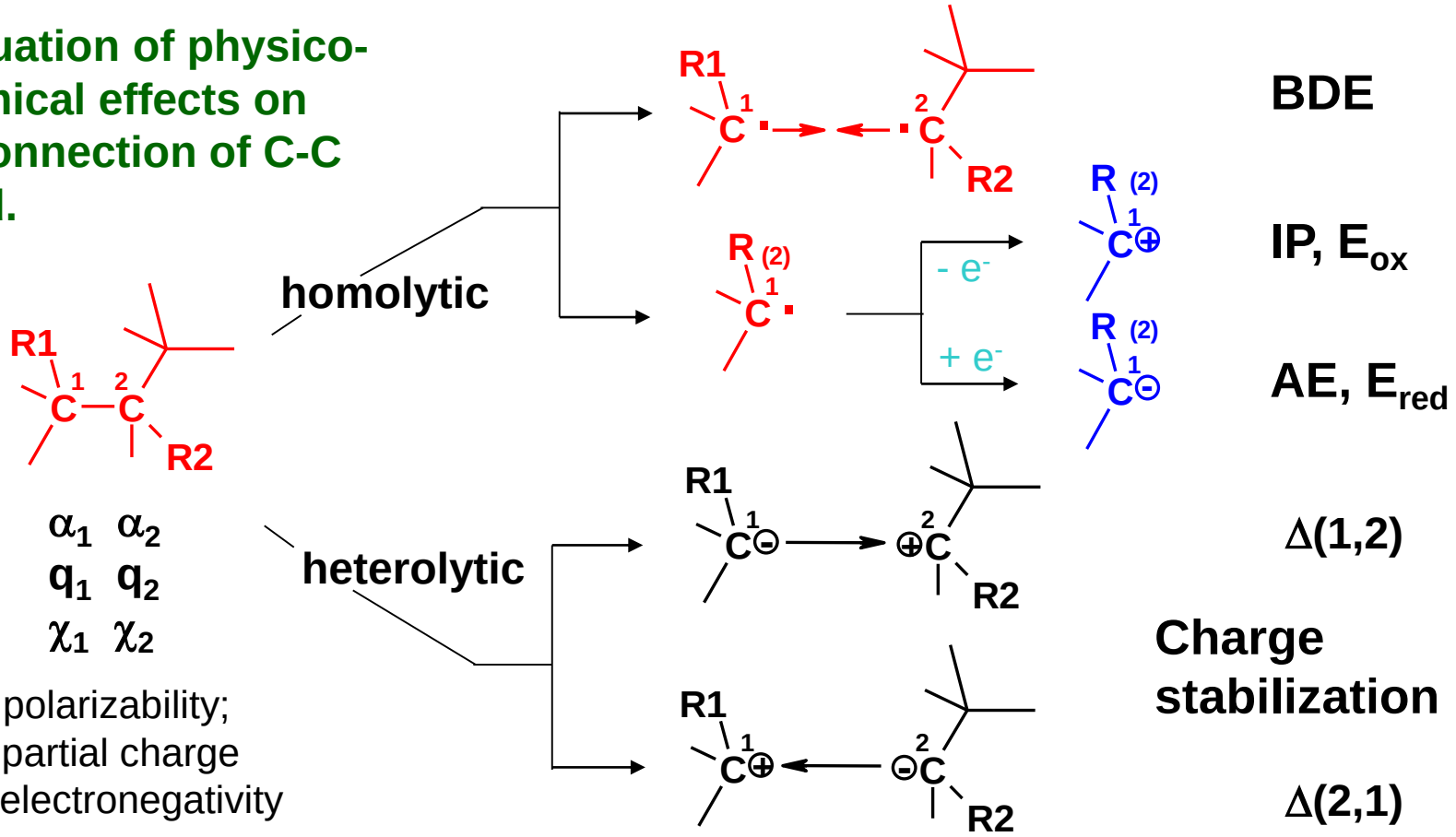


10 g, 97%, $C_{10}H_{16}O$



Synthesis Strategy – Bond Indices.

Evaluation of physico-chemical effects on disconnection of C-C bond.



α_1 α_2
q_1 q_2
χ_1 χ_2

α = polarizability;
q = partial charge
χ = electronegativity

BDE

IP, E_{ox}

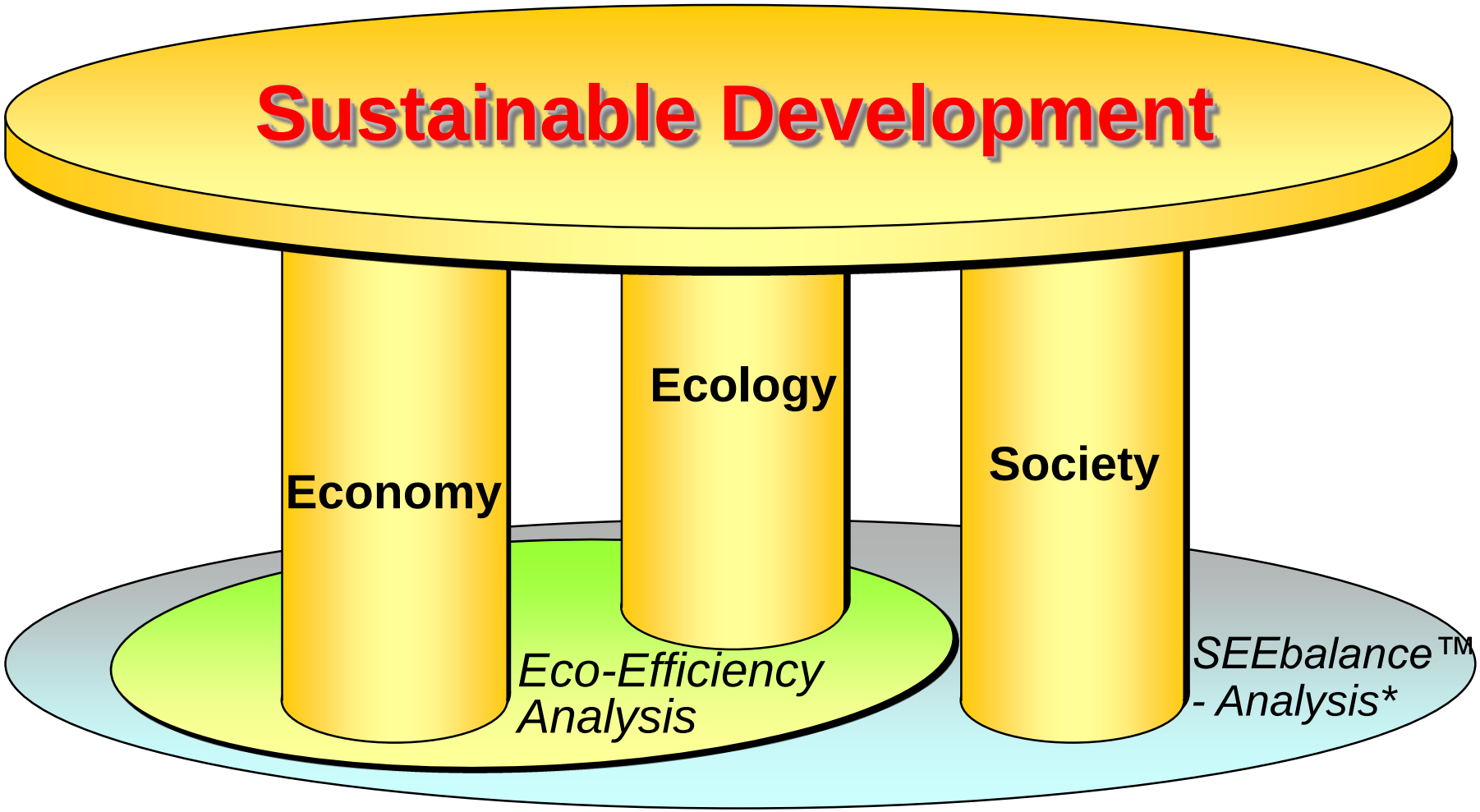
AE, E_{red}

Δ(1,2)

Charge stabilization

Δ(2,1)

Sustainable Development is Based on Three Pillars.



* SEE balance = SocioEcoEfficiency Analysis (developed by BASF)

Process Sustainability Indicators.

1) Renewable sources
2) Atom efficiency - E Factor
3) Purification Index
4) Process Intensification
5) Risk evaluation

Process Indicators

6) Used Energy (based on lifecycle)
7) Produced CO_2
8) VOC and released pollutants

Environmental Indicators

9) SEEbalance™

Socio-eco-efficiency balance analysis

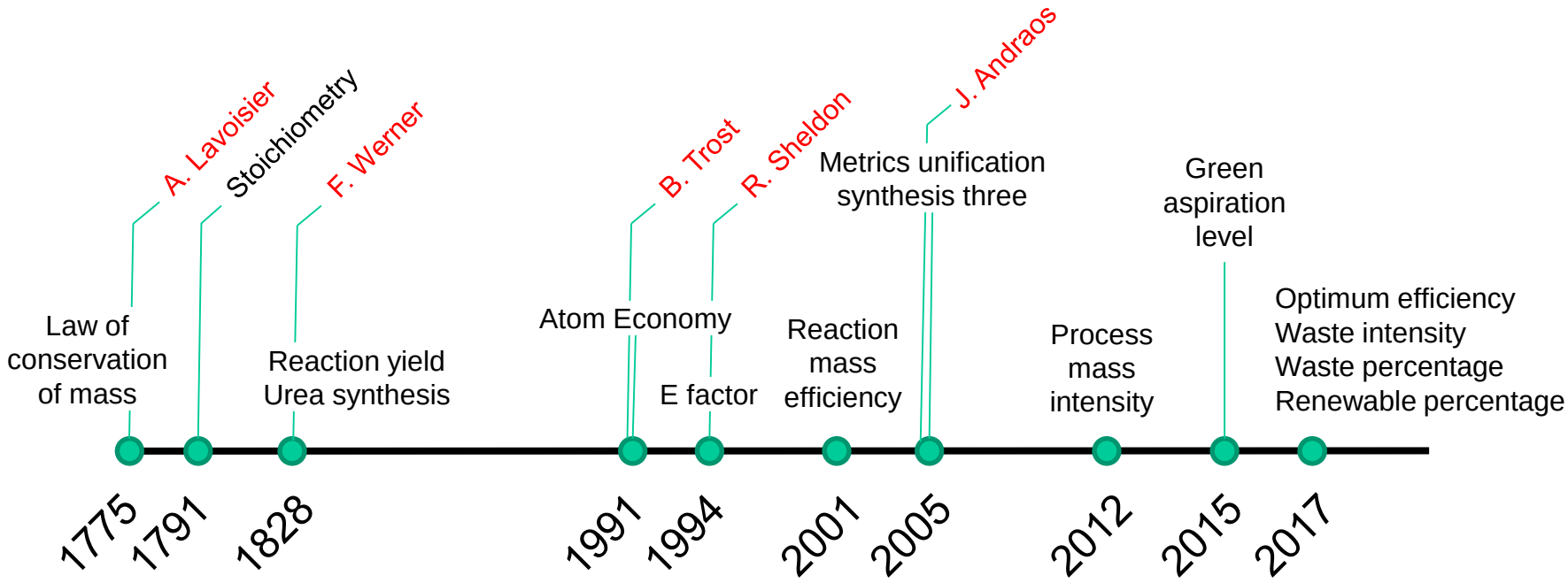
* SEE balance = SocioEcoEfficiency Analysis (developed by BASF)

Alternative Processes.

By implementing:

- Alternate synthetic pathways (catalyst, atom economy, etc.)
- Alternate reaction conditions and solvents (solid supported reagents, non-toxic and non-volatile solvents, etc.)
- Incorporate safer chemicals in design (starting materials/products) (safer and renewable feed stock, non-persistent product, etc.)
- Minimize energy consumption (fewer steps, RT as opposed to heating, energy efficiency, etc.)
- Introduce new technological approaches (new energy sources, new reactors, new separation technology, micro e meso equipment, sensor-actuator controls, etc.)

Timeline of Introduction of Key Concepts in Green Metrics



Source: J. Andraos, *Reaction Green Metrics*, CRC Press, 2019

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Atom Economy and Efficiency.

Synthetic Methods must be designed to Maximize the Incorporation of All Materials Used in the Process into Final Product

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Specific Aspects of Green Metrics: *Atom Efficiency and Atom Economy.*

"*Because an Atom is a Terrible Thing to Waste*"

Barry Trost, Stanford University

How many of the atoms of the reactant are incorporated into the final product and how many are wasted? *Infusing green chemistry into inorganic, organic and organometallic chemistry.*

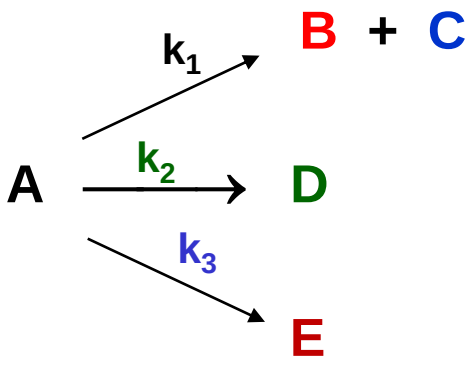
Chemical Transformation:

A + B → C + co-products + by-products

A, B = Reagents
C = Product
Co-product = product formed intrinsically in the reaction
By-product = product formed by a parallel or a consecutive reaction

Co-products and By-products of a Reaction.

In obtaining a chemical (**B**) via a reaction starting from a reagent **A** we need always to recognize that the reaction of interest can result in the simultaneous formation of other products (co-products) but also that can be concurrent to other parallel reactions of **A** to give other compounds (**D**, **E**) or that the obtained product **B** reacts further in the medium to give other products (**F**) in a consecutive reaction. If compound **B** is of interest, compounds **D**, **E** and **F** are named *by-products*, whereas **C** is named the *co-product* of the reaction.



Parallel reactions

Consecutive reaction

Chemical Reaction: Yield, Selectivity, and Conversion.

Reaction Yield

- $$\text{Yield \%} = \frac{\text{(real amount of obtained product)}}{\text{(theoretical amount of foreseen product)}} \times 100$$

Reaction Selectivity

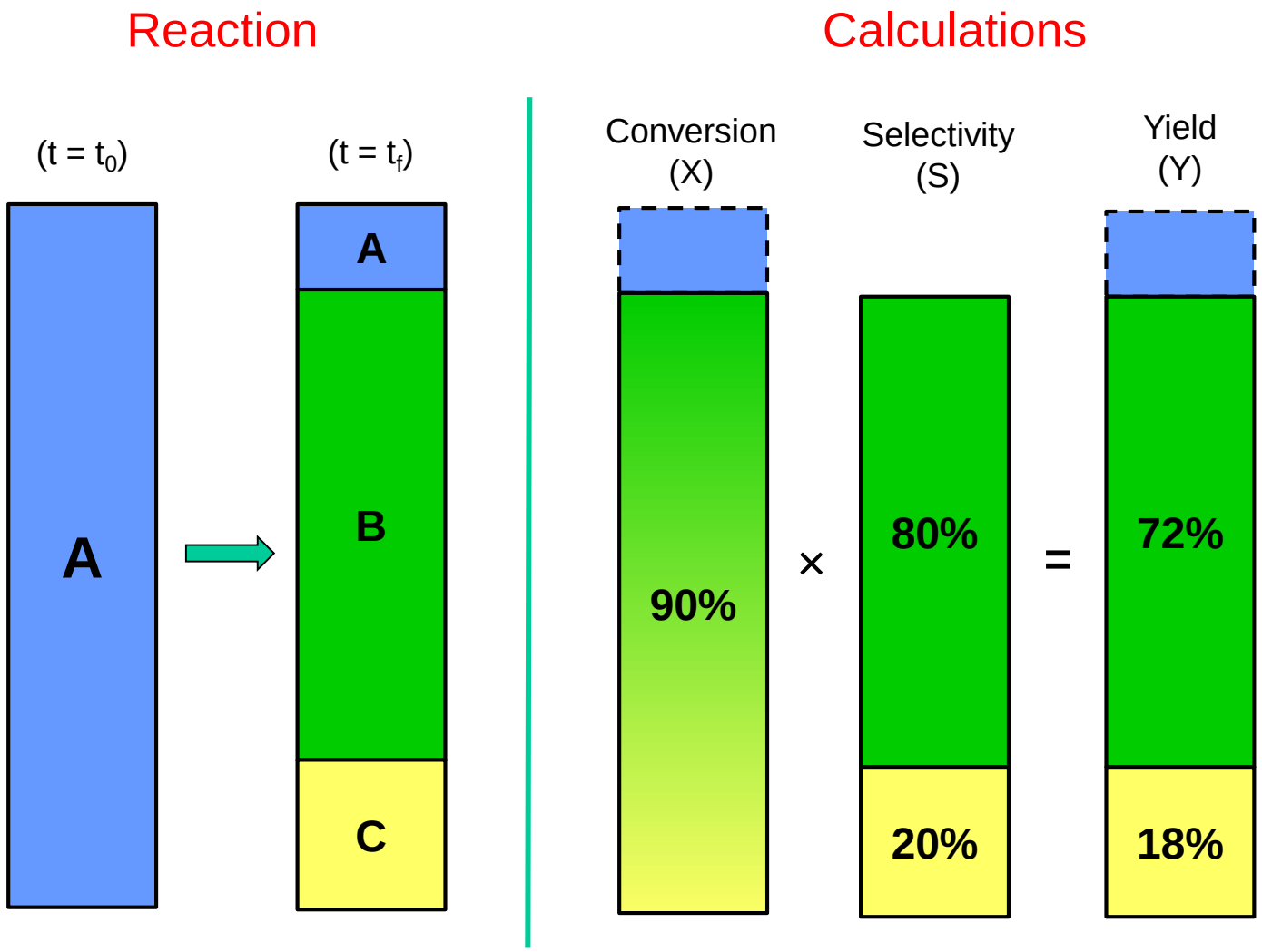
- $$\text{Selectivity \%} = \frac{\text{(yield of desired product)}}{\text{(amount of converted substrate)}} \times 100$$

Conversion

- $$\text{Conversion \%} = \frac{\text{(amount of recovered substrate)}}{\text{(amount of starting substrate)}} \times 100$$

N.B.: Balance must be made **in mol** base on limiting reagent and on reaction stoichiometry.

Relation in mol between Conversion (X), Selectivity (S), and Yield (Y).



Per cent Yield.

Per cent Yield:

Yield % = (actual yield / theoretical yield) × 100

What has been forgotten?

- Which co-products were formed?
- Which and how much by-products were formed?
- How much wastes were generated? These waste are benign?
- Co-products are benign and/or employed?
- How much energy was used?
- Purification steps are necessary?
- Which solvents were used? (are they benign and/or recyclable?
- The “catalyst” is a true catalyst? (stoichiometric vs. catalytic?)

*Reactions must be balanced for **all** reagents and products involved!*

Examples of Common Green Metrics.

- Atom Economy
- Atom Efficiency
- Effective Mass Yield
- Carbon Efficiency (and Efficiency of other elements)
- Reaction Mass Efficiency
- E-Factor (Solvent and by-products Minimization)

- Other Issues not addressed by these metrics:
  - Energy concerns (Process – interior and exterior)
  - Renewable Feedstocks (starting materials)
  - Reaction Types
    - Catalysts vs. stoichiometric reagents
    - Safety
  - Life Cycle Analysis
  - Environmental Quotient
  - …….

See also: Andraos, J.; Hent, A. *J. Chem. Educ*. 2015, 92 (11), 1820–1830.

A Simple Example of AE Calculation.

In the production of ammonium nitrate...

ammonia + nitric acid $\Rightarrow$ ammonium nitrate

$NH_{3(g)} + HNO_{3(aq)} \Rightarrow NH_4NO_{3(aq)}$

(1 mol) $NH_3 = 17g$ $HNO_3 = 63g$ $NH_4NO_3 = 80g$

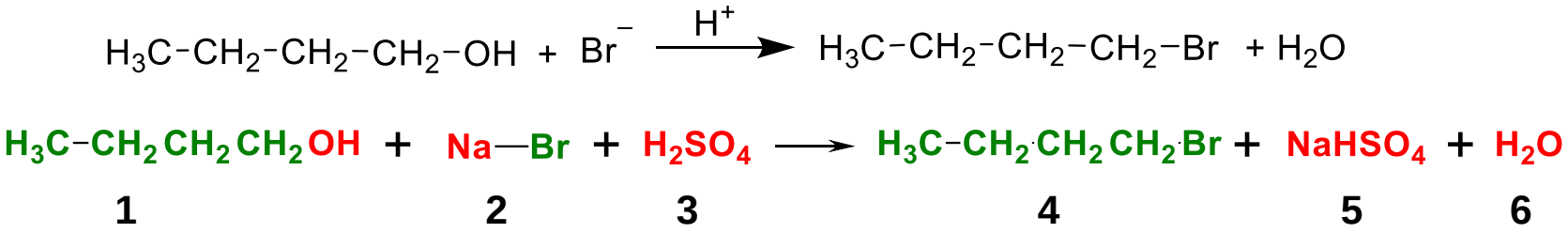
Calculate the atom economy for this reaction (complete and without by-products):

Atom economy = $\dfrac{80g}{(17g + 63g)} \times 100 = 100\%$

As there are no waste products in this reaction and the conversion is 100%, the atom economy is 100%.

A Simple Example of AE Calculation (2).

Synthesis of 1-bromobutane from n-butanol:



Reagents Formula	Reagents MW or FW	Utilized Atoms	Weight of Utilized Atoms	Unutilized Atoms	Weight of Unutilized Atoms
1 C_4H_9OH	74	4C,9H	57	OH	17
2 NaBr	103	Br	80	Na	23
3 H_2SO_4	98	——	0	2H,4O,S	98
Total 4C,12H,5O, BrNaS	275	4C,9H,Br	137	3H,5O,Na,S	138

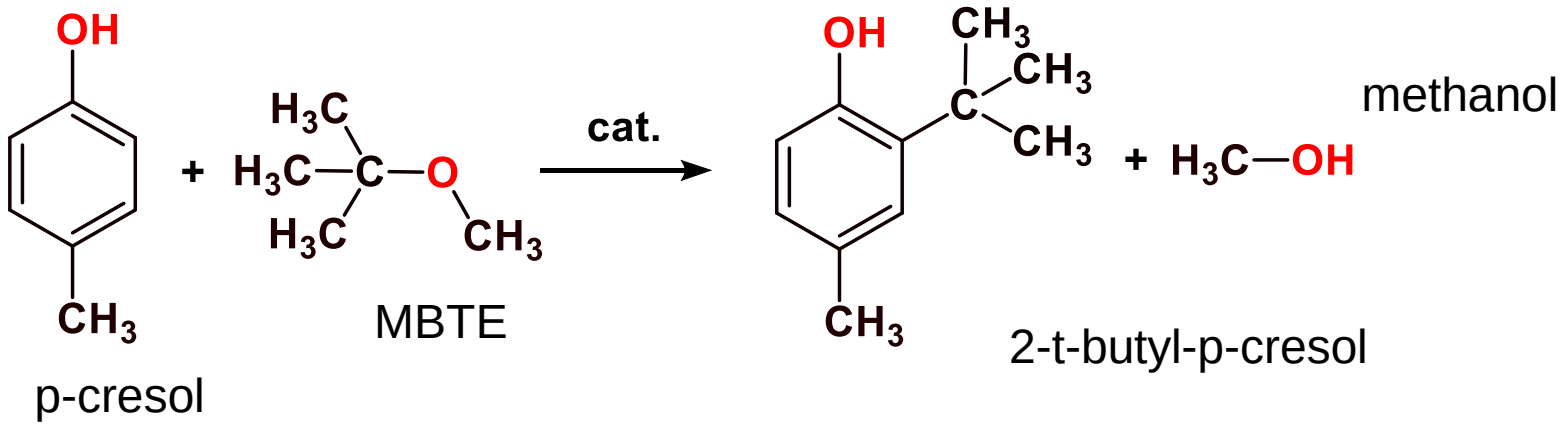
% Atom Economy = (MW of atoms utilized / MW of all reactants) × 100 = (137/275) × 100 = 50%

Example: Determination of Yield, Selectivity and Atom Economy in a Real-world Reaction.

***Alkylation of p-cresol using an heterogeneous acid catalyst*.**

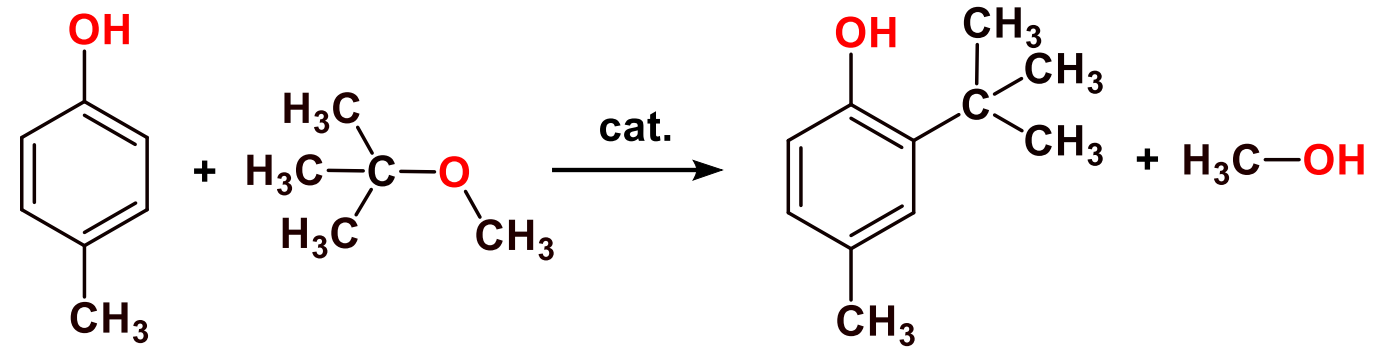
Conditions: *p*-cresol (19.61 *g*, 0.22 *mol*), MTBE (24.31 *g*, 0.22 *mol*) and a silica/zirconia catalyst (3.5 % in weight) are heated at 100°C for 3 hours. After cooling the products are identified by GC. The main product is 2-*t*-butyl-*p*-cresol (13.0 *g*), 10.78 *g* of *p*-cresol remain unreacted.

Calculate yield, selectivity and atom economy.



Yadav, Green Chem., 1999, 1, 269

Example of Yield, Selectivity and Atom Economy.



MW = 108

MW = 164

Theoretical Yield = (19.61/108) × 164 = 29.77 *g* (via mol)

Yield % = 100 × 13/29.77 = 43.7% (via weight/mol)

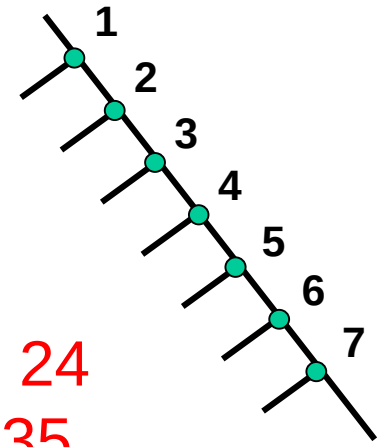
Selectivity % = 100 × 13/29.77 [(19.61 - 10.78)/19.61]

= 13/13.4 = 97% (via conversion)

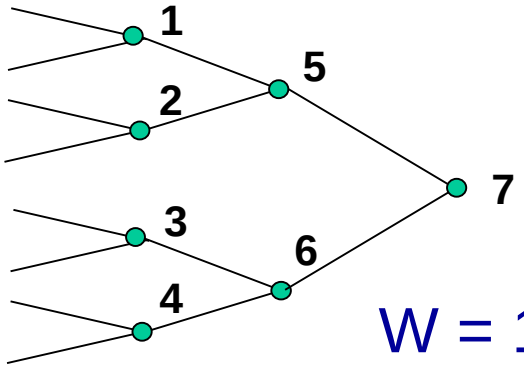
AE = 164/(164 + 32) = 0.836 (via co-products)

Comparison of Linear and Convergent Syntheses.

7 Steps, 80% yield per step



W = 24
S = 35

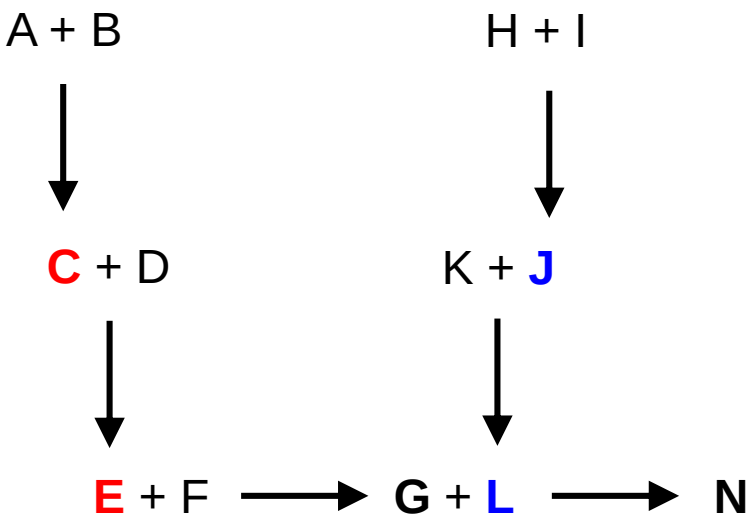


W = 16
S = 24

W = total wt. of all SM
S = sum of steps each SM must pass through

J.S. Hendrickson, *Pure App Chern*, 1988, 60 (11), 1563.

Atom Economy in Multiple Converging Reactions.

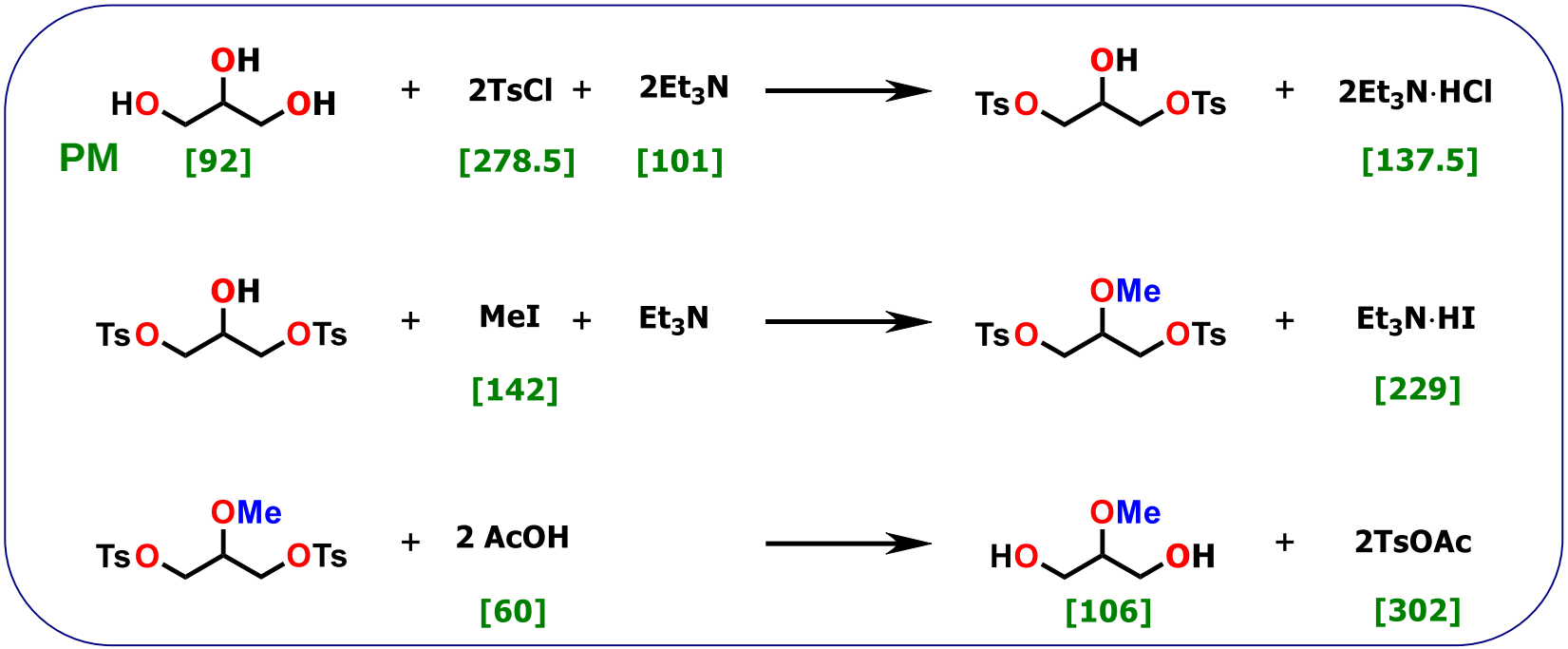


$$\%\ \text{Atom Economy of G} = \frac{\text{GMW(G)}}{\text{GMW(A + B + D + F)}} \times 100\%$$

$$\%\ \text{Atom Economy of } \mathbf{N} = \frac{\text{GMW(G)}}{\text{GMW(A + B + D + F + H + I + K)}} \times 100\%$$

Green Metrics

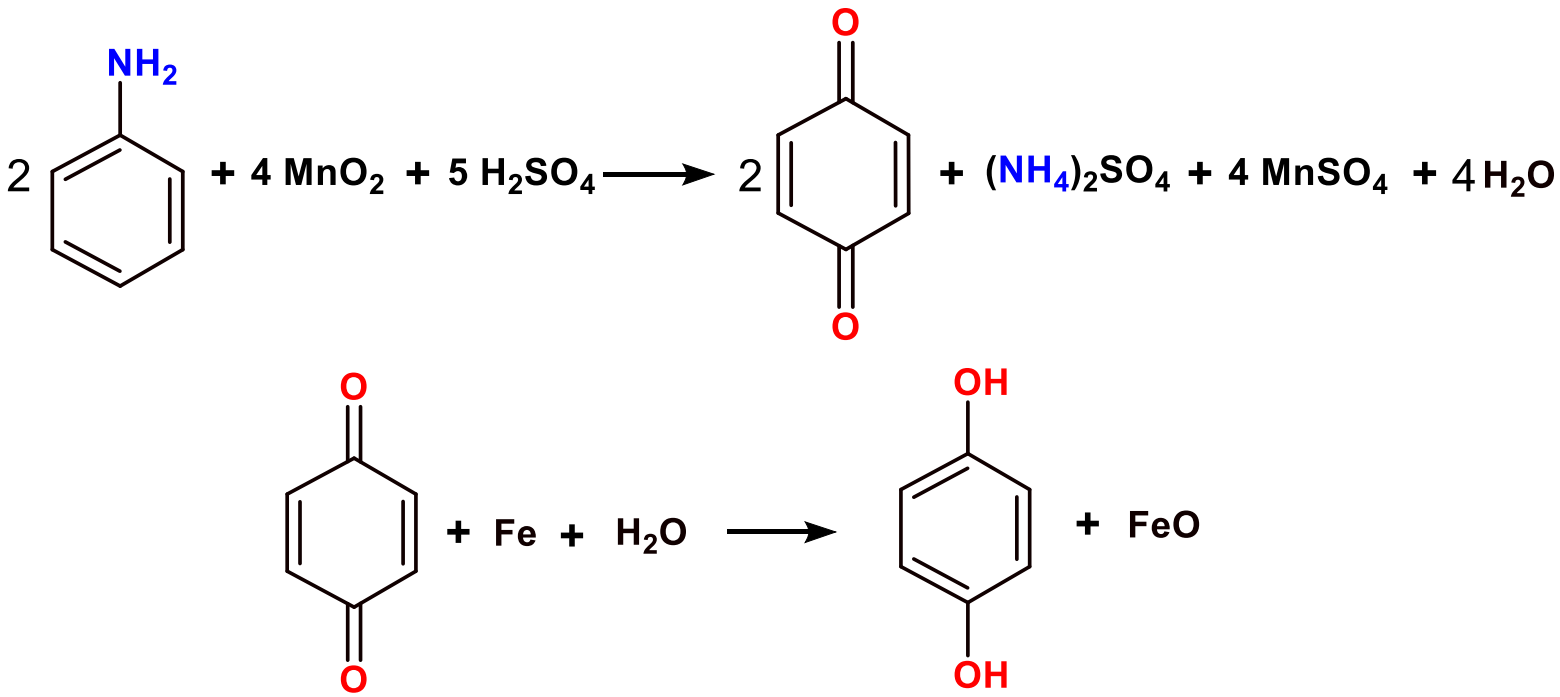
Synthesis of 2-Metoxypropan-1,3-diol from Glycerol.



Assuming a 100% yield, no reaction or working solvent, no reagent in excess, 1 *kg* of glycerol produces 1.15 *kg* of 2-methyl ether and 12.04 *kg* of waste!

Ts = tosyl chloride

Reactions Can Give 100% Yield but with Low AE - Classical Route to Hydroquinone.



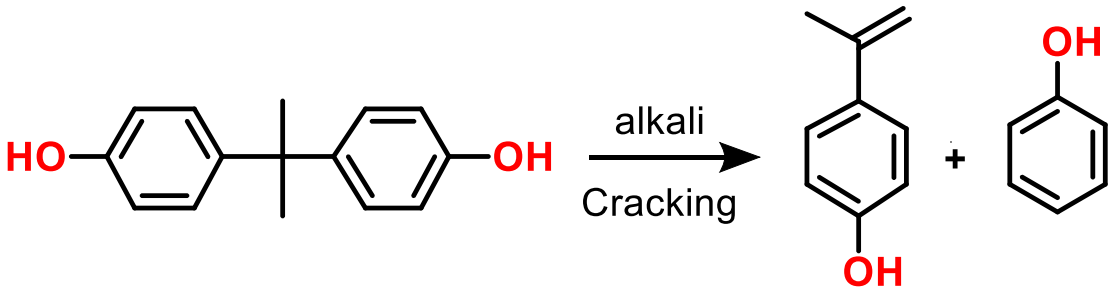
% AE = 100 (MW of desired product /MW of all products)

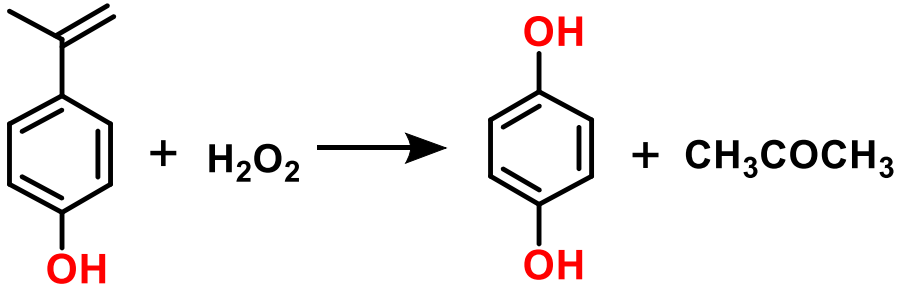
= 110 / [110 + 72 + 0.5(132) + 2(151) + 2(18)] (react. stoichiometry)

= 110 / 586 = **18.8%**

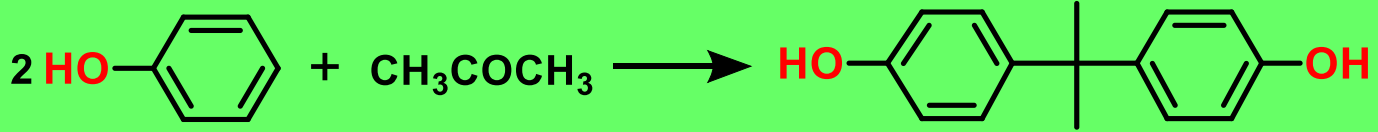
Therefore – yield can be 100% but less than 20% of useful product is obtained!

Upjohn Route to Hydroquinone.



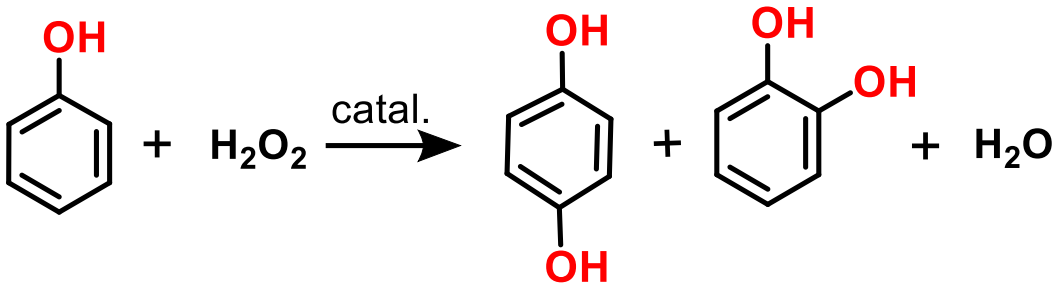


co-products recycle:



In principle: AE% = 100% with complete recycle of acetone and phenol.

ENI Route to Hydroquinone.



Hydroquinone (10-70%)

Catechol (30-90%)

(separation by fractional distillation)

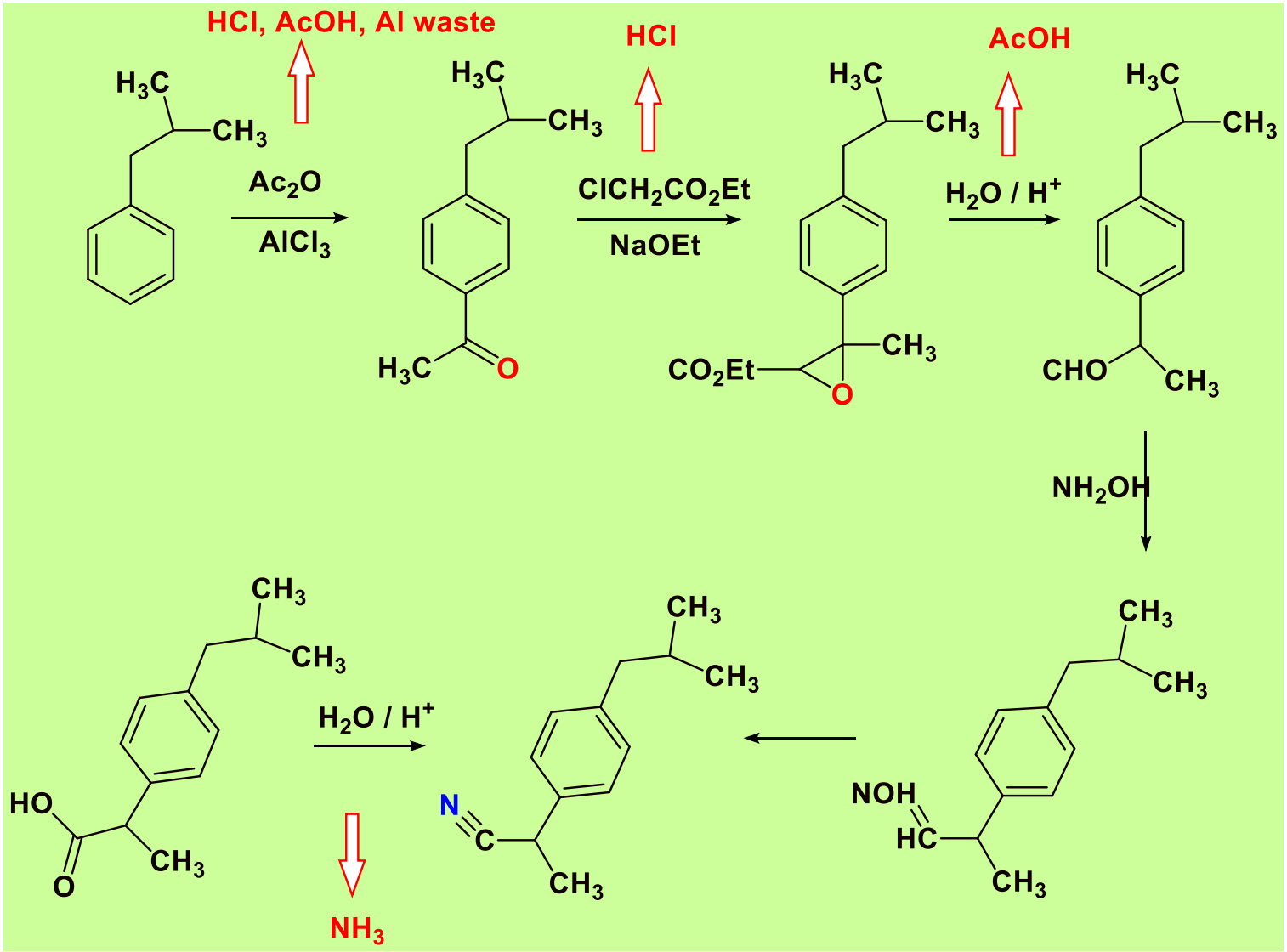
Catalyst: year '80 (homogeneous, Fe^{2+}, then $Fe(cp)_2$ cp = cyclopentadienyl)

year '90 (heterogeneous, Titanium-silicalite (zeolite))

% AE = 110 (× 0.7) / [94 + 34] (reaction to hydroquinone only)

= 77 / 128 = **60.2%**

Classical Route to Ibuprofen (Boots).



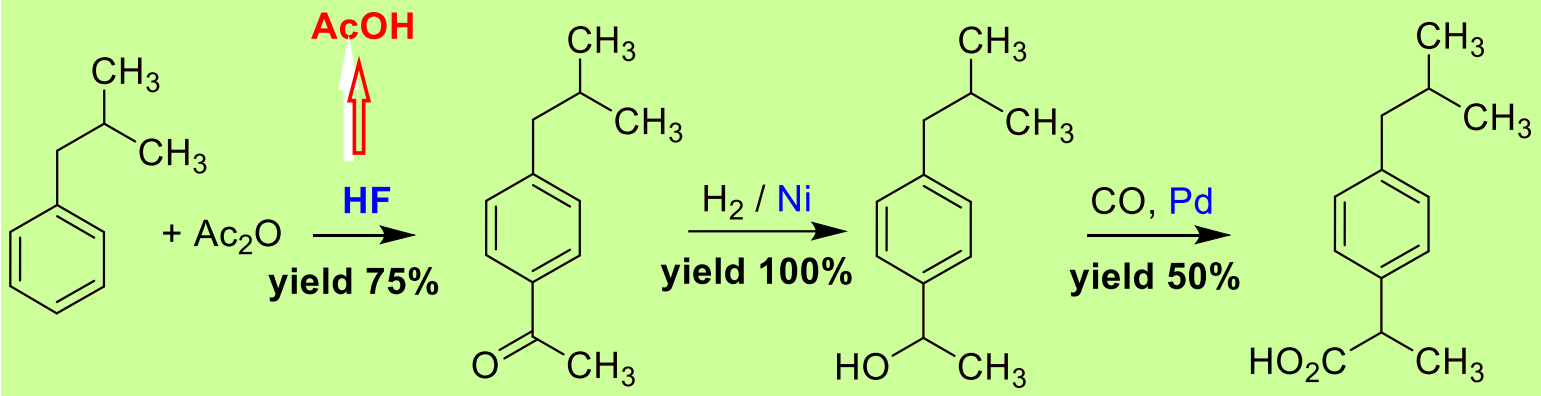
Atom Economy in the Boots Synthesis of Ibuprofen.

Reagent Formula	Reagents PM	Utilized Atoms	Weight of Utilized Atoms	Unutilized Atoms	Weight of Unutilized Atoms
1 $C_{10}H_{14}$	134	10C,13H	133	H	1
2 $C_4H_6O_3$	102	2C,3H	27	2C,3H,3O	75
4 $C_4H_7ClO_2$	122.5	C,H	13	3C,6H,Cl,2O	109.5
5 C_2H_5ONa	68	——	0	2C,5H,O,Na	68
7 H_3O	19	——	0	3H,O	19
9 NH_3O	33	——	0	3H,N,O	33
12 H_4O_2	36	H,2O	33	3H	3
Total: 20C,42H,N,10O, Cl,Na	514.5	Ibuprofen 13C,18H,2O	Ibuprofen 206	Waste Products 7C,24H,N,8O, Cl,Na	Waste Products 308.5

% Atom Economy = (PM of atoms utilized/PM of all reactants) × 100

= (206/514.5) × 100 = 40 %

Hoechst Route to Ibuprofen.



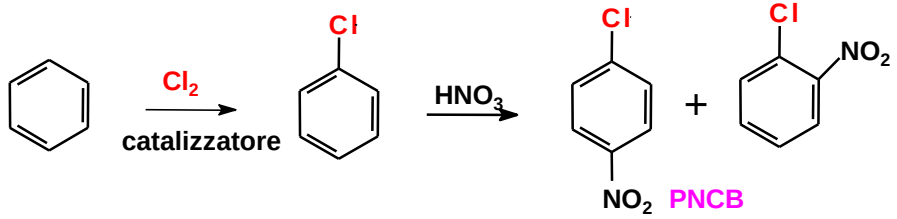
Reagent Formula	Reagents PM	Utilized Atoms	Weight Used Atom	Unutilized Atoms	Weight of Unutilized Atoms
1 $C_{10}H_{14}$	134.0	10C,13H	133	H	1
2 $C_4H_6O_3$	102.0	2C,3H,O	27	2C,3H,3O	59
4 H_2	2.0	2H	2	3C,6H,Cl,2O	0
6 CO	28.0	——	28	2C,5H,O,Na	0
Total 15C,22H,4O,	266.0	Ibuprofen 13C,18H,2O	Ibuprofen 206	Waste Products 2C,3H,2O,	Waste Products 60.0

% Atom Economy = (PM of atoms utilized/PM of all reactants) × 100

= (206/266) × 100 = **77 %**

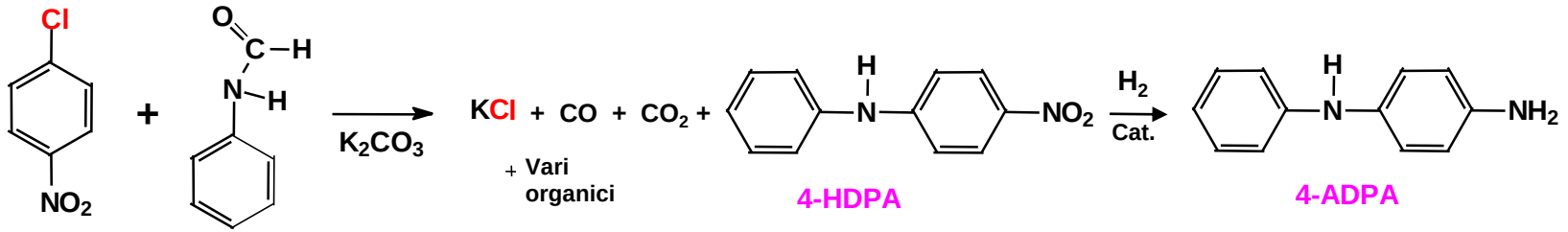
4-Aminodiphenylamine (ADPA) - Traditional Brown Route and New VNC Amination.

Aromatic Electrophilic Substitution

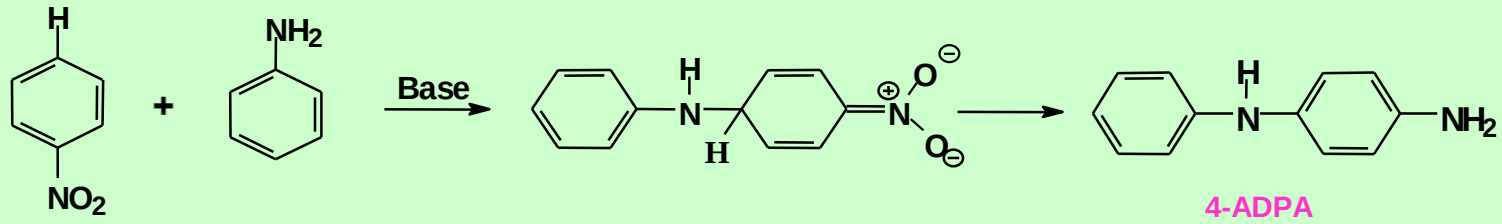


- Via Halorganic
- Harmful solvents used
- Large wastes

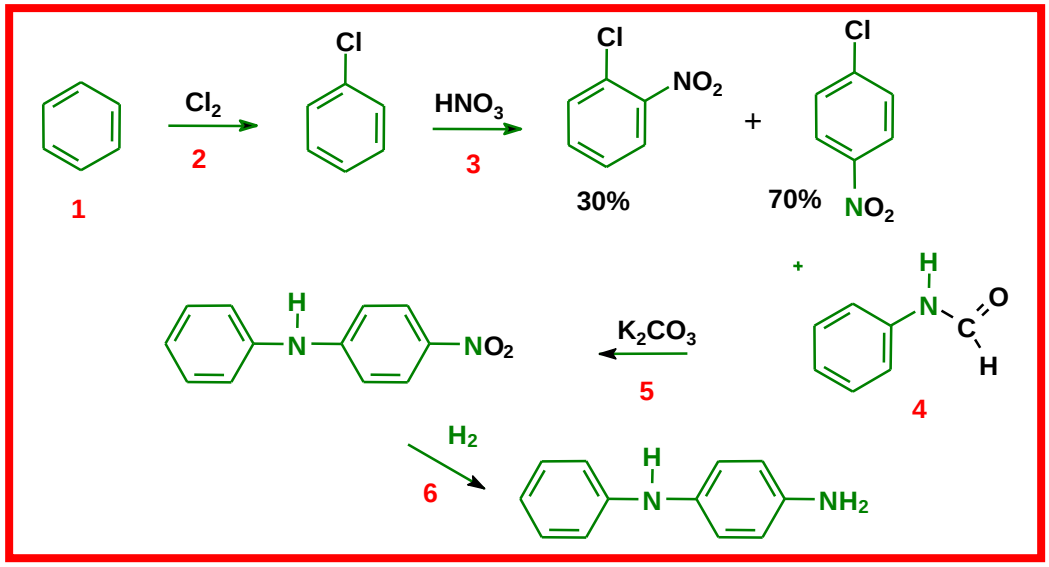
Aromatic Nucleophilic Substitution



Base promoted coupling reaction



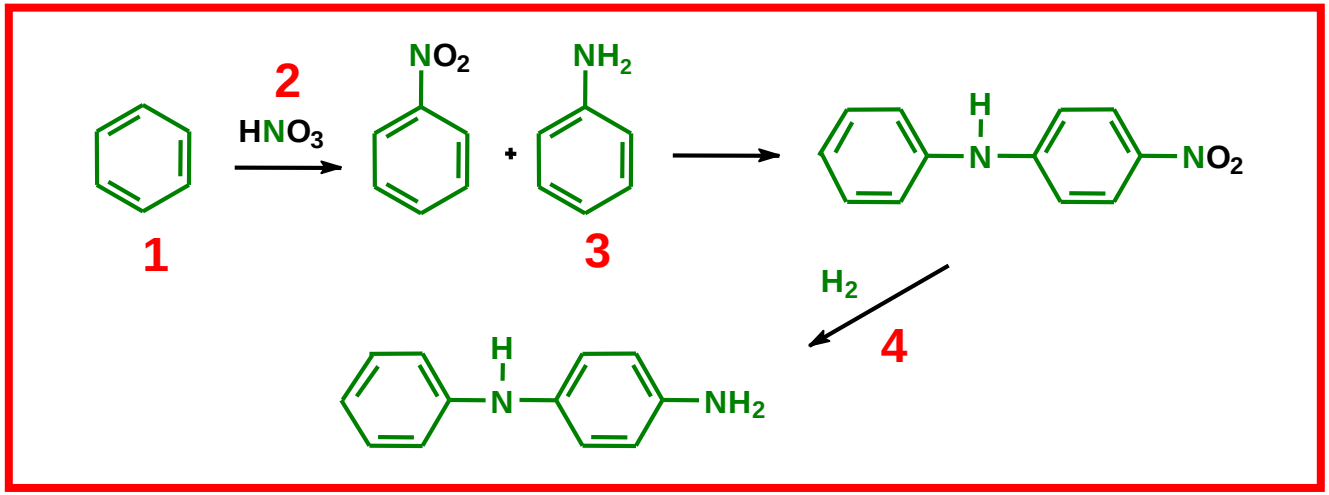
Atom Economy in the Traditional Chemistry to ADPA.



% AE = (184/433) × 100
= **42 %**

Reagent Formula	Reagent FW	Used Atoms	Wt.	Unused Atoms	Wt.
1 C_6H_6	78	6C, 4H	76	2H	2
2 Cl_2	71	----------	0	2Cl	71
3 HNO_3	63	1N	14	1H, 3O	49
4 C_7H_7NO	121	6C, 6H, 1N	92	1C, 1O, 1H	29
5 K_2CO_3	98	----------	0	2K, 1C, 3O	98
6 H_2	2	2H	2	----------	0
TOTAL	**433**	**12C, 12H, 2N**	**184**	**2C, 4H, 2C, 2K, 7O**	**248**

Atom Economy in VNC Synthesis of ADPA.



Reagent Formula	Reagent FW	Used Atoms	Wt.	Unused Atoms	Wt.
1 C_6H_6	78	6C, 4H	76	2H	2
2 HNO_3	63	1N	14	1H, 3O	49
3 C_6H_7N	93	6C, 6H, 1N	92	1H	1
4 H_2	2	2H	2	----------	0
TOTAL	**236**	**12C, 12H, 2N**	**184**	**4H, 3O**	**52**

% Atom Economy = (PM of atoms utilized/PM of all reactants) × 100 = (184/236) × 100 = **78 %**

Propylene Oxide (PO): Research of the Ideal Catalyst.

$CH_3CH=CH_2 + HOCl \rightarrow CH_3CH(OH)CH_2Cl$

$Ca(OH)_2 \rightarrow PO + CaCl_2 + H_2O$

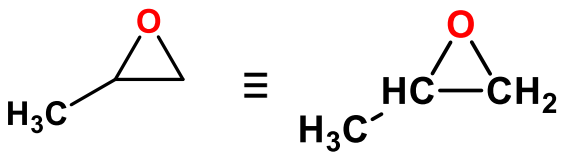
$CH_3CH(CH_3)CH_3 + O_2 \rightarrow (CH_3)_3COOH$

$(CH_3)_3COOH + CH_3CH=CH_2 \rightarrow PO + TBA$

$C_2H_5C_6H_5 + O_2 \rightarrow Hydroperoxide$

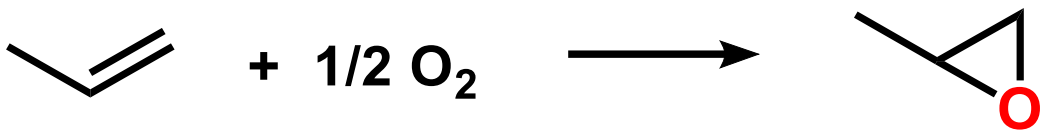
$Hydroper. + CH_3CH=CH_2 \rightarrow PO + Styrene$

$CH_3CH=CH_2 + H_2O_2 \xrightarrow[\text{silicalite}]{Ti} PO + H_2O$ cost??

PO =  ≡

- Chloridrine route
  - Stoichiometric amount of waste salt $CaCl_2$
- ARCO route
  - Good if MTBE can be used
- POSM route
  - Increasing recognized, but styrene as co-product
- **Direct oxidation**
  - Not yet available but studied by several companies.

Propylene Oxide: Some Future Possibilities.



BP Amoco - cat. Cr/Ag – selectivity : 50% at 15% conv.
Olin - cat. Mo - selectivity: 60% at 12 % conv.

Green = from natural products

D-Glucose + propene + O_2 + 2 "H" ⟶ D-Fructose + PO + H_2O

Cetus - 4 stages process using enzymatic catalysis -
Process at low concentration - Costs??

Atom Efficiency (AE_f).

Atom Efficiency = %Yield × Atom Economy

- Importance:
  - Could be used to replace Yield and Atom Economy

    Example: atom economy could be 100% and yield 5% making this a not very green and sustainable process!!

- The closer AE_f to **100%**, the greener the process
  - **(0-100%)**

Atom and Mass Efficiency.

Atom Efficiency

- the fraction of starting material incorporated into the desired product -

$$C_6H_5\text{-}OH + NH_3 \rightarrow C_6H_5\text{-}NH_2 + H_2O$$

- Carbon - 100%
- Hydrogen - 7/9 × 100 = 77.8%
- Oxygen - 0/1 × 100 = 0%
- Nitrogen - 100%

Mass Efficiency (basis 1 mole of product)

$$C_6H_5\text{-}OH + NH_3 \rightarrow C_6H_5\text{-}NH_2 + H_2O$$

- Mass in Product = (6 C)·(12) + (7 H)·(1) + (0 O)·(16) + (1 N)·(14) = 93 grams
- Mass in Reactants = (6 C)·(12) + (9 H)·(1) + (1 O)·(16) + (1 N)·(14) = 111 g
- Mass Efficiency = 93/111 × 100 = 83.8%

Carbon Efficiency (CE).

$$\% \text{ Carbon Efficiency} = 100 \times \frac{\text{Mass of Carbon in Product}}{\text{Mass of Carbon in Reactants}}$$

$$CE = 100 \times \frac{(\#\text{ moles of Product}) \times (\#\text{ of Carbons in Product})}{(\text{moles A} \times \text{Carbons in A}) + (\text{moles B} \times \text{Carbons in B})}$$

A + B → C + co-products + by-products

- *Definition*: "the percentage of carbon in the reactants (A + B) that remain in the final product C" (Constable *et al.*)
- Takes into account: yield and stoichiometry
- *Importance*: directly related to greenhouse gases
- **Larger** number is better
  - **(0-100%)**

“Waste and Material Efficiency Ratios”.

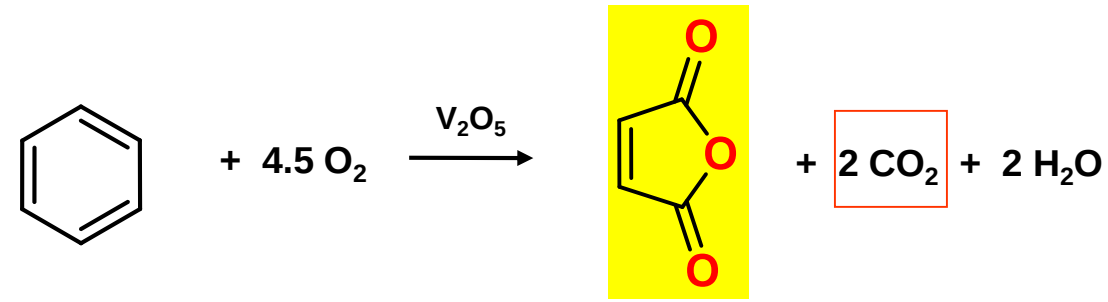
- The waste ratio was developed by 3M Company to encourage the conversion of wastes in byproducts (residuals which can be reused in manufacturing) and waste reduction.

$$\text{Waste ratio} = \frac{\text{waste}}{\text{product} + \text{co-products} + \text{waste}} = \frac{\text{waste}}{\text{total outlet}}$$

- Because a waste is considered a sign of inefficient manufacturing, the ratio gives an indicator of waste generation along with the loss of product and materials. However, other researches prefer the “material efficiency ratio (MER)” instead of “waste ratio” owing to the absence of an agreement on definition of "waste."

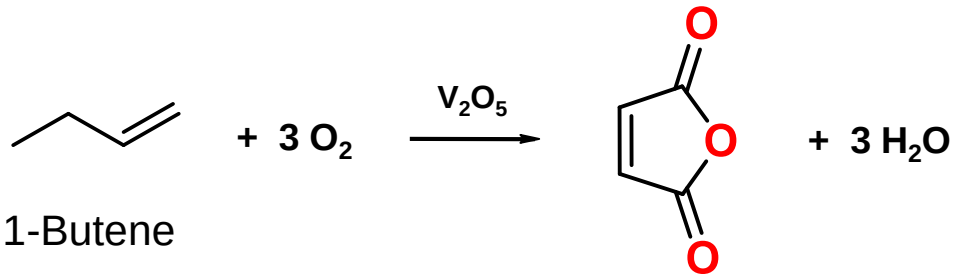
$$\text{MER} = \frac{\text{sell product}}{\text{all purchased materials}}$$

Maleic Anhydride - A Lesson of Atom Economy.

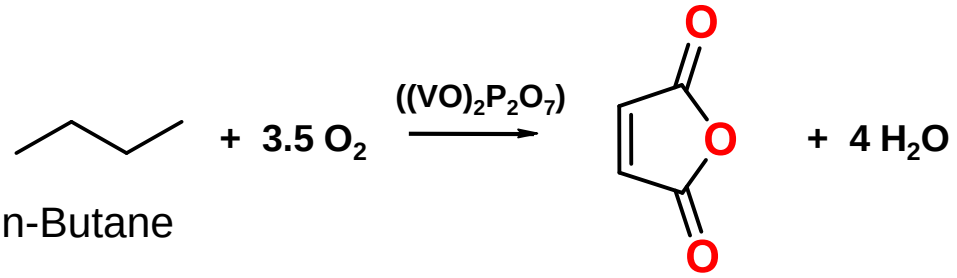


Benzene

Maleic Anhydride

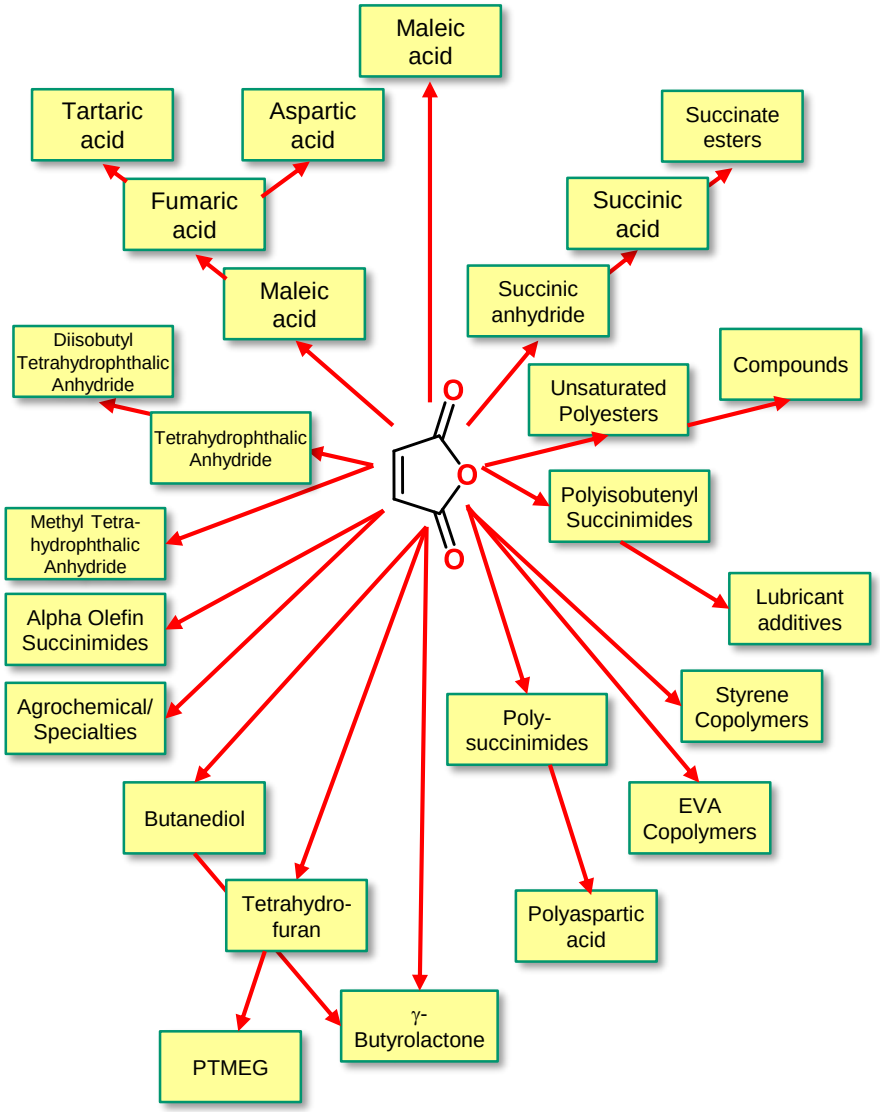


1-Butene



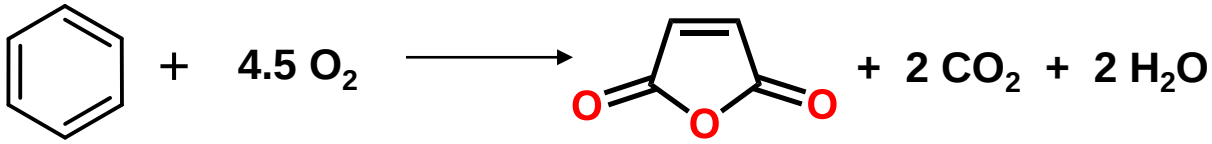
n-Butane

Maleic Anhydride Derivatives.



Atom Economy for Different Routes to Maleic Anhydride.

Benzene Oxidation

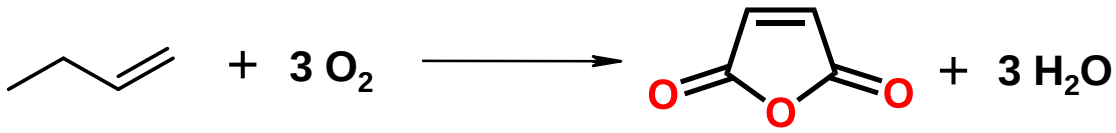


Molecular Weight

78 4.5 × 32 = 144 98

Atom Economy % = 100 × 98/(78+144) = 100 × 98/222 = 44.1%

1-Butene Oxidation



Molecular Weight

56 3 × 32 = 96 98

Atom Economy % = 100 × 98/(56+96) = 100 × 98/152 = 64.5%

Atom Efficiency in MA Syntheses.

- As anticipated, seldom is useful analyze the atom economies of specific elements, i.e. carbon, sulfur, etc.
- This is particularly useful when the formation of nontoxic materials, i.e. water, distorts the overall A.E.
- It is calculated dividing the % of the atom numbers in the product by the atom numbers in the starting material.

Atom Efficiency in the Manufacture of Maleic Anhydride

	from Benzene	from 1-Butene	from Butane
Carbon %	67 (4/6)	100 (4/4)	100 (4/4)
Hydrogen %	33	25	20
Oxygen %	33	50	43

Reaction Mass Efficiency (RME).

$$\textbf{RME} = 100 \times \frac{\text{Mass of product C (Kg)}}{\text{Mass of A (Kg) + Mass of B (Kg)}}$$

$$= \text{yield} \times \frac{\text{MW of product C}}{\text{MW of A + (MW of B} \times \text{molar ratio B/A)}}$$

$$\mathbf{A + B \rightarrow C}$$

- Defined: “the percentage of the mass of the reactants that remain in the product” (*Constable et al.)*
- Takes into account: atom economy, yield, reactant stoichiometry
- **Larger RME** number is better
  - (0-100%)

Constable et al. Metrics to ‘green’ chemistry – which are best? Green Chem. 2002, 4, 521-7.

Maleic Anhydride Synthesis
Benzene vs Butane - Mass Efficiency.

Benzene Route (Hedley et al. 1975, reference in Ch. 8)

$$2\ C_6H_6 + 9\ O_2\ (\text{air}) \xrightarrow[MoO_3]{V_2O_5} 2\ C_4H_2O_3 + H_2O + 4\ CO_2$$

95% Yield of Maleic Anhydride from Benzene in Fixed Bed Reactor

$$\text{Mass Efficiency} = \frac{2(4)(12)+3(2)(16)+2(2)(1)}{2(6)(12)+9(2)(16)+2(6)(1)}(100) = \boxed{44.4\%}$$

Butane Route

$$C_4H_{10} + 3.5\ O_2\ (\text{air}) \xrightarrow{(VO)_2P_2O_5} C_4H_2O_0 + 4\ H_2O$$

60% Yield of Maleic Anhydride from Butane in Fixed Bed Reactor

$$\text{Mass Efficiency} = \frac{(4)(12)+(3)(16)+(2)(1)}{(4)(12)+3.5(2)(16)+(10)(1)}(100) = \boxed{57.6\%}$$

Felthouse et al., 1991, "Maleic Anhydride, ..", in Kirk-Othmer Encyclopedia of Chemical Technology, V. 15, 893 - 928

Maleic Anhydride Synthesis
Benzene vs. Butane - Summary Table.

	Stoichiom. [1]	$/lb [2]	TLV [3]	TW [4]	Persistence [5] Air (d)	Persistence [5] Water (d)	log BCF [5]
Benzene Process							
Benzene [71-43-2]	-1.19	0.184	10	100	10	10	1.0
Maleic Anhydride	1.00	0.530	0.25	----	1.7	7×10^{-4}	----
Butane Process							
Butane [106-97-8]	-1.22	0.141	800	----	7.25	----	----
Maleic Anhydride	1.00	0.530	0.25	----	1.7	7×10^{-4}	----

1 Rudd et al. 1981, "Petroleum Technology Assessment", Wiley Interscience, New York
2 Chemical Marketing Reporter (Benzene and MA 6/12/00); Texas Liquid (Butane 6/22/00)
3 Threshold Limit Value, ACGIH - Amer. Conf. of Gov. Indust. Hyg., Inc. , www.acgih.org
4 Toxicity Weight, www.epa.gov/opptintr/env_ind/index.html and www.epa.gov/ngispgm3/iris/subst/index.html
5 ChemFate Database - www.esc.syrres.com, EFDB menu item

Maleic Anhydride Synthesis
Benzene vs. Butane – Safety Assessment.

(TLV Index)

$$\text{Environmental Index (non-carcinogenic)} = \sum_i |\nu_i| \times (\text{TLV}_i)^{-1}$$

Benzene Route

$$\text{TLV Index} = (1.19)(1/10) + (1.0)(1/.25) = 4.12$$

Butane Route

$$\text{TLV Index} = (1.22)(1/800) + (1.0)(1/.25) = 4.00$$

EPA Index

$$\text{Environmental Index (carcinogenic)} = \sum_i |\nu_i| \times (\text{Maximum toxicity weight})_i$$

Benzene Route

$$\text{EPA Index} = (1.19)(100) + (1.0)(0) = 119$$

Butane Route

$$\text{EPA Index} = (1.22)(0) + (1.0)(0) = 0$$

History of Maleic Anhydride Production.

Pre 1960 - specialty of very high value, moderate competition

- Oxidation of Benzene

1962 – more widely used, higher competition

- Denka introduces the process of 1-butene oxidation

Late 1960 – the 1-butene price increases

- Denka plant is converted to benzene

Year 1970's - petrol crisis : the benzene price increases

- Monsanto builds a plant for butane oxidation
- Denka converts its plant to butane

Start 1980 - no benzene oxidation plant remains in US and EU

Years 1990 – environmental hazard - UCB & BASF isolate the MA co-produced in the PA process.

Worldwide Production : 1,400.000 tons per year

US Production: 280.000 tons per year

Maleic Anhydride (MA) Production.

Level 1. Input / Output Information

Benzene Process

V_2O_5-MoO_3

$$2C_6H_6 + 9O_2 \rightarrow 2C_4H_2O_3 + 4CO_2 + 4H_2O$$

$$2C_6H_6 + 9O_2 \rightarrow 12CO + 6H_2O$$

$$2C_6H_6 + 15O_2 \rightarrow 12CO_2 + 6H_2O$$

$$C_4H_2O_3 + O_2 \rightarrow 4CO + H_2O$$

$$C_4H_2O_3 + 3O_2 \rightarrow 4CO_2 + H_2O$$

Benzene conversion, 95%
MA Yield, 70%
Air/Benzene, ~ 66 (moles)
Temperature, 375 °C
Pressure, 150 kPa

n-Butane Process

VPO

$$2C_4H_{10} + 7O_2 \rightarrow 2C_4H_2O_3 + 8H_2O$$

$$2C_4H_{10} + 9O_2 \rightarrow 8CO + 10H_2O$$

$$2C_4H_{10} + 13O_2 \rightarrow 8CO_2 + 10H_2O$$

$$C_4H_2O_3 + 3O_2 \rightarrow 4CO_2 + H_2O$$

$$C_4H_2O_3 + O_2 \rightarrow 4CO + H_2O$$

n-butane conversion, 85%
MA Yield, 60%
Air/*n*-butane, ~ 62 (moles)
Temperature, 400 °C
Pressure, 150 kPa

MA Production: Early Design Costs.

Level 1. Input / Output Information

"Case 1" Economic analysis (raw materials costs only)

Benzene Process

(1 mole/0.70 mole) × (78 g/mole) × (0.00028 $/g) = 0.0312 $/mol of MA

MA Yield | Bz MW | Benzene cost

N-butane process has lower cost

n-Butane Process

(1mole/0.60 mole) × (58 g/mole) × (0.00021 $/g) = 0.0203 $/mol of MA

MA Yield | nC4 MW | nC4 cost

Assumption: raw material costs dominate total cost of the process

MA Production: Environmental Impacts.

Level 1. Input / Output Information
"Case 1" Environmental Impact Analysis

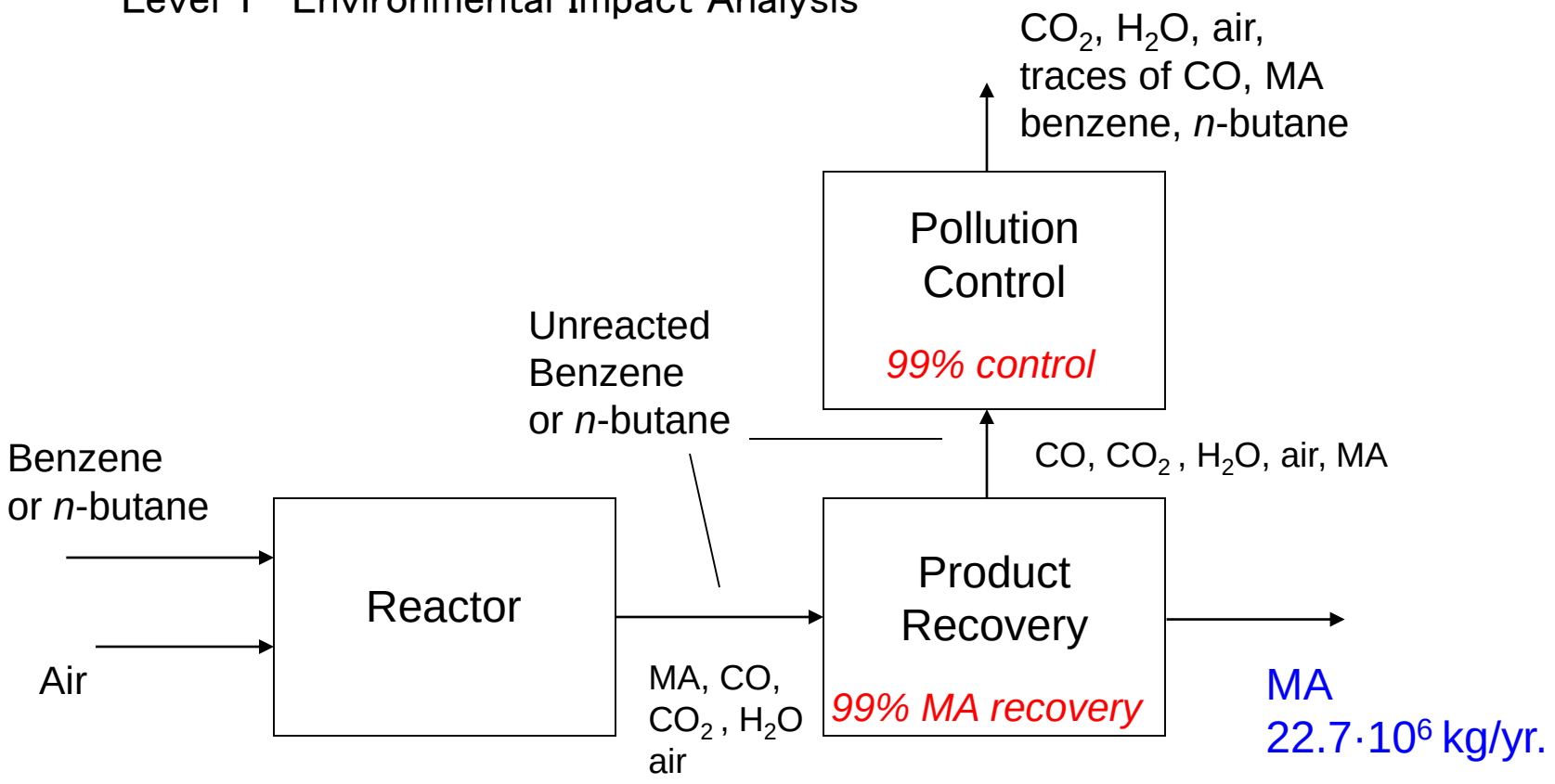
Based on Products and Byproducts from the Reactor

Alternative "case 1" assessment approaches

- Toxicity and stoichiometry
- Toxicity, other impact potentials, and stoichiometry
- Toxicity, other impact potentials, stoichiometry, and environmental fate
- **Toxicity, other impact potentials, stoichiometry, environmental fate, and pollution control**.

MA Production: IO Assumptions.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis



Emission Estimation.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis

Emissions to Air

- Emission factors from US EPA
  - Reactors, separation devices
  - Air Clearinghouse for Inventories and Emission Factors
  - Air CHIEF http://www.epa.gov/ttn/chief/index.html
- CO, CO_2 generation from the reactor
  - Benzene process
    - Benzene: 0.07 mol benzene / mol MA
    - CO + CO_2: 4.1 mol / mol MA
  - n-butane process
    - *n*-butane: 0.25 mol butane / mol MA
    - CO + CO_2: 1.7 mol / mol MA

Conversions, Yields

Environmental / Toxicity Properties.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis

Environmental/Toxicological Properties

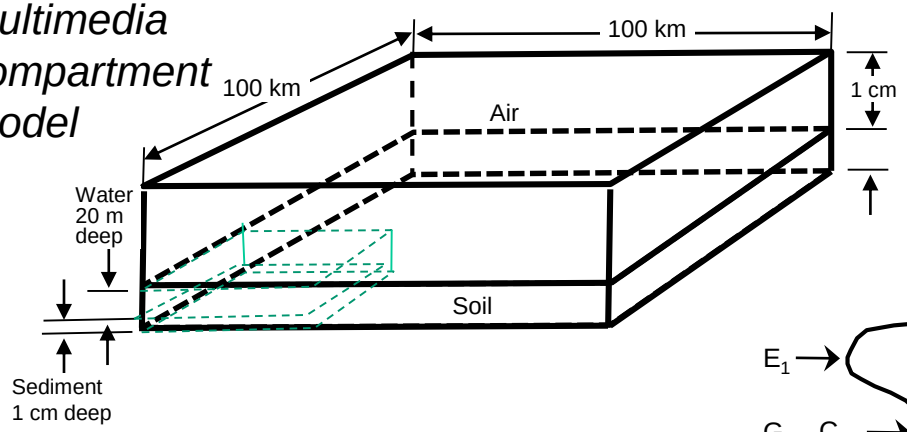
- Estimation Software
  - EPI (Estimation Program Interface) Suite
  - http://www.epa.gov/oppt/exposure/docs/episuite.htm
  - Henry's constant, partitioning, degradation, toxicity
- Online Database
  - Environmental Fate Database
  - http://es.epa.gov/ssds.html

Compilation in: Appendix F.
Allen, D.T. and Shonnard, D.R., *Green Engineering : Environmentally-Conscious Design of Chemical Processes*, Prentice Hall, pg. 552, 2002

Environmental Fate Calculations.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis

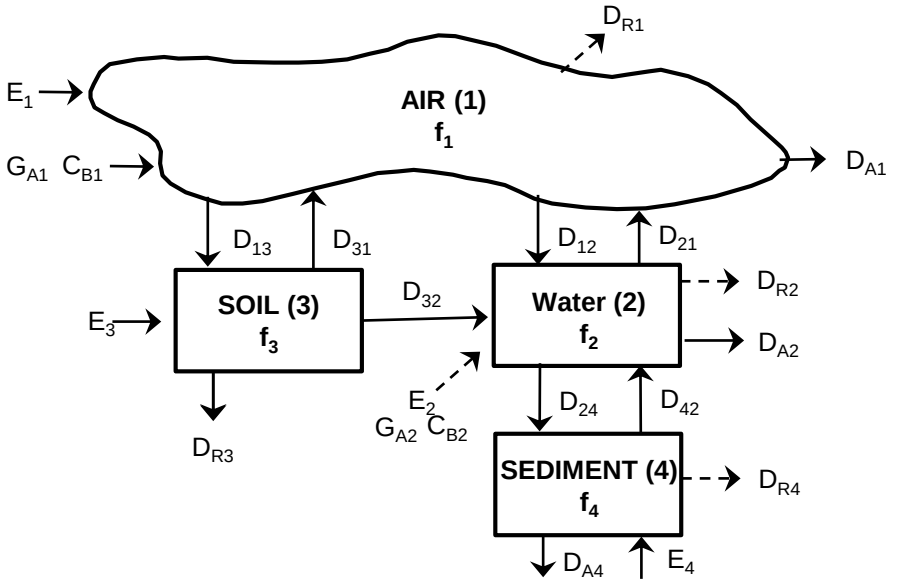
Multimedia compartment model



MODEL DOMAIN (Not to scale)

Processes modeled

- emission inputs, E
- advection in and out, D_A
- inter-compartment mass transfer, $D_{i,j}$
- reaction loss, D_R



Model Domain Parameters

- surface area - 10^4 -10^5 km^2
- 90% land area, 10% water
- height of atmosphere - 1 km
- soil depth - 10 cm
- depth of sediment layer - 1 cm
- multiphase compartments

Mackay, D. 1991, "Multimedia Environmental Models", 1st edition,, Lewis Publishers, Chelsea, MI

Impact Indicator Calculation.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis

Carcinogenic Risk Example (inhalation route)

$$\text{Relative Risk} = \frac{\left[\frac{(C_a \times CR \times EF \times ED)}{(BW \times AT)} \times SF\right]_i}{\underbrace{\left[\frac{(C_a \times CR \times EF \times ED)}{(BW \times AT)} \times SF\right]_{Benchmark}}}$$

$$= \frac{[C_a \times SF]_i}{[C_a \times SF]_{Benchmark}}$$

Multimedia compartment model concentration in air

Carcinogenic Slope Factor, SF (toxicological property)

Indicators for the Ambient Environment.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis

The TRACI method and software contains a comprehensive listing of impact categories and indicators.

Relative Risk Index	Equation
Global Warming	$I^*_{GW,i} = GWP_i$
	$I^*_{GW,i} = N_C \frac{MW_{CO_2}}{MW_i}$
Ozone Depletion	$I^*_{OD,i} = ODP_i$
Smog Formation	$I^*_{SF,i} = \frac{MIR_i}{MIR_{ROG}}$
Acid Rain	$I^*_{AR,i} = \frac{ARP_i}{ARP_{SO_2}}$

GWP = global warming potential, N_C = number of carbons atoms, ***ODP*** = ozone depletion potental, ***MIR*** = maximum incremental reactivity, ***ARP*** = acid rain potential.

Compilation impact parameters in: Appendix D.
Allen, D.T. and Shonnard, D.R., *Green Engineering : Environmentally-Conscious Design of Chemical Processes*, Prentice Hall, pg. 552, 2002

Indicators of Toxicity.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis

The TRACI method and software contains a comprehensive listing of impact categories and indicators.

Relative Risk Index	Equation
Human Toxicity Ingestion Route	$I^*_{ING} = \frac{C_{W,i}\ LD_{50,Toluene}}{C_{W,Toluene}\ LD_{50,i}}$
Human Toxicity Inhalation Route	$I^*_{INH} = \frac{C_{A,i}\ LC_{50,Toluene}}{C_{A,Toluene}\ LC_{50,i}}$
Human Carcinogenicity Ingestion Route	$I^*_{CING} = \frac{C_{W,i}\ HV_i}{C_{W,Benzene}\ HV_{Benzene}}$
Human Carcinogenicity Inhalation Route	$I^*_{CINH} = \frac{C_{A,i}\ HV_i}{C_{A,Benzene}\ HV_{Benzene}}$
Fish Toxicity	$I^*_{FT} = \frac{C_{W,i}\ LC_{50f,PCP}}{C_{W,PCP}\ LC_{50f,i}}$

LD_{50} = lethal dose 50% mortality, **LC_{50}** = lethal concentration 50% mortality, and **HV** = hazard value for carcinogenic health effects.

Indicators for MA Production.

Level 1. Input / Output Information
"Level 1" Environmental Impact Analysis

$$\text{Process Index } (I) = \sum_{i=1}^{N} (I_i^*) \times (m_i)$$

Chemical	Benzene	*n*-butane
I_{FT} *(kg/mole MA)*	5.39×10^{-6}	2.19×10^{-6}
I_{ING} "	3.32×10^{-3}	3.11×10^{-3}
I_{INH} "	8.88×10^{-2}	3.93×10^{-2}
I_{CING} "	1.43×10^{-4}	0.00
I_{CINH} "	1.43×10^{-4}	0.00
I_{OD} "	0.00	0.00
I_{GW} "	2.01×10^{-1}	1.17×10^{-1}
I_{SF} "	3.04×10^{-5}	4.55×10^{-6}
I_{AR} "	0.00	0.00

n-butane process has lower environ-mental impacts

Process Diagnostic Summary Tables: Environmental Impacts, nC4.

Normalization

$$I_N^k = \frac{I_k}{\hat{I}_k}$$

I_k — Process Index

$\hat{I}_k$ — National Index

Chemical	I_{FT}	I_{ING}	I_{INH}	I_{CING}	I_{CINH}	I_{OD}	I_{GW}	I_{SF}	I_{AR}
Sulfur dioxide	0.00E+00	0.00E+00	1.49E+01	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	1.35E+02
TOC	1.36E-02	1.49E-02	6.62E+01	0.00E+00	0.00E+00	0.00E+00	4.11E+03	4.24E+02	0.00E+00
Carbon dioxide	4.36E+02	0.00E+00	8.91E+01	0.00E+00	0.00E+00	0.00E+00	6.09E+07	0.00E+00	0.00E+00
Carbon monoxide	1.90E-01	0.00E+00	1.65E+07	0.00E+00	0.00E+00	0.00E+00	2.33E+05	2.03E+03	0.00E+00
Dibutyl phthalate	7.70E+01	1.00E+02	3.01E+00	0.00E+00	0.00E+00	0.00E+00	2.56E+02	0.00E+00	0.00E+00
Maleic Anhydride	5.10E+02	7.27E+05	0.00E+00	0.00E+00	0.00E+00	0.00E+00	3.49E+04	0.00E+00	0.00E+00
n-Butane	6.98E-02	0.00E+00	2.38E+05	0.00E+00	0.00E+00	0.00E+00	6.97E+04	0.00E+00	0.00E+00
Nitrogen dioxide	2.10E-01	0.00E+00	2.89E+03	0.00E+00	0.00E+00	0.00E+00	4.09E+06	0.00E+00	7.16E+04
Totals	1.02E+03	7.27E+05	1.67E+07	0.00E+00	0.00E+00	0.00E+00	6.54E+07	2.46E+03	7.17E+04
Contribution to I_{PC}	1.55%	0.34%	86.63%	0.00%	0.00%	0.00%	4.85%	0.14%	6.50%
I_{PC}	6.13E-04								

Process composite index

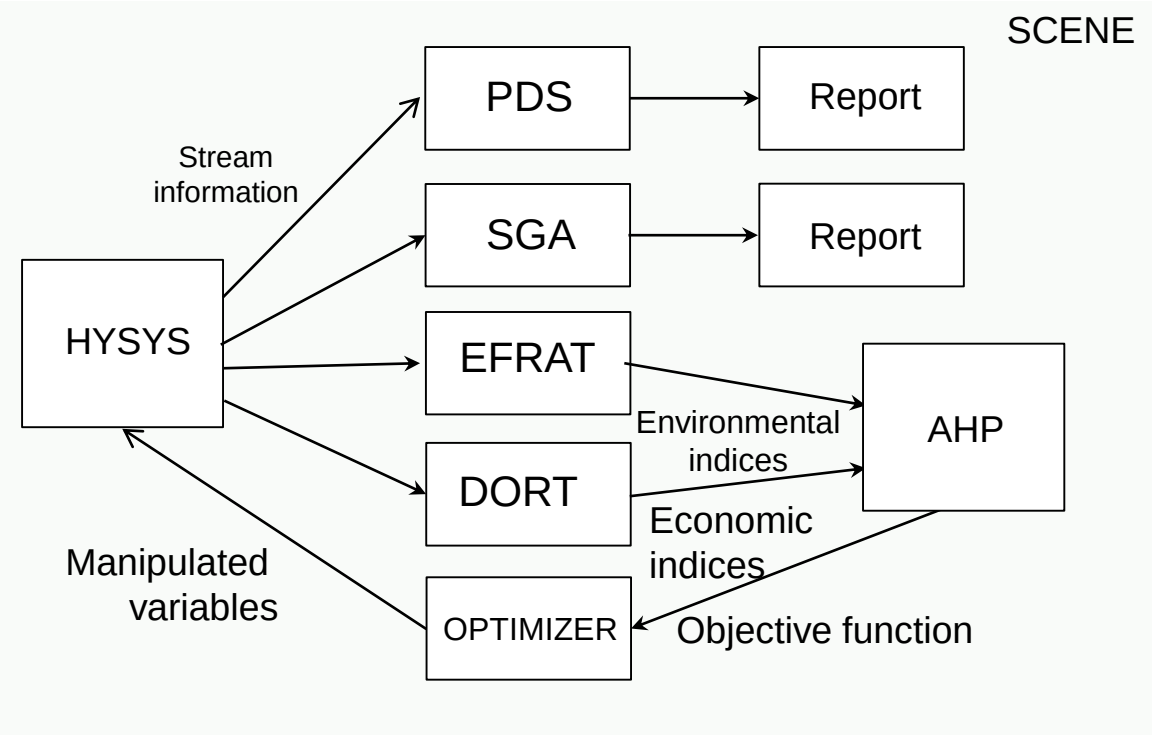
$$I_{PC} = \sum_k (I_N^k \times W_k)$$

Source: Eco-Indicator 95 framework for life cycle assessment, Pre Consultants, http://www.pre.nl

Weighting Factors

global warming	*2.5*
ozone depletion	*100*
smog formation	*2.5*
acid rain	*10*
carcinogenic	*5*
noncarcinogenic	*5*
ecotoxicity	*10*

Integrated Process Simulation and Assessment Method and Software.



HYSYS – a commercial chemical process simulator software, **EFRAT** – a software for calculating environmental impacts, **DORT** - a software to estimate equipment costs and operating costs, **AHP** (Analytic Hierarchy Process) – multi-objective decision analysis, **PDS** – Process Diagnostic Summary Tables, **SGA** – Scaled Gradient Analysis

Process Diagnostic Summary Tables: Energy Input/output for nC4 Process.

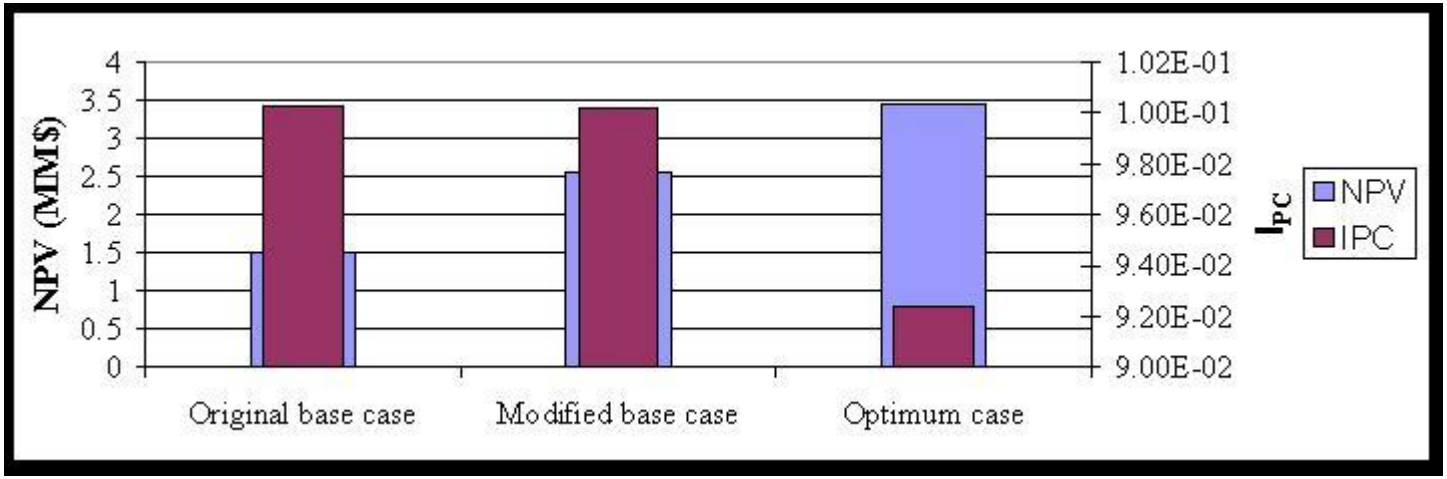
Stream	Available temperature (In,Out)(?F)	Available Pressure (In,Out)(psia)	Energy flow (MM Btu/hr)	% of total energy
	Input			
Air	77	14.696	0.0000	0.00%
n-Butane	50	22.278	-0.0424	-0.11%
Make-up solvent	95	18.13	0.0004	0.00%
Solvent pump	472.87~472.96	1.2505~18.13	0.0107	0.03%
Air compressor	77~167.18	14.696~22.278	3.9588	9.92%
n-Butane vaporizer	50~50.004	22.278	1.0059	2.52%
Reactor feed heater	160.62~770	22.278	29.8800	74.90%
Reboiler	472.87	1.2505	5.0774	12.73%
Total			39.8908	100.00%
	Output			
Absorber off-gas	120.53	18.275	2.0033	1.80%
Distillation off-gas	95.043	0.3897	0.0002	0.00%
Crude MA	95.043	0.3897	0.0368	0.03%
Reactor 1	770		23.6340	21.29%
Reactor 2	770		23.6340	21.29%
Reactor 3	770		23.6340	21.29%
Reactor off-gas cooler	770~230	18.943	26.8940	24.23%
Solvent subcooler	234.95~95	18.13	7.1588	6.45%
Condenser	95.043	0.3897	4.0202	3.62%
Total			111.0153	100.00%

Process Diagnostic Summary Tables: Manufacturing Profit and Loss, nC4.

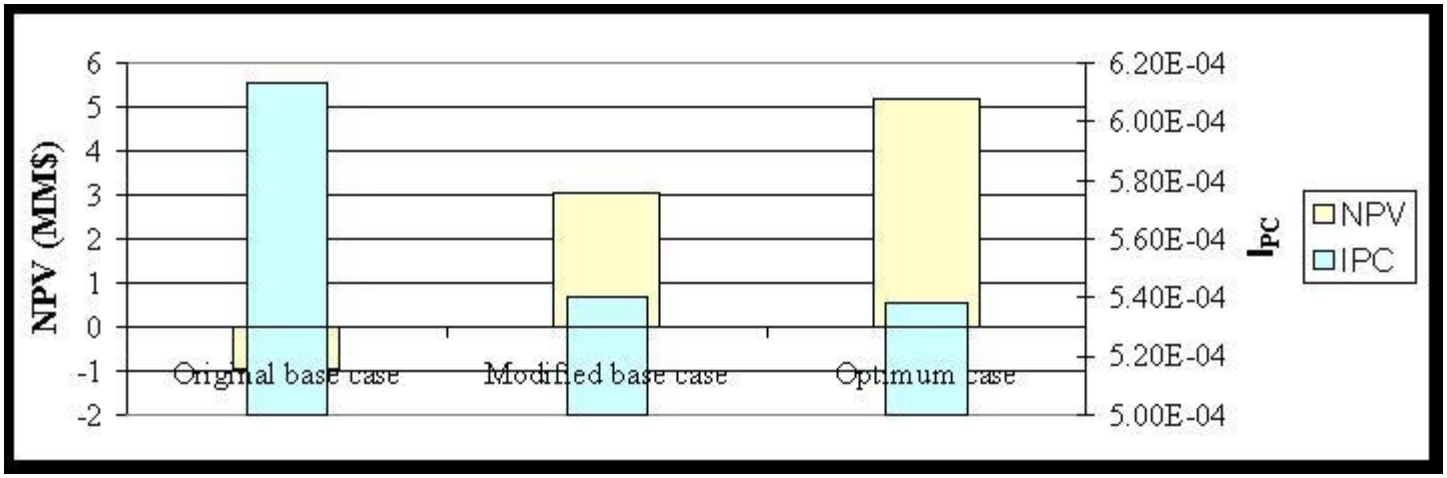
	Name	Total ($/yr)	% of total cost
Revenue			
	Maleic anhydride	21,258,236	100.00%
	Total Sales Revenue	**21,258,836**	**100.00%**
Manufacturing Expenses			
	Raw Materials		
	N-Butane cost	4,760,866	55.80%
	Make-up solvent	81,343	0.95%
	Utilities		
	Cooling water (tower)	159,913	1.87%
	Electricity (on site)	679,014	7.96%
	Steam (50 psi)	58,014	0.68%
	Steam (600 psi)	580,303	6.80%
	Natural gas	2,212,796	25.93%
	Total Manufacturing Expenses	**8,532,249**	**100.00%**

Continuous Improvement of Design Performance.

benzene process design



n–butane process design



Net Present Value (NPV); Process composite index (IPC)

Effective Mass Yield (EMY).

$$\text{Eff. Mass Yield (\%)} = 100 \times \frac{\text{Product (Kg)}}{\text{Hazardous Reagents (Kg)}}$$

Definition: “the percent of desired product mass relative to the mass of all non-benign materials used in its synthesis” (Hudlicky *et al.*)

What is benign? Who decide?

- *This metric ignores recovery* (EMY)
  - Does not consider benign solvents. What occurs if benign solvents are combined with other non-benign *in-situ* to form non-benign solutions?
- As for atom economy, an higher percent of EMY **is better**
  - (0-100%)

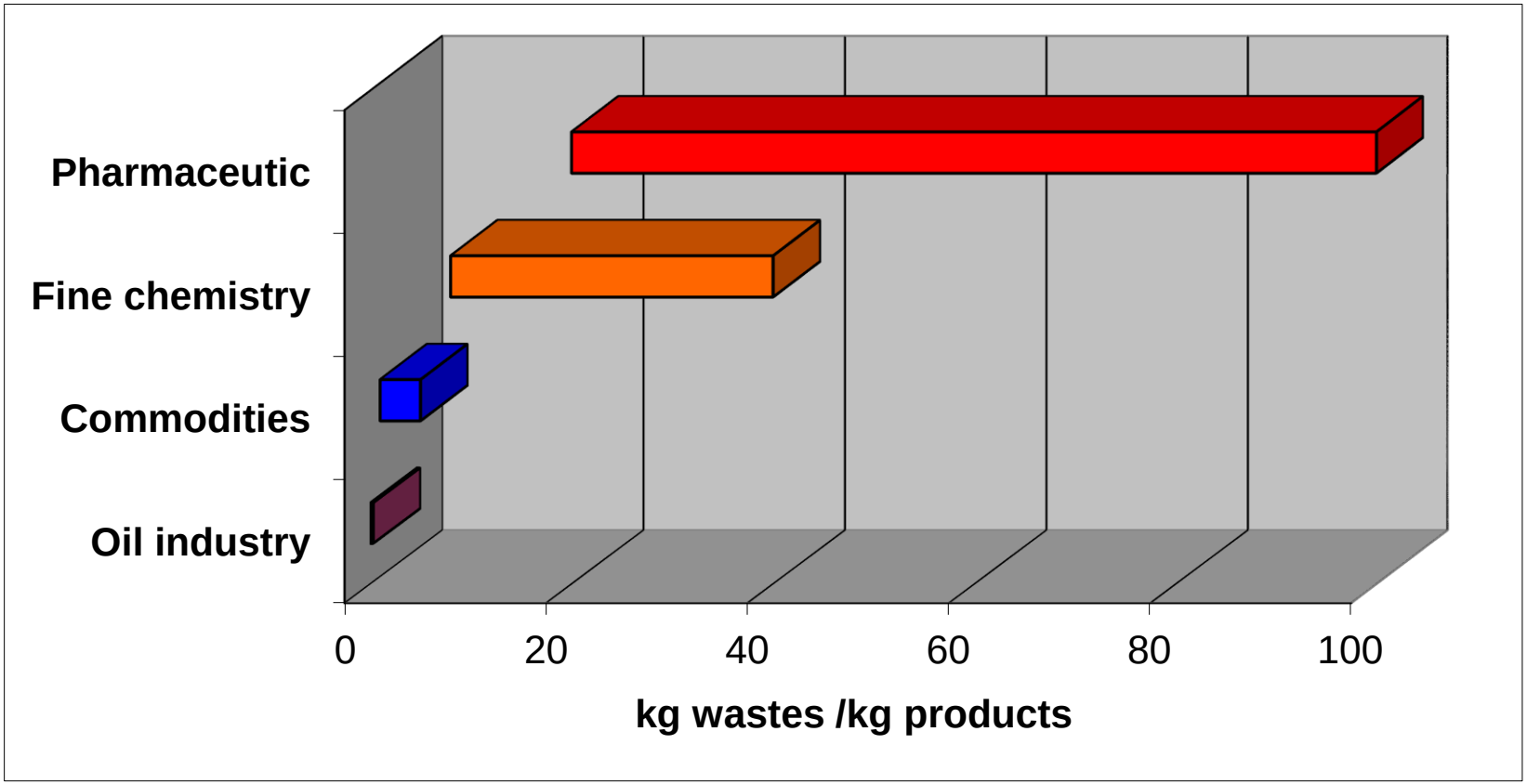
E Factor.

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

- **Depends on definition of waste**
  - Include:
    - process use only
    - or chemicals needed for scrubbing
- **Very useful metric for Industry**
- **E factor can be split into different sub-categories**:
  - Organic waste
  - Aqueous waste ……..
- **The smaller** the E number, the closer to **zero waste** being produced
  - **(0- ∞)**

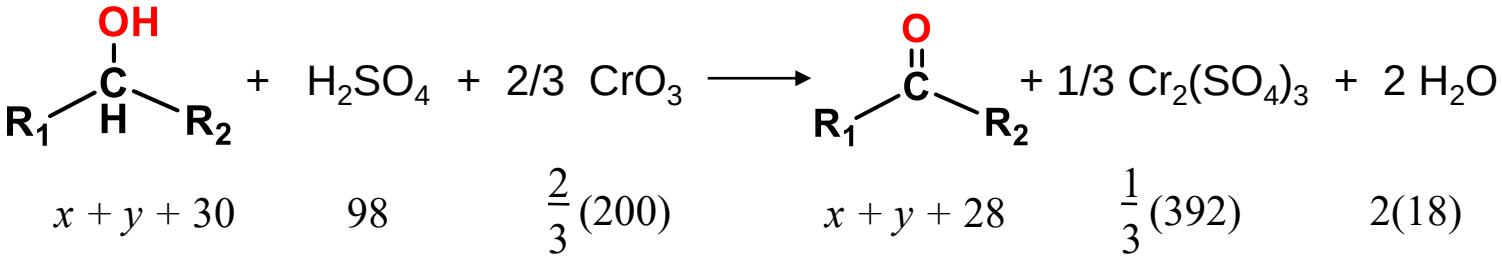
Sheldon, 1992

“E” Factor in the Production of Chemical Compounds.



Estimated!

Jones Oxidation of Secondary Alcohols.

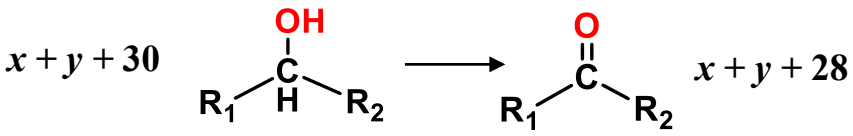


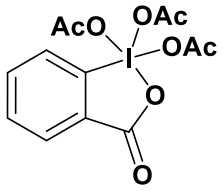
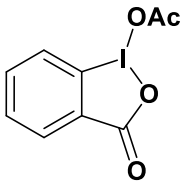
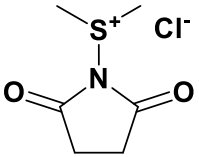
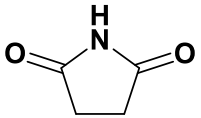
$$AE = \frac{x + y + 28}{x + y + 194.67} \qquad E = \frac{166.67}{x + y + 28}$$

$$AE_{\min} = 0.15$$

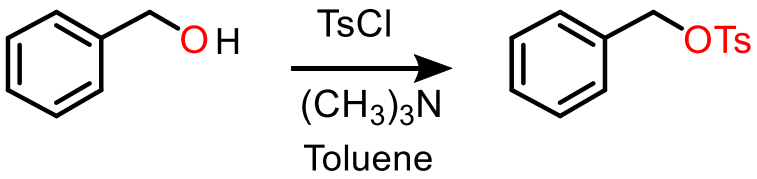
$$E_{\max} = 5.55$$

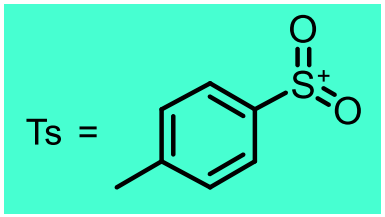
Oxidation of Secondary Alcohols.



Reactant	Oxidizing Agent	Byproducts	AE	E(max)
Dess-Martin		 2 AcOH	0.062	15.21
Swern	DMSO	Me_2S, Et_3NHCl, ClOCCOCl	0.083	11
Corey-Kim		Me_2S, Et_3NHCl, NHS 	0.086	10.66
Pfitner-Moffatt	DMSO	Me_2S, $[Cy\text{-}NH]_2C{=}O$	0.09	10.14
Jones	CrO_3	$Cr_2(SO_4)_3$, 2 H_2O	0.14	5.95
Permanganate	$KMnO_4$	2 MnO_2, 4 H_2O, K_2SO_4	0.17	5.0
Hydrogen peroxide	H_2O_2	H_2O	0.44	1.29
Theoretical limit	?????	H_2	0.93	0.075

Example of Reaction RME.





Reactant	Benzyl alcohol	10.81 g	0.10 mol	FW 108.1
Reactant	Tosyl Chloride	21.9 g	0.115 mol	FW 190.65
Solvent	Toluene	500 g		
Auxiliary	Triethylamine	15 g		FW 101
Product	Sulfonate ester	23.6 g	0.09 mol	FW 262.29

E-Factor = [(10.81 + 21.9 + 500+ 15) – 23.6] / 23.6 = 22.2 Kg waste /1 Kg Prod.

Atom Economy = 262.29 / (108.1 + 190.65 + 101) × 100 = 65.8%

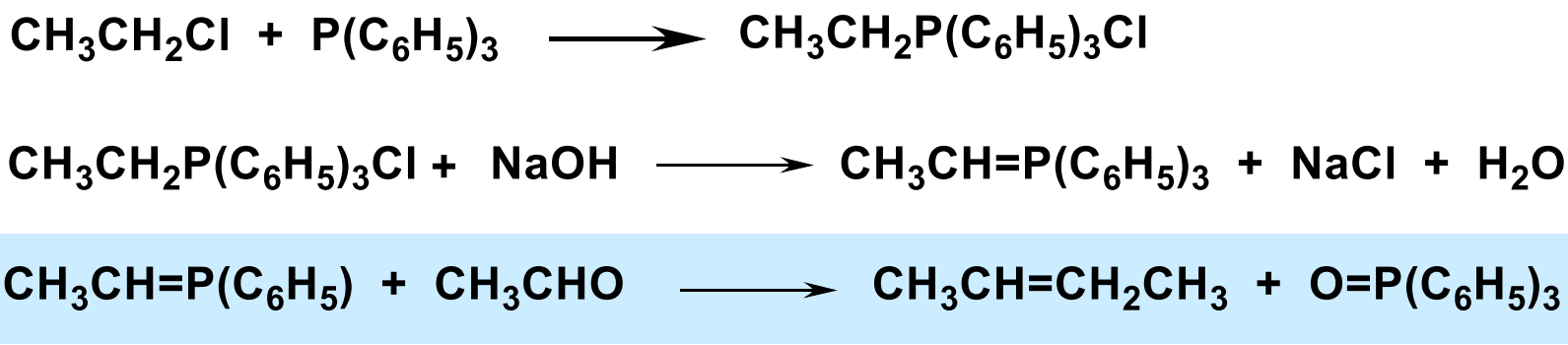
Atom Efficiency = 90% × 65.8% = 59.2%

Carbon Efficiency = (0.09 × 14)/((0.1 × 7) + (0.115 × 7)) × 100 = 83.7%

Reaction Mass Efficiency = 23.6/(10.81 + 21.9) × 100 = 70.9%

Wittig Reaction (Addition with Co-product).

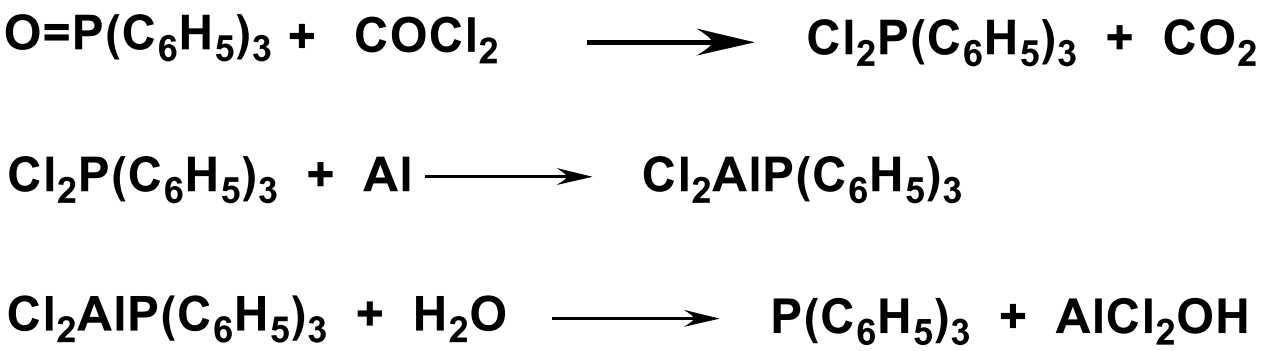
Versatile method to synthesize alkenes with double bonds in fixed positions - affords high yield and can be carried out under mild conditions. Used to prepare vitamins and pharmaceutical products.



- Costly because of the low atom economy due to formation of triphenylphosphine oxide (FW 278).

Possible Solution for Wittig Reaction.

Conversion of TPPO into TPP for the recycle



Limits are due to toxicity of phosgene and aluminum co-products (partially used as catalysts).

General Reactions: Stoichiometric Conditions.

	A + B	⟶	Q + P
MW (g/mol)	*a* *b*		*q* *p*
Moles	*x* *x*		*y* *y*
Mass (g)	*ax* *bx*		*qy* *py*

Conservation of Mass Law: *ax + bx = qx + px = qy +py +w*

Atom economy, $AE = \frac{p}{a+b} = \frac{p}{q+p}$ Trost

Yield, $\varepsilon = \frac{py}{px} = \frac{y}{x}$

Reaction mass efficiency, $RME = \frac{py}{ax+bx} = \frac{p\varepsilon}{a+b} = (\varepsilon)(AE)$

Environmental impact factor based on MW, $E = \frac{q}{p}$ Sheldon

Environmental impact factor based on actual mass, $E_m = \frac{qy+w}{py} = \frac{1}{(\varepsilon)(AE)} - 1$

Andraos, J. *Org. Proc. Res. Develop.* 2005, *9*, 149; 404

General Reactions:
Non Stoichiometric Conditions.

	A + B		Q + P	
MW (g/mol)	*a*	*b*	*q*	*p*
Moles	*x*	*z*	*y*	*y*
Mass (g)	*ax*	*bz*	*qy*	*py*

Mass Conservation Law: $ax + bz = qy + py + w,\ z > x,\ \phi = z - x$

Atom economy, $AE = \frac{p}{a+b} = \frac{p}{q+p}$

Yield, $\varepsilon = \frac{py}{px} = \frac{y}{x}$

Reaction mass efficiency, $RME = \frac{py}{ax+bx} = \frac{py}{ax+bz} = \frac{p\varepsilon}{a+b+(b\phi/x)} = \frac{(\varepsilon)(AE)}{SF}$

Stoichiometric factor, $SF = 1 + \frac{b\phi}{x(a+b)} = 1 + \frac{b\phi}{x(q+p)}$

Environmental impact factor based on MW, $E = \frac{q}{p}$

Environmental impact factor based on actual mass, $E_m = \frac{qy+w}{py} = \frac{SF}{(\varepsilon)(AE)} - 1$

Summary of Key Relationships.

Stoichiometric Reactions (SF = 1)

$$AE = \frac{1}{1+E}$$

$$E_m = \frac{1}{RME} - 1$$

$$RME = (\varepsilon)(AE)$$

$$\frac{AE}{RME} = \frac{1+E_m}{1+E} = \frac{1}{\varepsilon}$$

Maximizing AE

⇩

Minimizing E

Non Stoichiometric Reactions (SF > 1)

$$AE = \frac{1}{1+E}$$

$$E_m = \frac{SF}{(\varepsilon)(AE)} - 1$$

$$RME = \frac{(\varepsilon)(AE)}{SF}$$

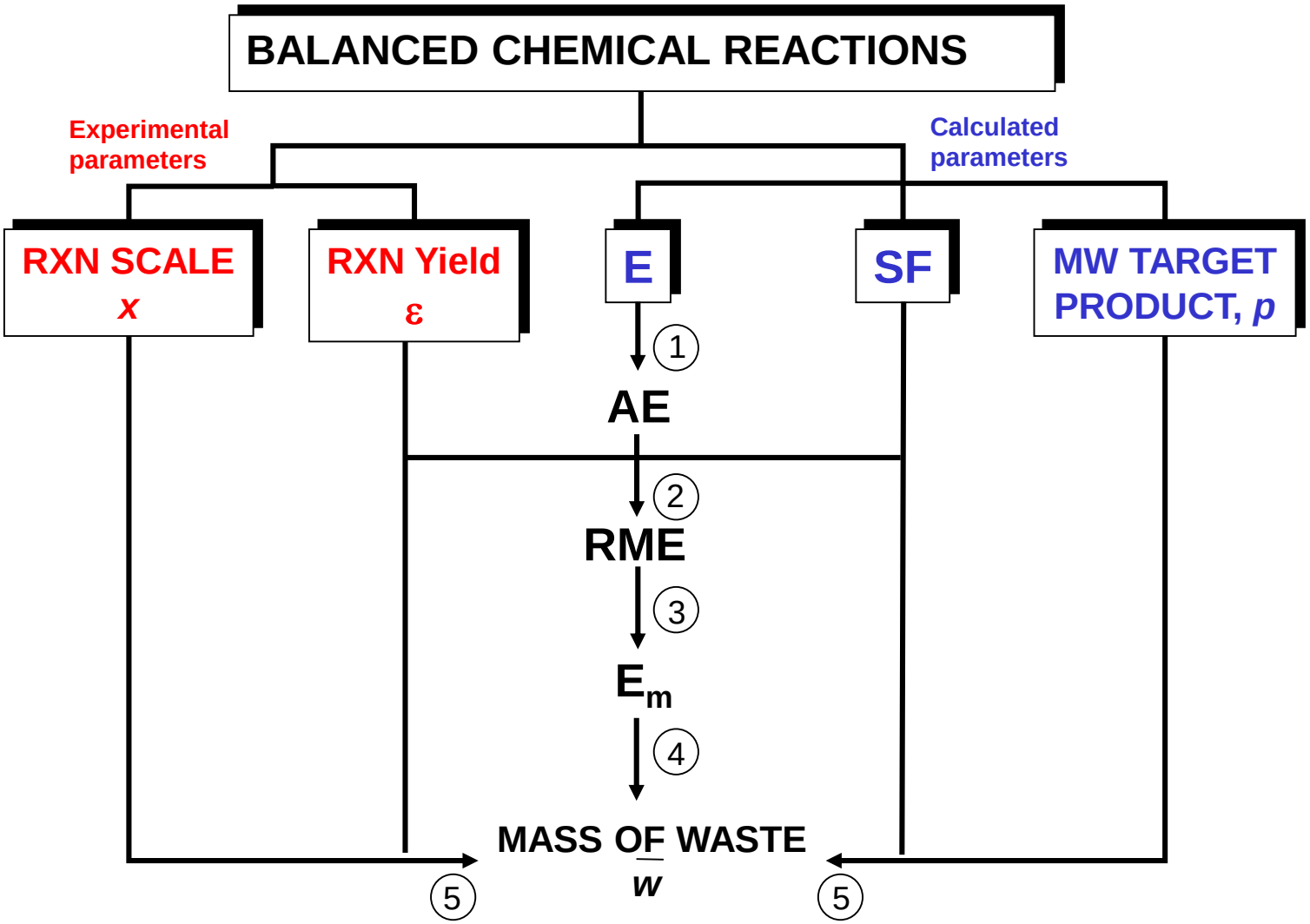
$$\frac{AE}{RME} = \frac{1+E_m}{1+E} = \frac{SF}{\varepsilon}$$

Minimizing AE

⇩

Maximizing E

Green Metrics.



Key Formula Linking Reaction Metrics.

① $$AE = \frac{1}{1+E}$$

② $$RME = \frac{\varepsilon(AE)}{SF}$$

③ $$E_m = \frac{1}{RME} - 1$$

④ $$\begin{cases} \bar{w} = px\varepsilon E_m \\ \bar{w}_j = E_m^j p_j x \left(\prod_{k=1}^{j} \varepsilon_k \right) \end{cases}$$

⑤ $$\bar{w}_j = \begin{cases} x\left(\frac{p}{AE}\right)(SF)\left[1 - RME\right] & j = 1 \\ x\left(\frac{p_j}{(AE)_j}\right)\left(\prod_{k=1}^{j-1} \varepsilon_k\right)(SF)_j\left[1 - (RME)_j\right] & j > 1 \end{cases}$$

$$E = \frac{\sum MW\ byproducts}{p}$$

$$SF = 1 + \frac{\sum masses\ excess\ reagents}{\sum masses\ reagents\ with\ no\ excess} = 1 + \frac{\sum_j b_j \phi_j}{x(a+b+\ldots)} = 1 + \frac{(AE)\sum_j b_j \phi_j}{xp}$$

$$E_m(total) = \frac{\sum_{j=1} \bar{w}_j}{px\left(\prod_{j=1}^{n} \varepsilon_j\right)}$$

$$PMC(total) = \sum_{j=1}^{n} \frac{\left(RMC_j^{100}\right)}{\varepsilon_j \varepsilon_{j+1} \ldots \varepsilon_n}$$

Metrics for Enantiomeric Products.

For special cases of reactions leading to 2 enantiomeric products for a partially enantio-selective reaction, RME becomes:

$$\left(RME\right)_j = \begin{cases} \left(\dfrac{\varepsilon_{overall}\left(AE\right)}{SF}\right)0.5\left(1+ee\right) \\ \left(\dfrac{\varepsilon_{overall}\left(AE\right)}{SF}\right)0.5\left(1-ee\right) \end{cases} = \begin{cases} \left(\left(RME\right)_{overall}\right)0.5(1+ee) \\ \left(\left(RME\right)_{overall}\right)0.5(1-ee) \end{cases}$$

$$\left(RME\right)_{overall} = \sum_{j=1}^{2}\left(RME\right)_j \qquad \varepsilon_j = \begin{cases} 0.5\varepsilon_{overall}(1+ee) \\ 0.5\varepsilon_{overall}(1-ee) \end{cases}$$

Effect of Recycling Solvents (s) and/or Catalysts (c).

Solvent recycled	Catalyst recycled	RME (stoichiometric conditions)	RME (non-stoichiometric conditions)
yes	yes	$\varepsilon(AE)$	$\frac{\varepsilon(AE)}{SF}$
yes	no	$\varepsilon(AE)\left[\frac{py}{py+c\varepsilon(AE)}\right]$	$\frac{\varepsilon(AE)}{SF}\left[\frac{py}{py+\frac{c\varepsilon(AE)}{SF}}\right]$
no	yes	$\varepsilon(AE)\left[\frac{py}{py+s\varepsilon(AE)}\right]$	$\frac{\varepsilon(AE)}{SF}\left[\frac{py}{py+\frac{s\varepsilon(AE)}{SF}}\right]$
no	no	$\varepsilon(AE)\left[\frac{py}{py+(c+s)\varepsilon(AE)}\right]$	$\frac{\varepsilon(AE)}{SF}\left[\frac{py}{py+(c+s)\frac{\varepsilon(AE)}{SF}}\right]$

Reaction Mass Efficiency - Master Equation.

$$RME = (\varepsilon)(AE)\left(\frac{1}{SF}\right)(MRP) = (\varepsilon)(AE)\left(\frac{1}{SF}\right)\left(\frac{1}{1+\frac{\varepsilon(AE)[c+s+\omega]}{(SF)(m_p)}}\right)$$

Parameters:

ε	reaction yield	
AE	atom economy	
SF	stoichiometric factor;	SF =1 implies no excess reagents
		SF > 1 implies excess reagents used
MRP	materials recovery parameter	

Recall: Lavoisier's law of conservation of mass for balanced chemical reaction/equation.

Andraos, J. ***Org. Proc. Res. Develop.*** 2005, ***9*****, 149; 404**

RME Evaluation (Specific Situations).

RME Expression

$$(\varepsilon)(AE)\left(\frac{1}{SF}\right)\left(\frac{1}{1+\frac{\varepsilon(AE)[c+s+\omega]}{(SF)(m_p)}}\right)$$

$$(\varepsilon)(AE)\left(\frac{1}{1+\frac{\varepsilon(AE)[c+s+\omega]}{(m_p)}}\right)$$

$$(\varepsilon)(AE)\left(\frac{1}{1+\frac{\varepsilon(AE)[c+\omega]}{(m_p)}}\right)$$

$$(\varepsilon)(AE)\left(\frac{1}{1+\frac{\varepsilon(AE)[c]}{(m_p)}}\right)$$

$$(\varepsilon)(AE)\left(\frac{1}{SF}\right)$$

$$(\varepsilon)(AE)$$

Conditions

- Excess reagents used, reaction catalyst destined for waste, reaction solvent destined for waste. Work-up and purification materials destined for waste. No excess reagent used
- reaction catalyst destined for waste reaction solvent destined for waste, work-up and purification materials destined for waste, no excess reagents used
- reaction catalyst destined for waste; reaction solvent recovered work-up and purification materials destined for waste; no excess reagents used
- reaction catalyst destined for waste; reaction solvent recovered; work-up and purification materials recovered
- excess reagents used; reaction catalyst reclaimed reaction solvent reclaimed; work-up and purification materials reclaimed
- no excess reagents used; reaction catalyst reclaimed; reaction solvent reclaimed; work-up and purification materials reclaimed.

Atom Economy/Reaction Mass Efficiency - E-factor Connecting Relationships.

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

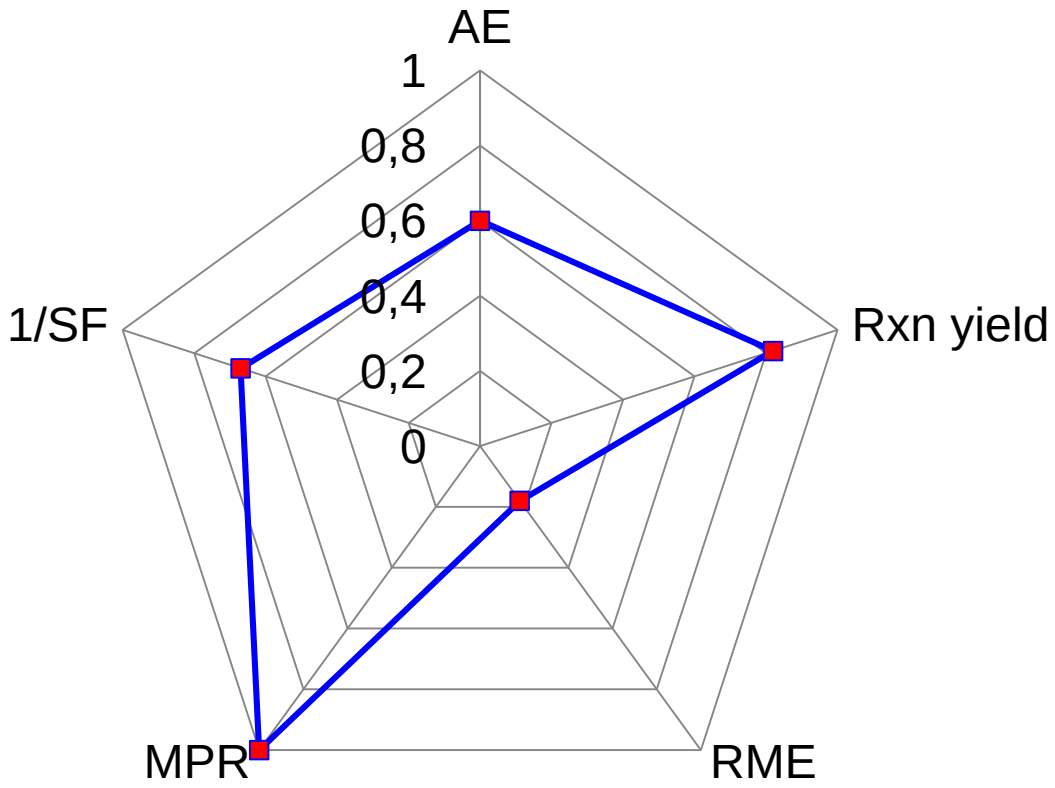
Criteria for “green” reactions:

(1) AE ≥ 61.8 % so that AE > E_{mw}

(2) RME ≥ 61.8 % so that RME > E_m

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

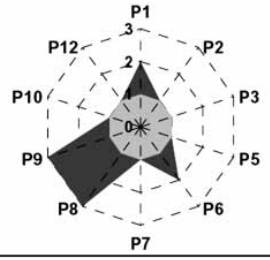
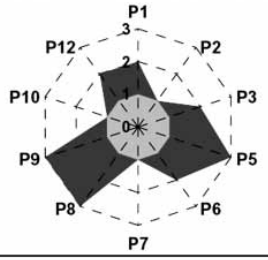
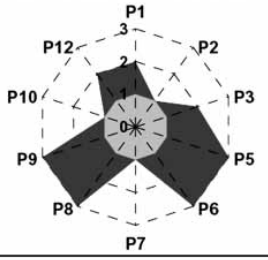
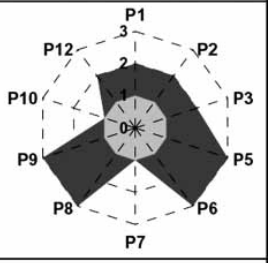
A Global View of Green Metric Parameters.



Materials Recovery Parameter (MRP)

$$MRP = \frac{1}{[1+(\varepsilon(AE)[c + s + \omega])/((SF)(m_p))]}$$

Green Stars Parameters and Metric for the Synthesis of Iron(II)oxalate Dihydrate.

Metric	GS1 Sulfuric acid, boiling temperature, 76% excess of oxalic acid	GS2 Ascorbic acid, boiling temperature, 76% excess of oxalic acid	GS3 Ascorbic acid, room temperature, 76% excess of oxalic acid	GS4 Ascorbic acid, room temperature, 4% excess of oxalic acid
GS				
GSAI	20.00	36.25	41.25	46.25
Yield %	92.0±1.9	93.6±0.3	96.1±0.2	87.5±1.2
E-factor	2.06±0.06	2.30±0.01	2.217±0.006	1.96±0.04
MI	3.06±0.06	3.30±0.01	3.217±0.006	2.96±0.04
AE	44.52	44.52	44.52	44.52
RME = AU	33.1±0.7	33.7±0.1	34.54±0.06	38.4±0.5
FeEE	92.0±1.9	93.6±0.3	96.1±0.2	87.5±1.2

*Number of experiments for every GS, N = 3; MI – Mass Intensity ;
AE – Atom Economy ; RME – Relative mass efficiency;
AU – Atom utilization; FeEE – Iron element efficiency

M. Gabriela et al. Green Chemistry 3:2, 149-159 (2010)

Factors Which Could Affect the Choice of a Synthetic Route.

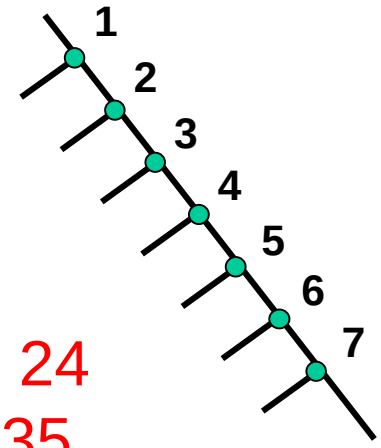
- ***Number of steps***
  - A short synthesis has many advantages
  - A convergent synthesis will be cheaper than a divergent synthesis with the same number of steps

(J.B. Hendrickson, *Pure App. Chem*., **1988**, *60*(11), 1563)

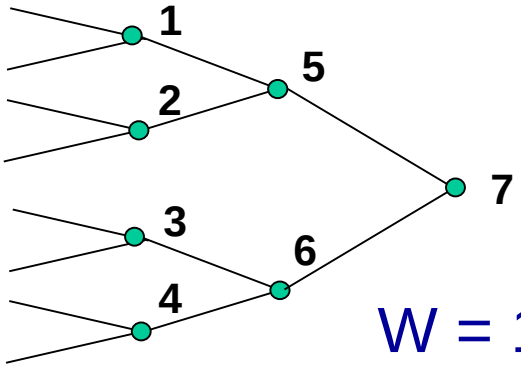
- ***Easiness to scale up***
  - Subjective judgment at early stage
  - Do not prejudge apparently difficult procedures
  - Engineering solutions can overcome handling problems for attractive routes
  - However SIMPLEST IS BEST

Comparison of Linear and Convergent Syntheses.

7 Steps, 80% yield per step



W = 24
S = 35

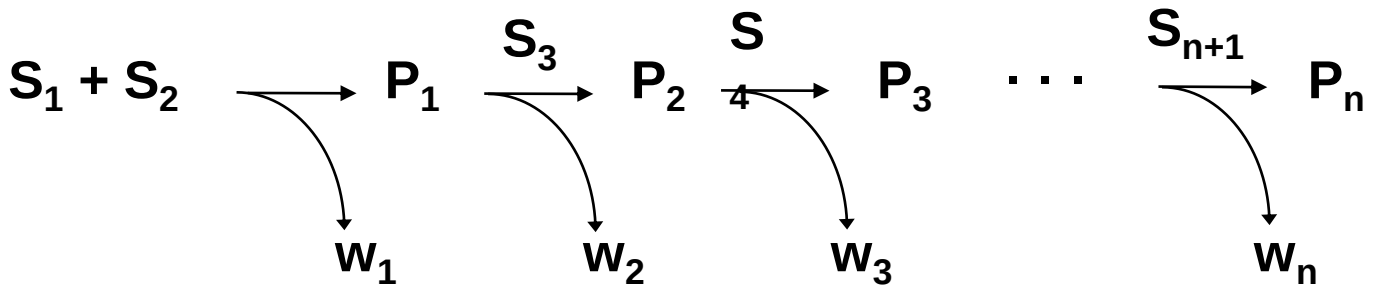


W = 16
S = 24

W = total wt. of all SM
S = sum of steps each SM must pass through

J.S. Hendrickson, *Pure App. Chern.*, 1988, 60 (11), 1563.

Linear Synthetic Sequences.



w_j =mass of waste in step j; c_j = mass of catalyst in step j
s_j = mass of solvent in step j; p_j = MW of target product in step j
ε_j = fractional yield in step j; x = moles of reagents in step 1 (scale reaction)

Assumption; stoichiometric conditions in each step

$$E_{m,total} = \frac{\sum_{j=1}^{n}\left(w_j + c_j + s_j\right)}{p_n x\left(\prod_{j=1}^{n}\varepsilon_j\right)} \qquad RME_{total} = \frac{1}{1+E_{n,total}}$$

$$Overall\ yield = \prod_{j=1}^{n}\varepsilon_j$$

$$Theoretical\ mass\ of\ \ final\ product = p_n x$$

Product yields is true only if all of collected intermediate product P_j is committed to succeeding (j + 1)th step.

Algorithm for Linear Sequences

1. Balance chemical equations accounting for all byproducts.
2. Determine E_j for each step.
3. Determine $(AE)_j$ for each step using $\left(AE\right)_j = \frac{1}{1+E_j}$
4. Determine overall E using $E_{overall} = \frac{\Sigma MW_{\text{byproducts}}}{\Sigma MW_{\text{target product}}}$
5. Determine overall AE using $\left(AE\right)_{overall} = \frac{1}{1+E_{overall}}$
6. Determine $(SF)_j$ for each step using $\left(SF\right)_j = 1 + \frac{\left(AE\right)_j \sum_k b_k \phi_k}{x_j p_j}$
7. Determine $(RME)_j$ for each step using $\left(RME\right)_j = \frac{\left(AE\right)_j \varepsilon_j}{\left(SF\right)_j}$

Algorithm for Linear Sequences (cont.).

8. Determine $E_{m,j}$ for each step using $E_m^j = \frac{1}{(RME)_j} - 1$

9. Determine mass of waste in step *j* using $\bar{w}_j = E_m^j p_j x \left(\prod_{k=1}^{j} \varepsilon_k \right)$ o

$$\bar{w}_1 = x \left(\frac{p_1}{(AE)_1} \right) (SF)\left(1-(RME)_1\right)$$

$$\bar{w}_j = x \left(\frac{p_j}{(AE)_j} \right) \left(\prod_{k=1}^{J-1} \varepsilon_k \right) (SF)_j \left(1-(RME)_j\right), \; j > 1$$

10. Determine $\sum_{j=1}^{n} \bar{w}_j$

11. Determine overall E_m using $E_m^{overall} = \frac{\sum_{j=1}^{n} \bar{w}_j}{x p_n \left(\prod_{k=1}^{n} \varepsilon_k \right)}$

12. Determine overall RME using $(RME)_{overall} = \frac{1}{1 + E_m^{overall}}$

Algorithm for Convergent Sequences.

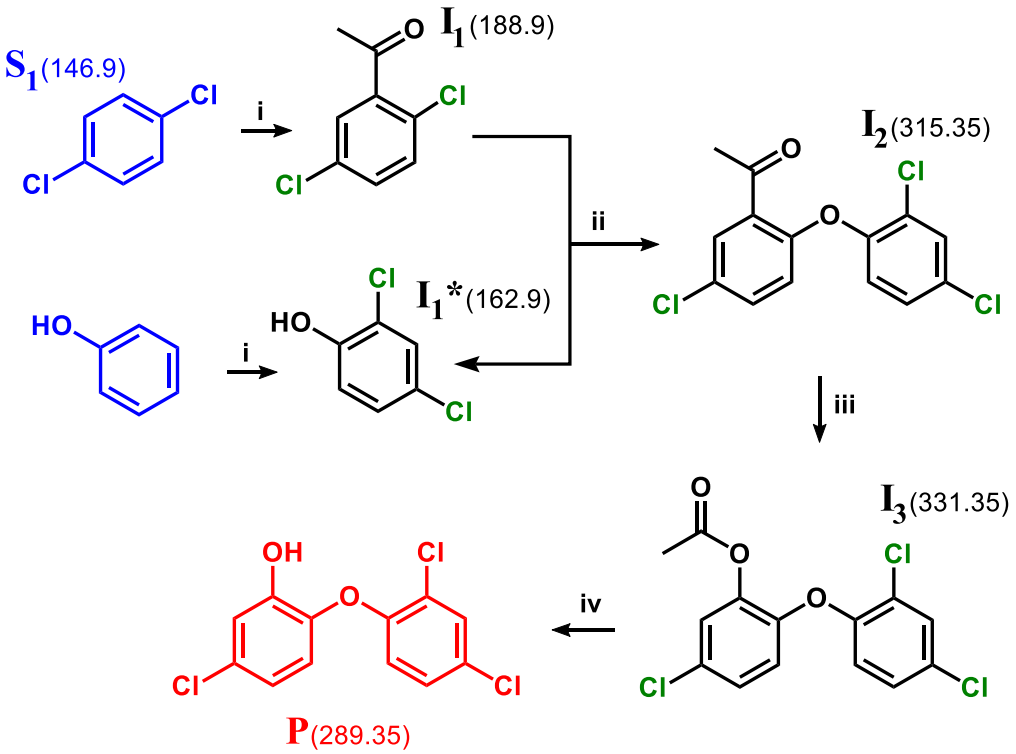
1. Analyze each linear sequence as above
2. Normalize scales of each sequence by multiplying smaller scale sequence by a factor given by

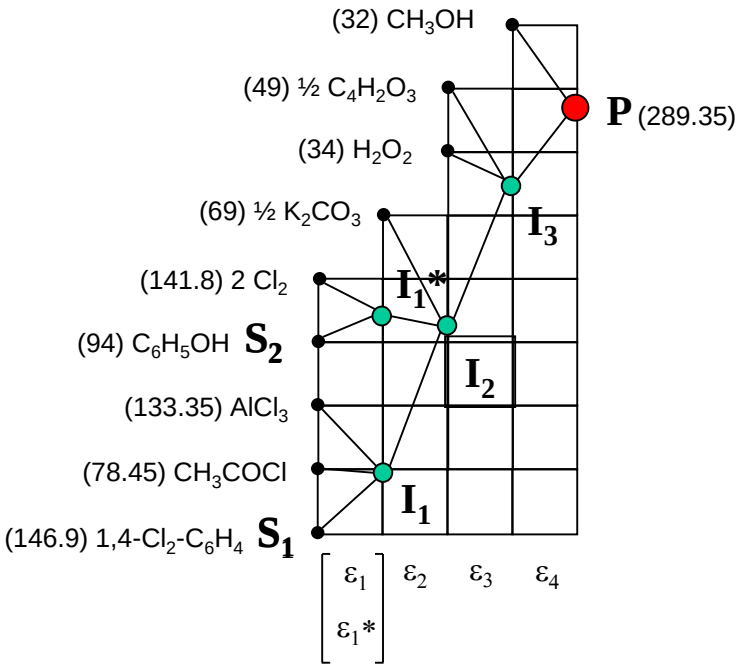
$$factor = \left(\frac{x_{\text{large}}}{x_{\text{small}}} \right) \left(\frac{\varepsilon_{overall}^{\text{large scale sequence}}}{\varepsilon_{overall}^{\text{small scale sequence}}} \right)$$

3. Analyze convergent step using larger scale of two sequences.
4. Sequence of steps following convergent step are analyzed as per algorithm for linear sequences using larger scale of two preceding sequences.
5. Overall yield for entire process is given by

$$\varepsilon_{total} = (\text{overall yield for larger scale path}) \cdot (\text{yield of convergent step}) \cdot (\text{overall yield for forward steps})$$

Graph Approach: Metric in Triclosan Synthesis.





[a] Reaction conditions: (i) acetyl chloride, $AlCl_3$ catalyst (94.3%); (i)* 2 Cl_2 (81%); ii) ½ K_2CO_3, CuCl catalyst, xylenes (48.3%); (iii) 62.5% H_2O_2, ½ maleic anhydride, CH_2Cl_2 (91.3%); (iv) MeOH, 35% HCl catalyst (94.5%). Molecular weights in g/mol are given in parentheses.

Andraos (2006)

Metrics for Alternative Triclosan Synthesis.

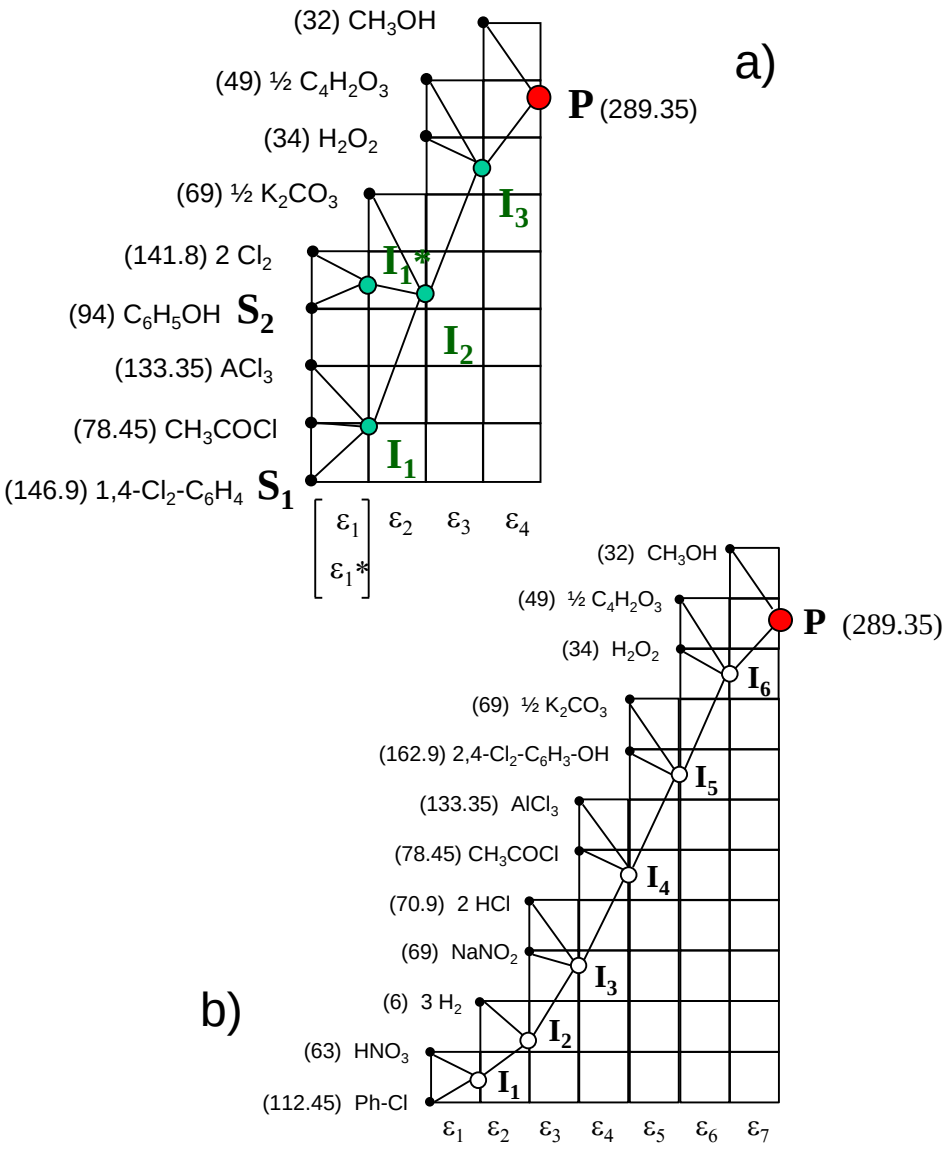


Table 3. **Summary of reaction metrics and synthesis tree parameters for triclosan synthesis plans shown in Figures 1 and 10**

	Figure 1 synthesis tree	Figure 10 synthesis tree
Kernel Reaction Metrics		
AE	0.3717	0.3288
E_{mw}	1.69	2.04
RME	0.152	0.1370
E_m	5.59	6.30
$\epsilon_{pseudo-overall}$ ($\epsilon_{overall}$)	0.408	0.417 (0.351)
number of reaction inputs, I	9	12
number of reaction steps, M	5	7
number of reaction stages, N	4	7
μ_1 (g/mol per reaction stage)	−171.03	−108.99
RMC[a] ($/mol)	333.95 ($1.15/g)	111.28 ($0.38/g)
Tree Parameters		
P coordinate	(4,217/32)	(7,20301/2048)
θ_p (deg)	76.411	63.601
θ_{mcr} (deg)	151.928	159.390
degree of convergence, δ	0.503	0.399
ρ_{actual}	1.695	1.416
ρ_{I-mcr}	4	5.5
relative rate of convergence, ρ_{rel}	0.424	0.258
asymmetry, β	0.695	0.802

[a] Based on unit costs ($/g) taken from an Aldrich 2003−2004 Catalogue in Canadian dollars using prices for the largest unit listed in the catalogue: methanol, 0.0108; maleic anhydride, 0.1047; hydrogen peroxide, 0.1888 (based on 30 wt % solution); potassium carbonate, 0.0462; chlorine, 0.6110; phenol, 0.047; aluminum trichloride, 0.0639; acetyl chloride, 0.0643; 1,4-dichlorobenzene, 0.0212; 2,4-dichlorophenol, 0.0563; hydrochloric acid, 0.0381 (based on 37 wt % solution); sodium nitrite, 0.0662; hydrogen, 0.2875 (assuming pressure of lecture bottle is 1800 psi); nitric acid, 0.0292 (based on 70 wt % solution); and chlorobenzene, 0.0129.

Unfriendliness Factor Q.

In order to take into account the different toxicity of products, the Q factor is introduced. The product of E factor and Q factor (EQ factor) is an indicator of the efficiency/environmental impact of a reaction:

« **EQ Factor** »

= E factor × « unfriendliness factor Q »

Q quantifies the undesirable character of by-products/wastes

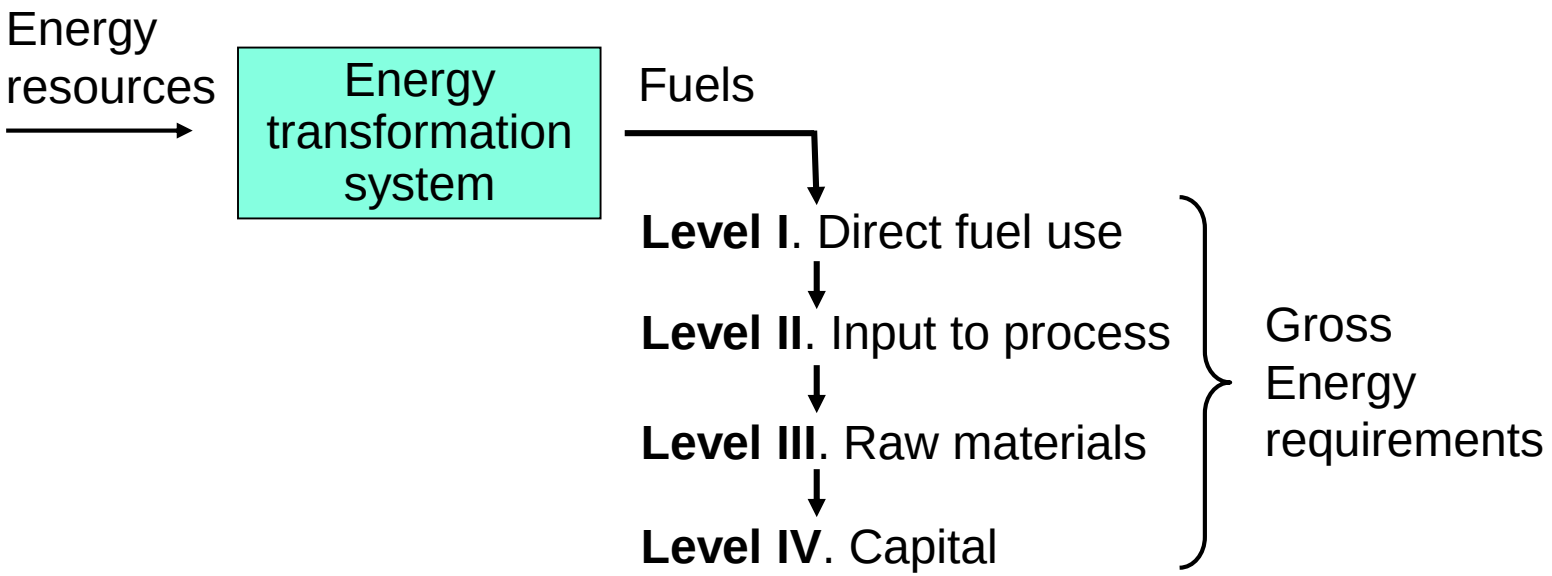
- Q = 0 for water
- Q =1 for « benign » salts as NaCl
- Q up to 1000 for very toxic products

« Waste prevention is always preferred over waste remediation »

Energy to Normalise Environmental Impacts.

Energy is one of the major constraints on the production process. Because energy is currently produced from depleting resources, there is a natural limit to how much energy can be produced. Therefore, less energy-intensive processes are more sustainable.

The analysis must take in consideration the contributions of the energy to transport, the manufacturing process, support to labour, production of energy itself, but also contributions from end-of-life and complete emissions abatement.



Green Metrics in Energy (Chemical Process)

$$E_n = \frac{\text{total process energy (MJ)}}{\text{mass of product (kg)}}$$

$$E_{rs} = \frac{\text{total solvent recovery energy (MJ)}}{\text{mass of product (kg)}}$$

Level of energy performance of chemical process.

Level 0	**Base case**	**Energy requirement by an unimproved process, energy produced by a process and recovered is included.**
Level 1	**Benchmark heat integration**	**Minor improvements including heat exchange networks, improved solvents, incorporation of power generation**
Level 2	**Optimum heat integration**	**Optimized heat exchange flow sheet, change in process conditions that enable further heat integration (the basic aspects of the process such as catalysts, feedstock, etc. are the same as in the base case)**
Level 3	**Process redesign**	**The same reaction chemistry as in base case but can incorporate changes in feedstock, improved catalyst, different process configuration, alternative separation techniques.**
Level 4	**Theoretical energy requirement**	**Change of enthalpy of reaction at standard conditions assuming 100% yield.**

Environmental Performance Metrics in Chemical Manufacturing and for Chemical Products.

Manufacturing

Resource Related

Material intensity

- Percent first-pass yield
- Percent ultimate yield
- Percent process uptime
- Percent *atomic efficiency*
- Percent *post-consumer waste used*
- Material efficiency (unit consumptions, including water/pound of product)

Energy intensity

- BTUs/pound
- Total energy use
- *Minimum "practical" energy use*

Packaging

- Total kgs
- kgs/kg of product

Product Use

Material intensity

- *Value per kg*
- *Pounds replaced*
- *Resources saved*

Energy intensity

- *Value/BTU used*
- *Energy saved by use*

Renewable

- *Percent of product recyclable*

Environmental Performance Metrics in Chemical Manufacturing and for Chemical Products (2).

Manufacturing

Environmental-Burden Related

Environmental incidents

- Frequency
- Severity
- Practical worst-case scenario

Toxic dispersion

- Airborne toxics
- Carcinogens
- Volatile organics
- Particulates
- Acid gases
- "Hazardous" wastes
- Aquatic toxicity/oxygen demand
- Listed hazardous air (and water) pollutants
- TRI chemicals (EPCRA Title III Section 313)
- 33/50 chemicals

Product use

Packaging

- *Recyclable*
- *Biodegradable*

Toxic dispersion

- Global warming
- Ozone depletion
- *Persistence*
- *Bioaccumulative*
- *Hormone mimics*

Environmental Performance Metrics in Chemical Manufacturing and for Chemical Products (3).

Manufacturing

Environmental-Burden Related

Product stewardship

- "Responsible Care"
- Environmental audits

Illnesses and injuries

- Illness frequency
- Injury frequency
- *Employee "wellness"*

Hazardous materials handling

- Worker training

Product use

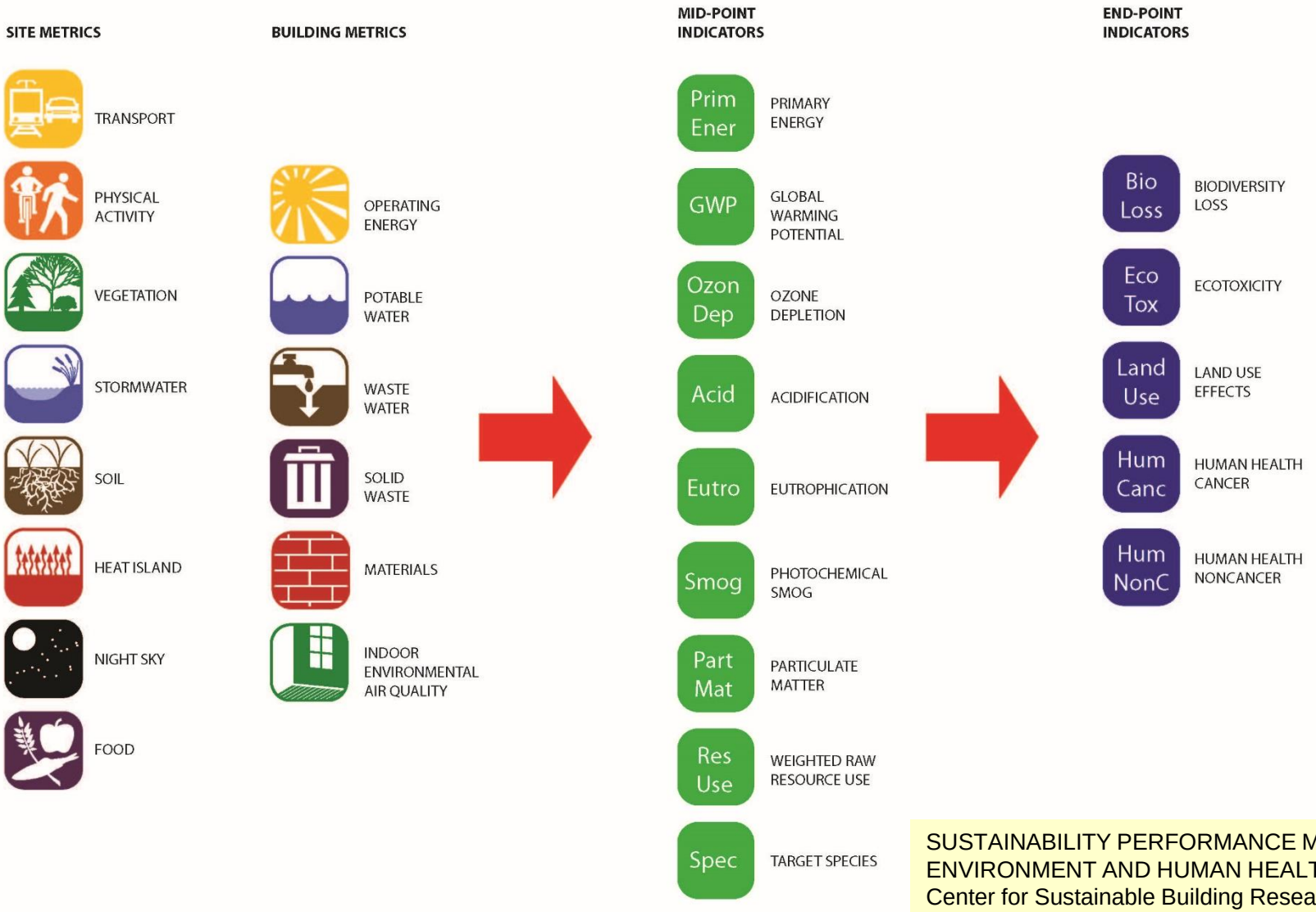
Product stewardship

- *"Responsible Care"*

Product stewardship

- Use warnings
- User training

Sustainability Performance Metrics of Buildings.



SUSTAINABILITY PERFORMANCE METRICS
ENVIRONMENT AND HUMAN HEALTH
Center for Sustainable Building Research
University of Minnesota

Indicators and the related Regulation criteria for assessing the economic, social and environmental impacts.

Domain	Sub-domain	Indicator	Regulation Criteria
Economic Impacts	**1.1 Production impacts**	I.1 Maximum value of production losses	AI S1 P4 a AI S1 P4 g AI S1 P4 i
		I.2 Share of EU production value affected	AI S1 P4 a
		I.3 Difficulty of eradication	AI S1 P4 h AI S1 P4 p
	1.2 Trade impacts	I.4 Number of importing countries expected to impose restrictions on trade	AI S1 P4 k
		I.5 Value of export losses	AI S1 P4 k
		I.6 Share of export losses over total reduction	AI S1 P4 k
		I.7 Trade dispersion	AI S1 P4 k
	1.3 Price and market impacts	I.8 Change in domestic price	AI S1 P4 j
		I.9 Change in domestic production over imports	AI S1 P4 j
	1.4 Impacts on other agents	I.10 Upstream effects	AI S1 P4 i
		I.11 Downstream effects	AI S1 P4 i
Social impacts	**2.1 Impact on employment**	I.12 Job losses	AI S1 P4 r AI S2 Pb i
	2.2 Impact on food security or food safety	I.13 Share of caloric supply	AI S1 P4q AI S2 Pb ii
		I.14 Share of protein supply	AI S1 P4 q AI S2 Pb ii
		I.15 Share of fat supply	AI S1 P4 q AI S2 Pb ii
		I.16. Ability to produce fungal toxins	AI S1 P4 q AI S2 Pb ii
	2.3 Impact on recreation, landscape or cultural heritage	I.17 Share of holdings with other gainful activities	AI S1 P4 s AI S2 Pb iii
		I.18 Products covered by EU quality labels	AI S1 P4 s AI S2 Pb iii
		I.19 Presence of affected hosts on cultural heritage landmarks	AI S1 P4 s AI S2 Pb iii
Environmental impacts	**3.1 Impact on street trees, parks and natural and planted areas**	I.20 Use of hosts as street trees and in parks	AI S1 P4 e
	3.2 Undesired impacts of control measures	I.21 Undesired effects of control measures	AI S1 P4 b AI S1 P4 d AI S1 P4 h AI S1 P4 m AI S1 P4 p AI S2 Pc ii
	3.3 Impact on biodiversity and ecosystem services	I.22 Soil erosion	AI S1 P4 o AI S2 Pc i
		I.23 Number of protected species and habitats related to hosts	AI S1 P4 o AI S2 Pc i
		I.24 Share of Natura 2000 area and sites affected	AI S1 P4 n AI S1 P4 o AI S1 P4 s AI S2 Pc iii
		I.25 Share under sustainable management practice	AI S1 P4 o AI S1 P4 s

Structure of Impact Indicator for Priority Pests (I2P2)

$$I2P2 = W_1\left(\Sigma\, w_{1j} \times X_{1j}\right)_{j=1,4} + W_2\left(\Sigma\, w_{2j} \times X_{2j}\right)_{j=1,3} + W_3\left(\Sigma w_{3j} \times X_{3j}\right)_{j=1,4}$$

W_1 1. Economic impact

w_{1j}	X_{1j}
$w_{1.1}$	1.1 Production impacts
$w_{1.2}$	1.2 Trade impacts
$w_{1.3}$	1.3 Price and market Impacts
$w_{1.4}$	1.4 Impacts in other agents

W_2 2. Social impact

w_{2j}	X_{2j}
$w_{2.1}$	2.1 Employment impact
$w_{2.2}$	2.2 Food security / food safety impacts
$w_{2.3}$	2.3 Recreation, landscape cultural heritage impacts

W_3 3. Environmental impact

w_{3j}	X_{3j}
$w_{3.1}$	3.1 Impact on street trees and parks
$w_{3.2}$	3.2 Impacts control measures
$w_{3.3}$	3.3 Impacts biodiversity and ecosystem services

$$\sum_{i=1}^{i=3} W_i = 100 \qquad \sum_{j=1}^{j=n} W_{ij} = 100 \;\forall\, i[1,3]$$

JRC Technical Report “The Impact Indicator for Priority Pests (I2P2): a tool for ranking pests according to Regulation (EU) No 2016/2031” - https://ec.europa.eu/jrc

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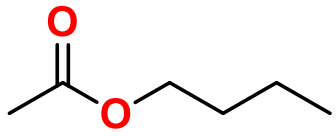
Exam Question

Butyl ethanoate is an ester used as a flavouring.
This ester can be synthesised from butan-1-ol by two different processes.

Process 1 is a one-step process that involves a **reversible reaction.**

$CH_3CH_2CH_2CH_2OH + CH_3COOH \rightleftarrows CH_3COOCH_2CH_2CH_2CH_3 + H_2O$

6.25 g of butan-1-ol forms **6.57 g** of butyl ethanoate.



Calculate
The percentage yield for **process 1** **67.1%.**
The atom economy for **process 1** **86.6%.**

$CH_3CH_2CH_2CH_2OH + CH_3COOH \rightarrow CH_3COOCH_2CH_2CH_2CH_3 + H_2O$

6.25 g (MW = 74 $g \cdot mol^{-1}$) 6.57 g (MW = 116 $g \cdot mol^{-1}$)

mol 6.25 / 74 = 0.0845 6.57/116 = 0.0566

% yield = 0.0566/0.0845 = **67.1 %**

MW of all reactants (= *M*W of all products) is 134.0 (*M*W of product) is 116.0

Atom Economy = 100 × 116.0/134.0 = **86.6%.**

Exam Question

Process 2 is a two-step process.

$CH_3COOH + SOCl_2 \rightarrow CH_3COCl + SO_2 + HCl$

$CH_3CH_2CH_2CH_2OH + CH_3COCl \rightarrow CH_3COOCH_2CH_2CH_2CH_3 + HCl$

5.450 grams of ethanoic acid produces 9.806 g of Butyl ethanoate

The overall percentage yield for **process 2** is: **93.1%.**
The overall atom economy for **process 2** is: **45.8%.**

	CH_3COOH	→	$CH_3COOCH_2CH_2CH_2CH_3$
	5.450 g (MW = 60)		9.806 g (MW = 116)
mol	5.45 / 60 = 0.0908		9.806 / 116 = 0.0845

Yield % = 0.0845 / 0.0908 = **93.1 %**

Total mass of products = 64 + 2 × 36.5 + 116 = 253
Total mass of reactants = 60 + 74 + 119 = 253

The atom economy is 116 / 253 = **45.8 %**

Exam Question

1) Explain why process **2** has a high % yield but a low atom economy.

- Link between yield AND explanation required: (high percentage) yield shows a high % conversion (of reactants into products)
- Link between atom economy AND explanation required: (low) atom economy shows a lot of waste (product) OR (low) atom economy shows not much desired product

2) Suggest two reasons why butyl ethanoate is manufactured by process **1** rather than by process **2**.

ANY TWO FROM - Comparison essential throughout:

- Less waste (products) OR higher atom economy
- Less toxic reactants OR less toxic (waste) products, OR less corrosive reactants, OR less corrosive (waste) products, OR less harmful reactants, OR less harmful (waste) products, OR less hazardous reactants, OR less hazardous (waste) products,
- Cheaper starting materials, OR more readily available starting materials.

  Fewer steps OR one step rather than two steps.