



# METRICS



Image: Wikimedia Commons, Life Cycle Thinking,  
Author: The National Institute of Standards and Technology (NIST)



## Topics To Be Covered

1. Why do we need metrics in green chemistry?
2. Established Metrics in Green Chemistry
  - Atom Economy
  - Environmental (E) Factor
  - Atom Utilization
  - Reaction Mass Efficiency
3. Additional Metrics Used in Green Chemistry
  - Process Mass Intensity
  - Life Cycle Assessment
  - Ecological Indicator/Ecological Footprint

# CONVENTIONAL METRICS: PERCENT YIELD

**Percent yield:**  $\% \text{ yield} = (\text{actual yield}/\text{theoretical yield}) \times 100$

## What is missing?

- What co-products are made?
- How much waste is generated?
- Is the waste benign waste?
- How much energy is required?
- Are purification steps needed?
- What solvents are used? (are they benign and/or reusable?)
- Is the “catalyst” truly a catalyst? (stoichiometric vs. catalytic)

## 1. Atom economy (atom efficiency)

$$\text{Atom Economy} = \frac{\text{Mass of desired product*}}{\text{Mass of all reactants*}}$$

*\*including the stoichiometric coefficient*

## 2. Environmental (E) factor

$$\text{E-factor} = \text{total waste (g)} / \text{product (g)}$$

## 3. Atom utilization (variation of atom economy)

$$\% \text{ Atom Utilization} = (\text{MW of desired product} / \text{MW of all products}) \times 100$$

## 4. Reaction mass efficiency (RME)

$$(\text{mass of product C} / (\text{mass of A} + \text{mass of B})) \times 100$$

# ADDITIONAL METRICS USED IN GREEN CHEMISTRY



## 5. Process Mass Intensity (PMI)

The total mass of materials to the mass of the isolated product.

## 6. Life Cycle Assessment (LCA)

An assessment of environmental impacts associated with all of the stages of a product's life.



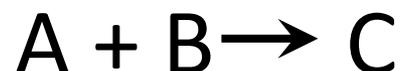
Barry M. Trost  
Stanford University

Atom-Economy is a calculation based on the overall balanced chemical equation. It is simply the mass of desired product divided by the total mass of products.

Or, since the mass of products equals the mass of reactants in a balanced chemical equation, atom economy is the mass of desired product divided by the total mass of reactants.



## Single Stage Process:



$$AE = \left( \frac{\text{m.w. of product C}}{\text{m.w. of A} + \text{m.w. of B}} \right) \times 100$$

m.w. = molecular weight



## Multi-Stage Process:



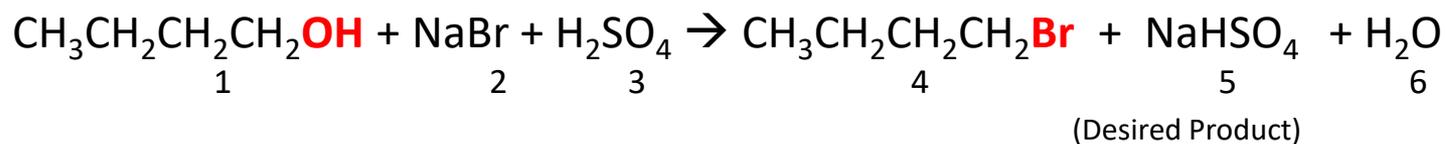
$$AE = \left( \frac{\text{m.w. of product G}}{\text{m.w. of A} + \text{m.w. of B} + \text{m.w. of D} + \text{m.w. of F}} \right) \times 100$$

# ATOM ECONOMY: EXAMPLE ONE



$$\text{Atom Economy} = \frac{\text{Mass of desired product*}}{\text{Mass of all reactants*}}$$

*\*including the stoichiometric coefficient*



$$\text{Atom Economy} = \frac{137}{(74.12 + 102.91 + 98.08)} \times 100\%$$

$$\text{Atom Economy} = 49.8 \%$$

| Reagent             | $M_w$ (g mol <sup>-1</sup> ) |
|---------------------|------------------------------|
| 1 (Reactant)        | 74.12                        |
| 2 (Reactant)        | 102.91                       |
| 3 (Reactant)        | 98.08                        |
| 4 (Desired Product) | 137                          |

275.11 g mol<sup>-1</sup>

# ATOM ECONOMY EXAMPLE TWO: IBUPROFEN SYNTHESIS

## GREEN CHEMISTRY



### ***The Problem:***

The traditional industrial synthesis of ibuprofen was developed and patented by the Boots Company of England in the 1960s (U.S. Patent 3,385,886). This synthesis is **a six-step process** and **results in large quantities of unwanted waste** chemical byproducts that must be disposed of or otherwise managed. Much of the waste that is generated is a result of **many of the atoms of the reactants not being incorporated into the desired product** (ibuprofen) but into unwanted byproducts (poor atom economy/atom utilization). The process also uses a variety of solvents, and catalysts (if any) are not used in stoichiometric amounts.

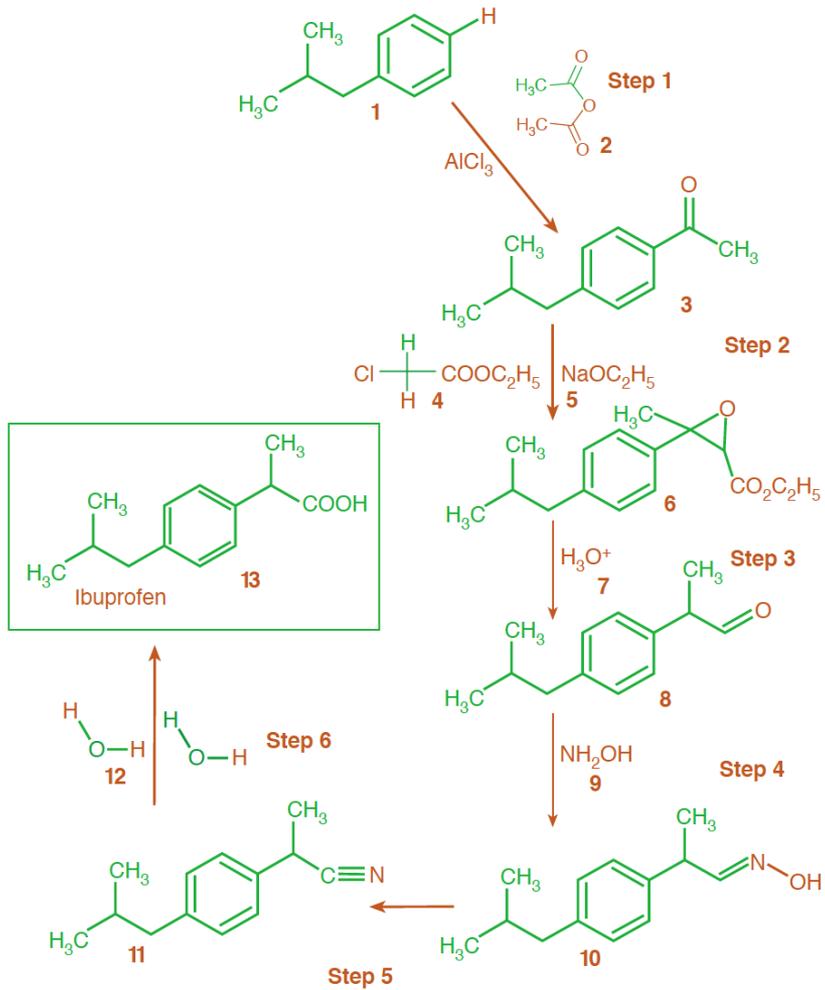
### ***The Solution:***

The BHC Company has developed and implemented a new greener industrial **synthesis of ibuprofen that is only three steps** (U.S. Patents 4,981,995 and 5,068,448, both issued in 1991). In this process, **most of the atoms of the reactants are incorporated into the desired product** (ibuprofen). This results in only small amounts of unwanted byproducts (very good atom economy/atom utilization) thus lessening the need for disposal and mediation of waste products. There are other environmental advantages to the green synthesis versus the brown synthesis, including solvents and catalyst.

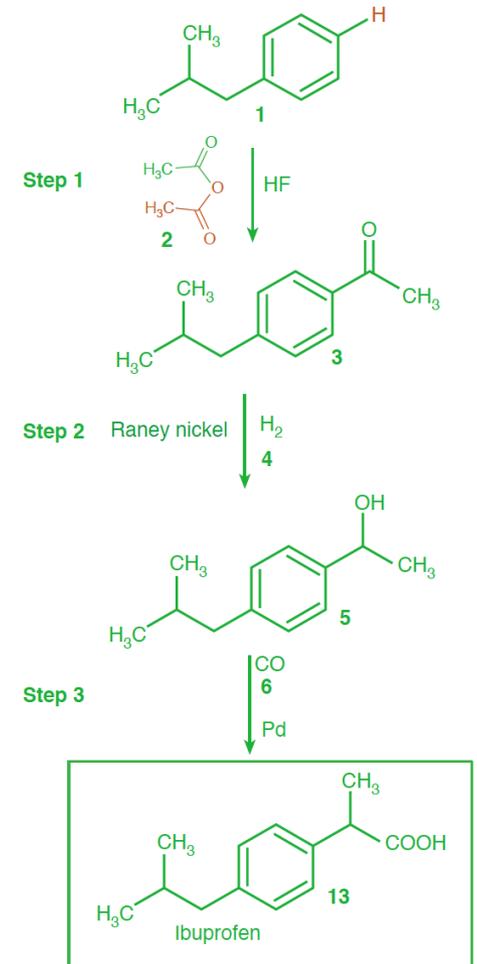
- from Cann, M.C.; and Connelly, M.E. Real World Cases in Green Chemistry, American Chemical Society: Washington, DC, 2000



# GREEN CHEMISTRY

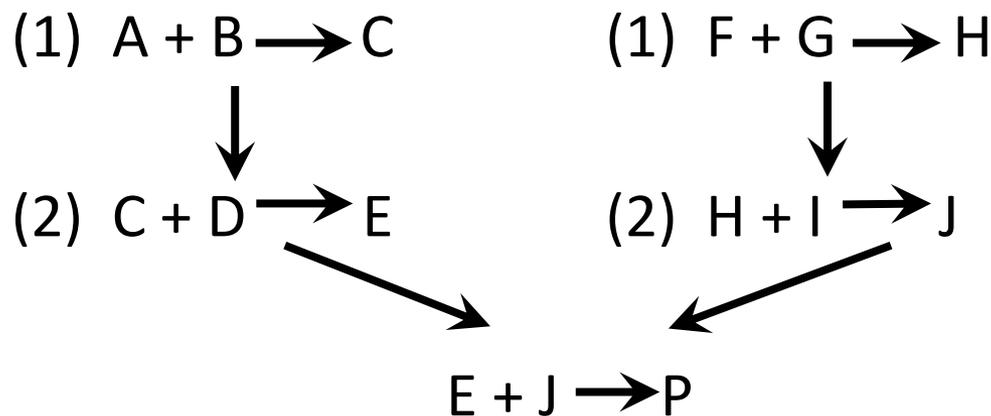


## Ibuprofen Synthesis



[www.chemed.org](http://www.chemed.org)





$$\text{AE} = \left( \frac{\text{m.w. of product P}}{\sum (\text{m.w. of A, B, D, F, G, I})} \right) \times 100$$

# EXERCISE: CALCULATE AE OF THE GREENER SYNTHESIS OF IBUPROFEN



| Reagent   |     | Utilized in ibuprofen |    | Unutilized in ibuprofen |    |
|---|-----|-----------------------|----|-------------------------|----|
| Formula   | FW  | Formula               | FW | Formula                 | FW |
| <b>1</b> C <sub>10</sub> H <sub>14</sub>              | 134 |                       |    |                         |    |
| <b>2</b> C <sub>4</sub> H <sub>6</sub> O <sub>3</sub> | 102 |                       |    |                         |    |
| <b>4</b> H <sub>2</sub>                               | 2   |                       |    |                         |    |
| <b>6</b> CO   | 28  |                       |    |                         |    |
| <b>Total</b>  |     |                       |    |                         |    |
| C <sub>15</sub> H <sub>22</sub> O <sub>4</sub>        | 266 |                       |    |                         |    |

Percentage Atom Economy

# EXERCISE: CALCULATE AE OF THE GREENER SYNTHESIS OF IBUPROFEN



| Reagent   |     | Utilized in ibuprofen                        |    | Unutilized in ibuprofen |    |
|---|-----|--|----|-------------------------|----|
| Formula   | FW  | Formula                                      | FW | Formula                 | FW |
| <b>1</b> C <sub>10</sub> H <sub>14</sub>              | 134 | C <sub>10</sub> H <sub>13</sub>              |    |                         |    |
| <b>2</b> C <sub>4</sub> H <sub>6</sub> O <sub>3</sub> | 102 | C <sub>2</sub> H <sub>3</sub> O <sub>1</sub> |    |                         |    |
| <b>4</b> H <sub>2</sub>                               | 2   | H <sub>2</sub>                               |    |                         |    |
| <b>6</b> CO   | 28  | CO   |    |                         |    |
| <b>Total</b>  |     |  |    |                         |    |
| C <sub>15</sub> H <sub>22</sub> O <sub>4</sub>        | 266 |  |    |                         |    |

Percentage Atom Economy = (FW ibuprofen/ FW of all reactants) × 100

# EXERCISE: CALCULATE AE OF THE GREENER SYNTHESIS OF IBUPROFEN



| Reagent   |     | Utilized in ibuprofen                        |     | Unutilized in ibuprofen                      |    |
|---|-----|--|-----|--|----|
| Formula   | FW  | Formula                                      | FW  | Formula                                      | FW |
| <b>1</b> C <sub>10</sub> H <sub>14</sub>              | 134 | C <sub>10</sub> H <sub>13</sub>              | 133 | H  | 1  |
| <b>2</b> C <sub>4</sub> H <sub>6</sub> O <sub>3</sub> | 102 | C <sub>2</sub> H <sub>3</sub> O <sub>1</sub> | 43  | C <sub>2</sub> H <sub>3</sub> O <sub>2</sub> | 59 |
| <b>4</b> H <sub>2</sub>                               | 2   | H <sub>2</sub>                               | 2   | —  | 0  |
| <b>6</b> CO   | 28  | CO   | 28  | —  | 0  |
| <b>Total</b>  |     |  |     |  |    |
| C <sub>15</sub> H <sub>22</sub> O <sub>4</sub>        | 266 |  |     |  |    |

Percentage Atom Economy = (FW ibuprofen/ FW of all reactants) × 100

# EXERCISE: CALCULATE AE OF THE GREENER SYNTHESIS OF IBUPROFEN



| Reagent   |     | Utilized in ibuprofen                          |     | Unutilized in ibuprofen                      |    |
|---|-----|--|-----|--|----|
| Formula   | FW  | Formula  | FW  | Formula                                      | FW |
| <b>1</b> C <sub>10</sub> H <sub>14</sub>              | 134 | C <sub>10</sub> H <sub>13</sub>                | 133 | H  | 1  |
| <b>2</b> C <sub>4</sub> H <sub>6</sub> O <sub>3</sub> | 102 | C <sub>2</sub> H <sub>3</sub> O <sub>1</sub>   | 43  | C <sub>2</sub> H <sub>3</sub> O <sub>2</sub> | 59 |
| <b>4</b> H <sub>2</sub>                               | 2   | H <sub>2</sub>                                 | 2   | —  | 0  |
| <b>6</b> CO   | 28  | CO   | 28  | —  | 0  |
| <b>Total</b>  |     | <b>Ibuprofen</b>                               |     | <b>Waste Products</b>                        |    |
| C <sub>15</sub> H <sub>22</sub> O <sub>4</sub>        | 266 | C <sub>13</sub> H <sub>18</sub> O <sub>2</sub> | 206 | C <sub>2</sub> H <sub>4</sub> O <sub>2</sub> | 60 |

Percentage Atom Economy = (FW ibuprofen/ FW of all reactants) × 100 = (206/266) × 100 = 77%

# THE BROWN SYNTHESIS OF IBUPROFEN

## GREEN CHEMISTRY



| Reagent   |       | Utilized in ibuprofen                          |     | Unutilized in ibuprofen                             |       |
|---|-------|--|-----|---|-------|
| Formula   | FW    | Formula  | FW  | Formula   | FW    |
| <b>1</b> C <sub>10</sub> H <sub>14</sub>                | 134   | C <sub>10</sub> H <sub>13</sub>                | 133 | H   | 1     |
| <b>2</b> C <sub>4</sub> H <sub>6</sub> O <sub>3</sub>   | 102   | C <sub>2</sub> H <sub>3</sub>                  | 27  | C <sub>2</sub> H <sub>3</sub> O <sub>3</sub>        | 75    |
| <b>4</b> C <sub>4</sub> H <sub>7</sub> ClO <sub>2</sub> | 122.5 | CH   | 13  | C <sub>3</sub> H <sub>6</sub> ClO <sub>2</sub>      | 109.5 |
| <b>5</b> C <sub>2</sub> H <sub>5</sub> ONa              | 68    |  | 0   | C <sub>2</sub> H <sub>5</sub> ONa                   | 68    |
| <b>7</b> H <sub>3</sub> O                               | 19    |  | 0   | H <sub>3</sub> O                                    | 19    |
| <b>9</b> NH <sub>3</sub> O                              | 33    |  | 0   | NH <sub>3</sub> O                                   | 33    |
| <b>12</b> H <sub>4</sub> O <sub>2</sub>                 | 36    | HO <sub>2</sub>                                | 33  | H <sub>3</sub>                                      | 3     |
| <b>Total</b>  |       | <b>Ibuprofen</b>                               |     | <b>Waste products</b>                               |       |
| C <sub>20</sub> H <sub>42</sub> NO <sub>10</sub> ClNa   | 514.5 | C <sub>13</sub> H <sub>18</sub> O <sub>2</sub> | 206 | C <sub>7</sub> H <sub>24</sub> NO <sub>8</sub> ClNa | 308.5 |

Percentage Atom Economy = (FW ibuprofen/FW all reactants) × 100 = (206/514.5) × 100 = 40%

[www.rhenkullensing.org](http://www.rhenkullensing.org)



# “INHERENT” ATOM ECONOMY OF REACTION CLASSES



| Some Atom Economic Reactions | Some Atom Un-Economic Reactions |
|------------------------------|---------------------------------|
| Rearrangement                | Substitution                    |
| Addition                     | Elimination                     |
| Diels-Alder                  | Wittig                          |
| Other concerted reactions    | Grignard                        |

# ENVIRONMENTAL FACTOR (E-FACTOR)

- ❑ Depends on the definition of waste
  - Non-recoverable starting materials, solvent, catalysts.
  - Undesired side products.
- ❑ Smaller E-factor means closer to zero waste
- ❑ E-factor can be used to estimate/calculate the total waste generated:
  - Amount of Waste = Amount of Product x E-factor

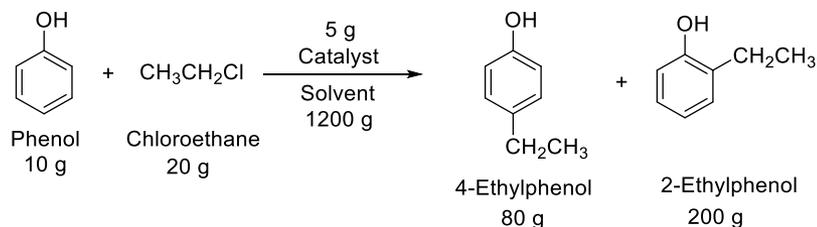
$$\text{E-factor} = \text{total waste (g)} / \text{product (g)}$$

| Industry sector | Annual production (t) | E-factor | Waste produced (t)              |
|-----------------|-----------------------|----------|---------------------------------|
| Oil refining    | $10^6$ - $10^8$       | Ca. 0.1  | $10^5 - 10^7$                   |
| Bulk chemicals  | $10^4$ - $10^6$       | <1-5     | $10^4 - 5 \times 10^6$          |
| Fine chemicals  | $10^2$ - $10^4$       | 5-50     | $5 \times 10^2 - 5 \times 10^5$ |
| Pharmaceuticals | $10$ - $10^3$         | 25-100   | $2.5 \times 10^2 - 10^5$        |

# E-FACTOR EXAMPLE

## Friedel-Craft Alkylation (Substitution)

All numbers represent the mass of the chemical after the reaction.



| Phenol | Chloroethane | Catalyst | Solvent | 4-Ethylphenol | 2-Ethylphenol | E-Factor | *3-ton scale |
|--------|--------------|----------|---------|---------------|---------------|----------|--------------|
| 10     | 20           | 5        | 1200    | 80            | 200           | 6.575    | 19.725       |

E-factor = total waste (g) / product (g)

Industrial reactions are run on the big scale, so assuming 3 tons of product, this is the new atom economy



For the generic reaction  $A + B \rightarrow C$

$$\text{RME} = \left( \frac{\text{mass of product C}}{\text{mass of A} + \text{mass of B}} \right) \times 100$$

# COMPARISON OF ATOM ECONOMY AND REACTION MASS EFFICIENCY FOR 28 DIFFERENT CHEMICAL REACTIONS



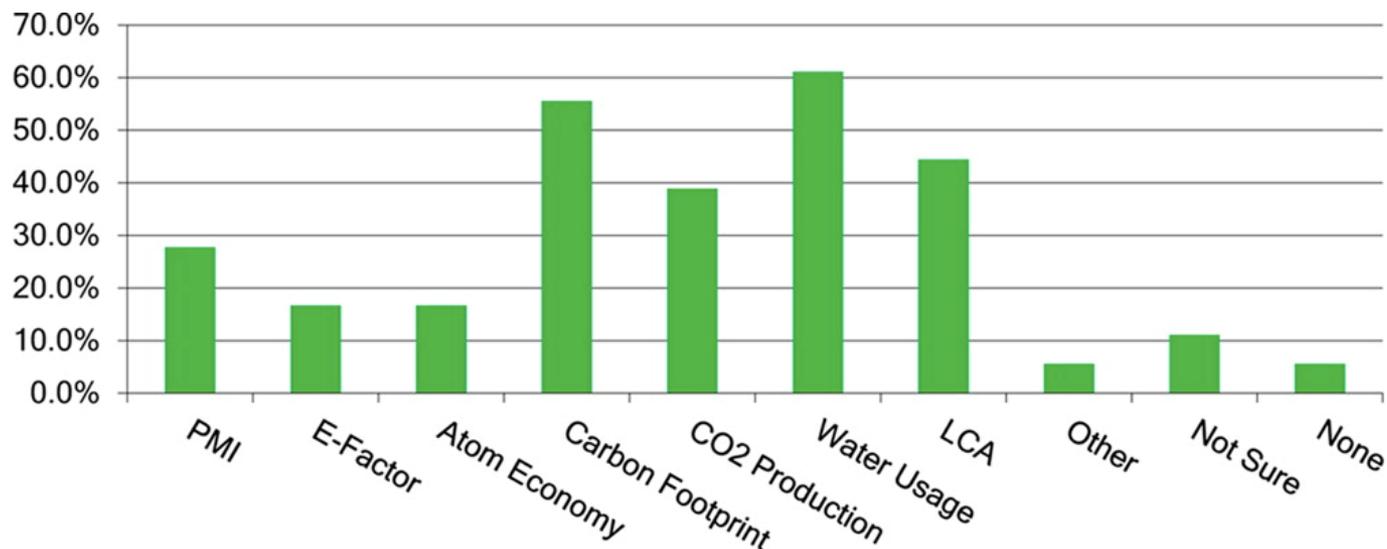
| Chemistry Type/Reagents | Atom Economy (%) | Reaction Mass Efficiency (%) | Chemistry Type | Atom Economy (%) | Reaction Mass Efficiency (%) |
|-------------------------|------------------|------------------------------|----------------|------------------|------------------------------|
| Resolution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

$$\text{PMI} = \frac{\text{total mass used in the synthesis (kg)}}{\text{mass of product (kg)}}$$

- PMI accounts for yield, reaction and reagent stoichiometry, catalysts and solvents.
- This includes everything that you put into the flask, but usually excludes water.
- Ideal PMI = low values (~1)

# GREEN CHEMISTRY-RELATED METRICS USED IN CHEMICAL MANUFACTURING

## GREEN CHEMISTRY



Chemical manufacturer responses ( $n = 18$ ) to the 2012 Roundtable survey question **“What green chemistry and engineering related metrics does your company use? Select all that apply.”**

Percentage of respondents indicating one or more metrics surveyed in use computed as the ratio of [total responses – (not sure + none)]/(total responses). PMI = process mass intensity = (mass of raw materials)/(mass of final product). E-factor = (mass of waste)/mass of final product). LCA = life cycle assessment.

**Implementing Green Chemistry in Chemical Manufacturing: A Survey Report** Robert J. Giraud, Paul A. Williams, Amit Sehgal, Ettigounder Ponnusamy, Alan K. Phillips, and Julie B. Manley  
*ACS Sustainable Chemistry & Engineering* 2014 2 (10), 2237-2242

[www.rhinkalliance.org](http://www.rhinkalliance.org)





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2. Established Metrics in Green Chemistry
  - Atom Economy
  - Environmental (E) Factor
  - Atom Utilization
  - Reaction Mass Efficiency
3. Additional Metrics Used in Green Chemistry
  - Process Mass Intensity
  - Life Cycle Assessment
  - Ecological Indicator/Ecological Footprint



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**GREEN  
CHEMISTRY**



# THANK YOU!

## QUESTIONS?

This training material was developed in close collaboration with the **Center for Green Chemistry and Green Engineering** at Yale University.

[www.greenchemistry-toolkit.org](http://www.greenchemistry-toolkit.org)



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# Atom Economic Reactions

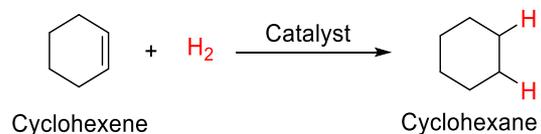
The “Good”

# Addition

Adding something to a molecule



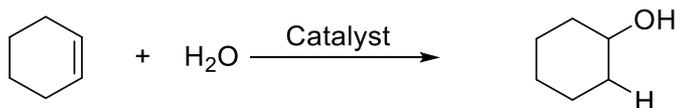
- Hydrogenation



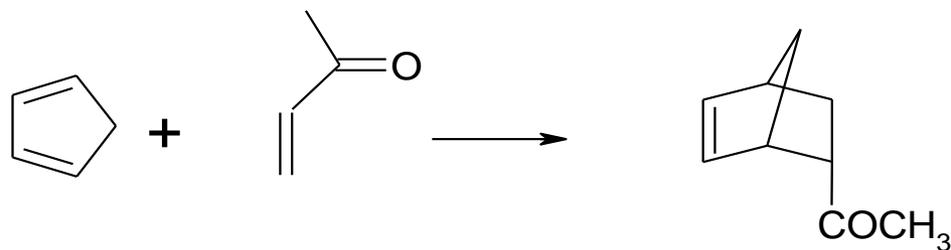
- Chlorination or Bromination on alkene



- Hydration



# Diels Alder Reactions



- ❑ An excellent way of forming 2 C-C bonds simultaneously.
- ❑ Concerted mechanism; highly regio- and stereoselective.
- ❑ Some reactions can be carried out in water or ionic liquids, which may also act as catalyst.



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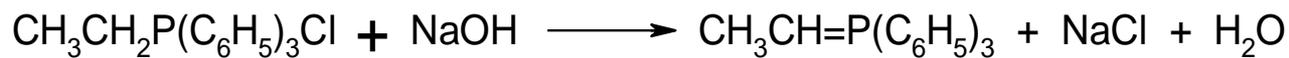
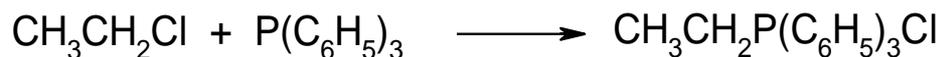


## Low atom economy reactions

The “Bad”

# Wittig Reactions

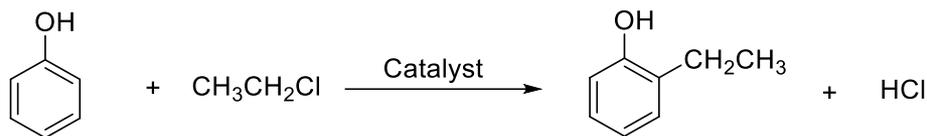
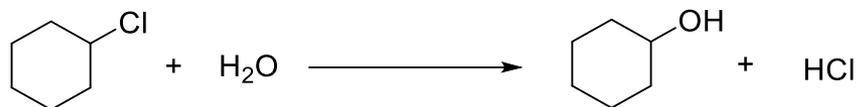
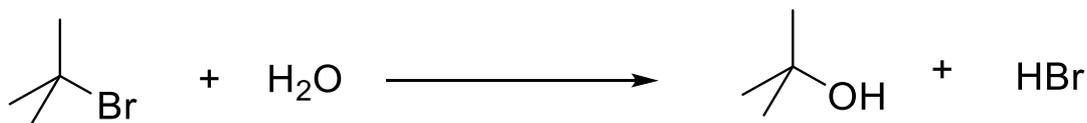
- A versatile method of preparing alkenes with an unambiguously placed double bond - gives high yields and takes place under mild conditions. Used for manufacture of vitamins and pharmaceuticals.



- Expensive because of poor atom economy, which is due to production of triphenylphosphine oxide (MWt 278).

# Substitution

Trading some parts of the molecule with another molecule

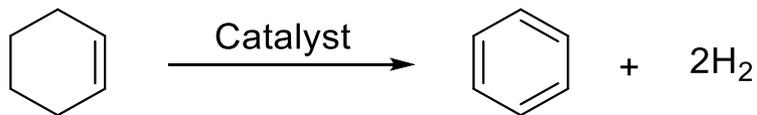


Friedel-Craft Reaction  
(Electrophilic Aromatic Substitution)

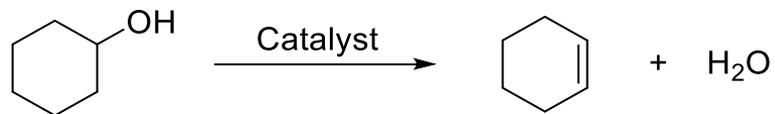
# Elimination

Taking part of a molecule out

- $A \rightarrow B + C$  or more
- Dehydrogenation



- Dehydroxylation



- Dehalogenation

