# Sustainable Industrial Synthesis of Agrochemicals

E.Godineau

November 2025

Classification: PUBLIC

# About me

| | |
|---|---|
| **2001- 2003** | Engineering School – Montpellier – France |
| **2002-2003** | Master of Science, Univ. Fredericton (Canada), Advisor Prof. Dr. David MaGee *Methodology, enantioselective catalysis* |
| **2003-2007** | PhD Univ. of Bordeaux Prof. Dr. Yannick Landais *Radical chemistry* |
| **2007-2009** | Post-Doc Max Planck, Mülheim a.d. Ruhr, Prof. Dr. Alois Fürstner *Total synthesis of natural products* |
| **2009–2014** | Syngenta Crop Protection AG, Stein, Switzerland, Team Leader Process Chemistry |
| **2014–2019** | Syngenta Crop Protection AG, Stein, Switzerland, Group Leader Process Chemistry |
| **2019-** | Syngenta Crop Protection AG, Stein, Switzerland, Syngenta Fellow Process Chemistry/Digital Chemistry |

Interests: Organic Synthesis, Process Chemistry, Sustainability, Data Science, Cheminformatics, Software Development

# Lecture Objectives & Key Takeaways

I will:

Provide a real-world perspective on large-scale chemistry in the agrochemical industry, where we manufacture products at 1,000-10,000 tons per year

My objectives is that you:

1. Recognize that industrial chemistry involves optimizing MANY factors simultaneously, not just reaction yield. Remembering all of them is NOT the objective. But rather to get you aware of the complexity.
2. Share concrete example of a few key criteria that drive decision-making in large-scale chemical agrochemical manufacturing. Shared using examples
3. Understand the relationship between sustainability and economics (they often align, but not always)

Key output: you take home a critical, multi-dimensional mindset when evaluating chemical processes for scale-up

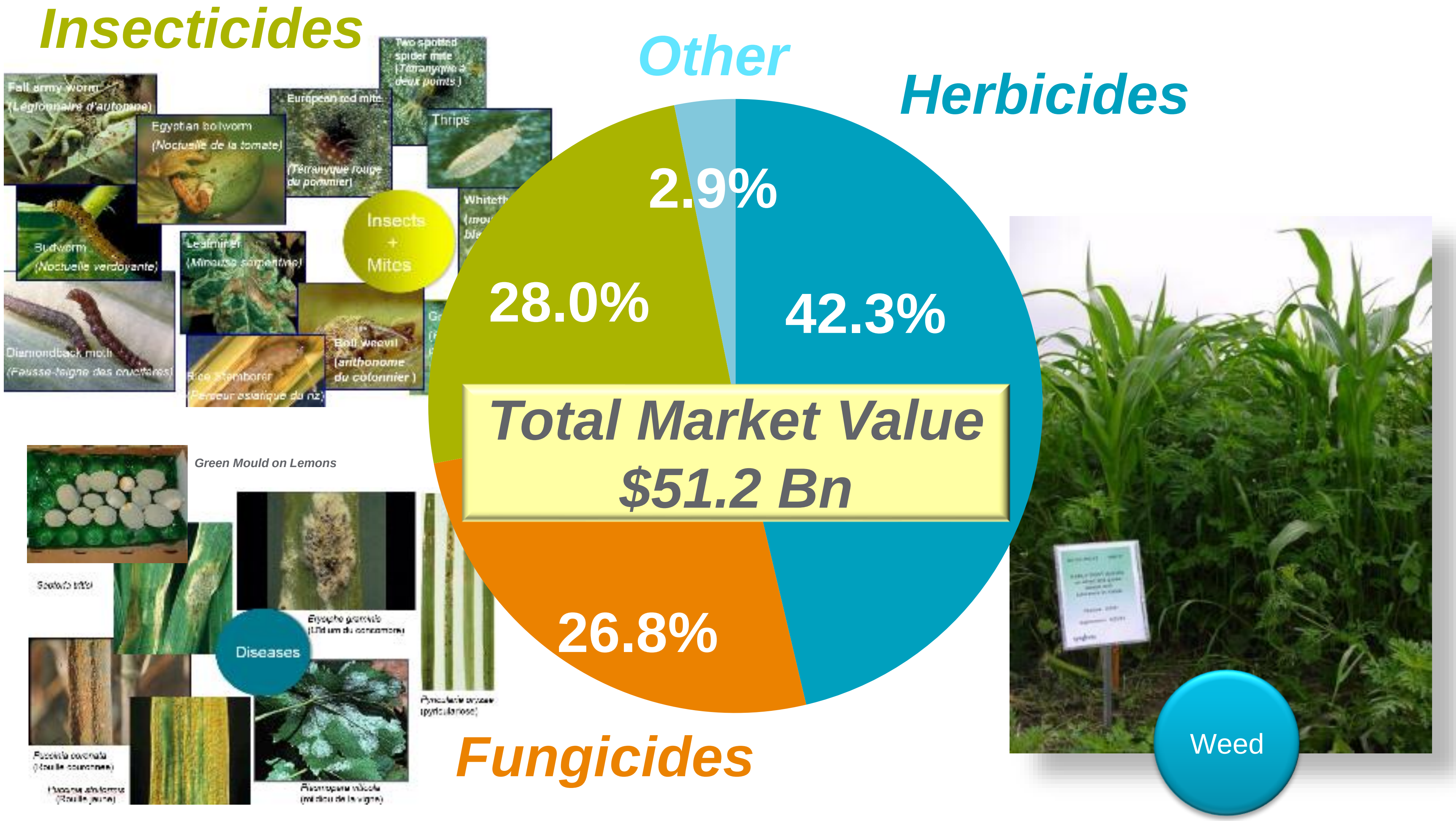
# What is an Agrochemical?

A chemical which can safely be applied to a crop in order to give the farmer:

- Higher yields
- Better quality product
- Reliability
- Ease of harvest

Agrochemicals include **insecticides**, **fungicides** and **herbicides** which are collectively known as pesticides or crop protection products.

# Crop Protection Market 2016



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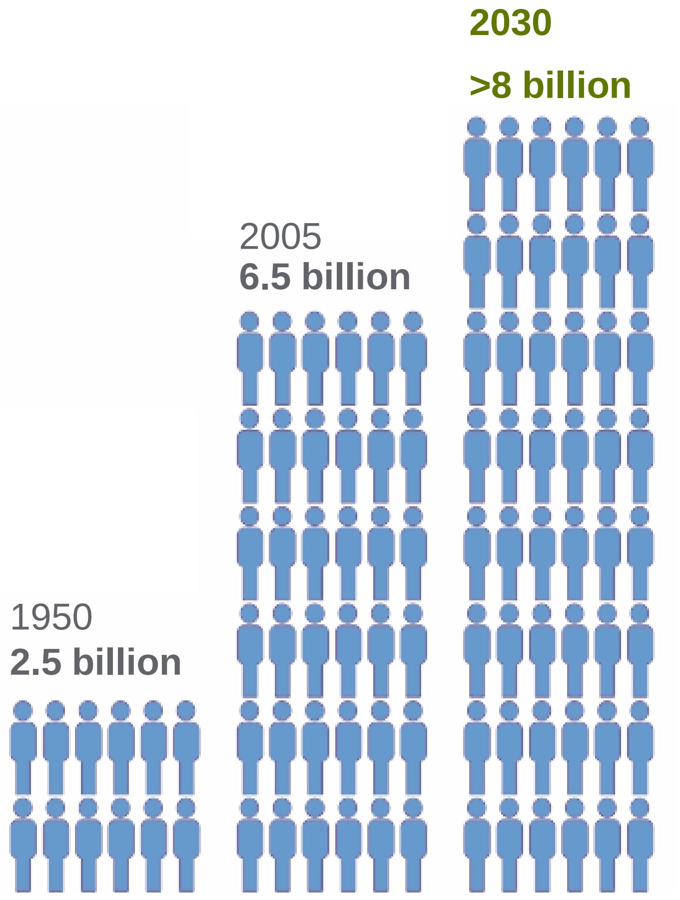
* Source: Phillips McDougall – AgriService 2016

# Demand is driven by population growth and land scarcity

## World population



1950
**2.5 billion**

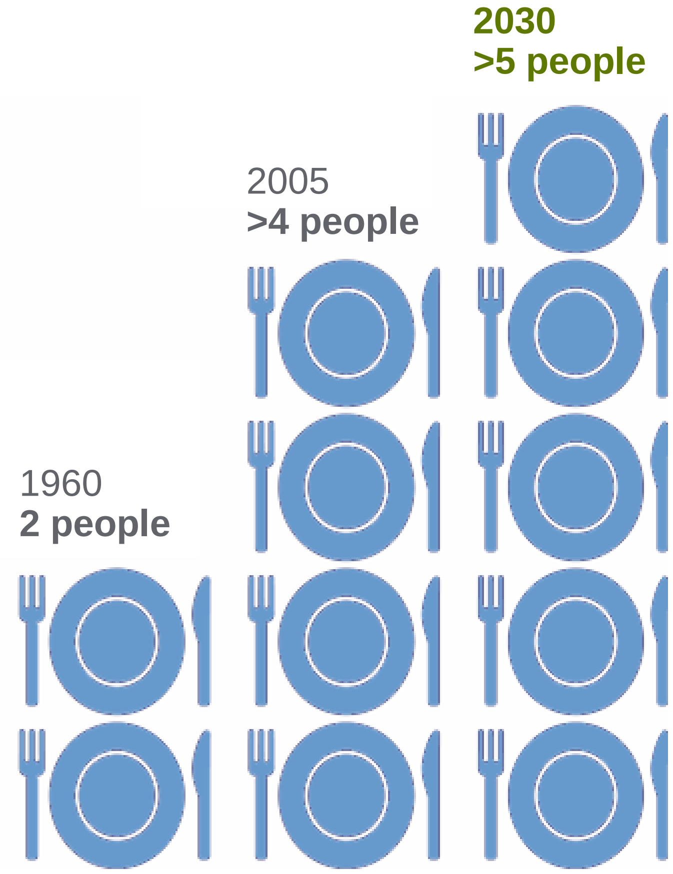
2005
**6.5 billion**

**2030**

**>8 billion**

Source: FAO, World Bank statistics, Syngenta

## People fed per hectare



1960
**2 people**

2005
**>4 people**

**2030**
**>5 people**

www.menti.com

71 95 70 73

link

# Food security

Figure 9: Growth in population, crop production, crop areas and yields 1960-2016

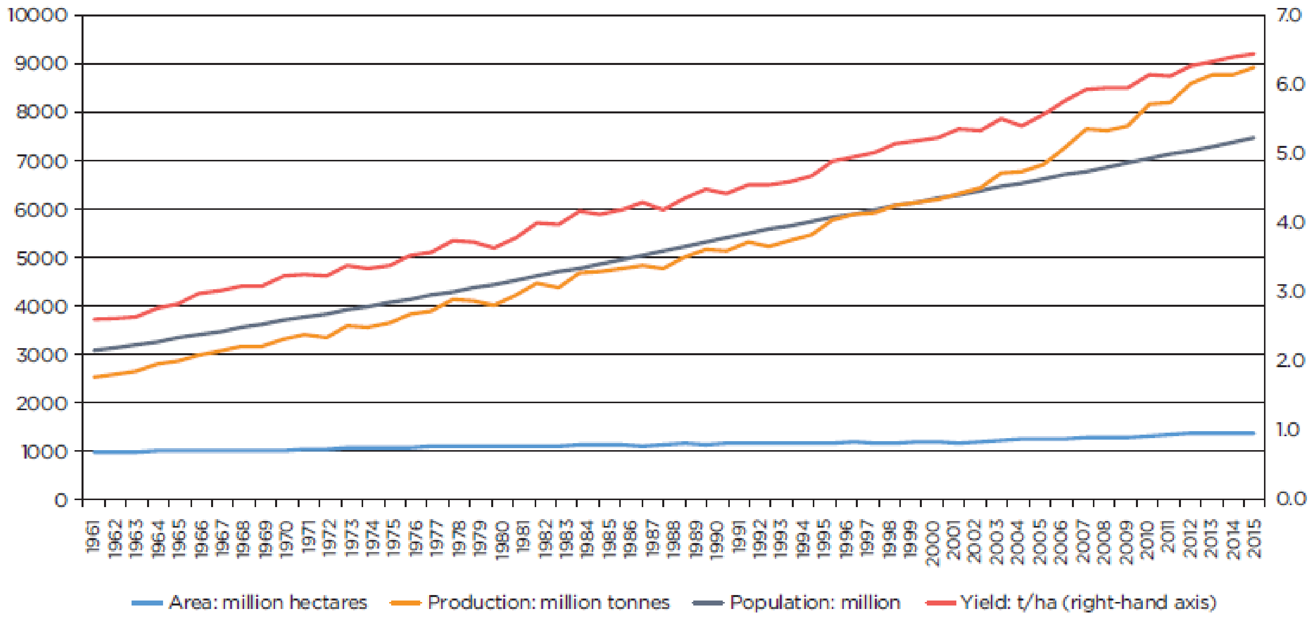
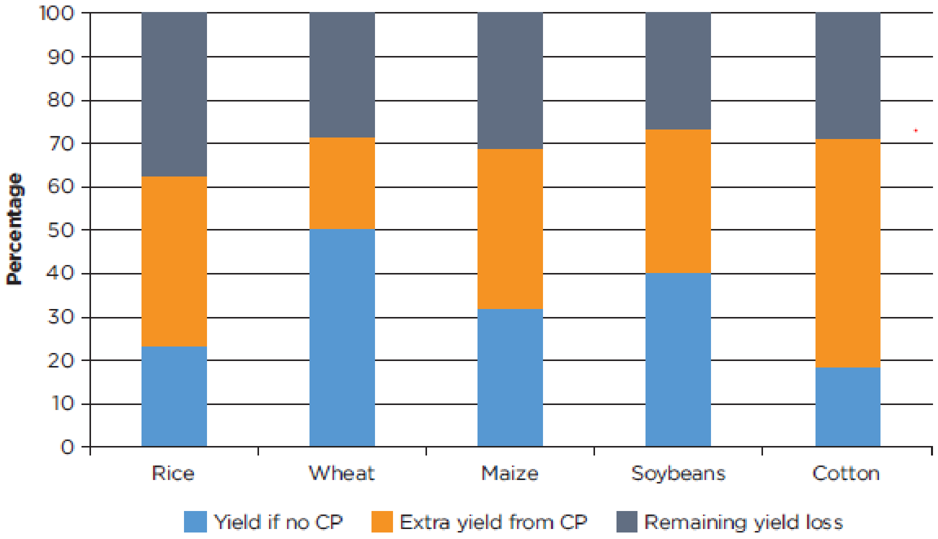


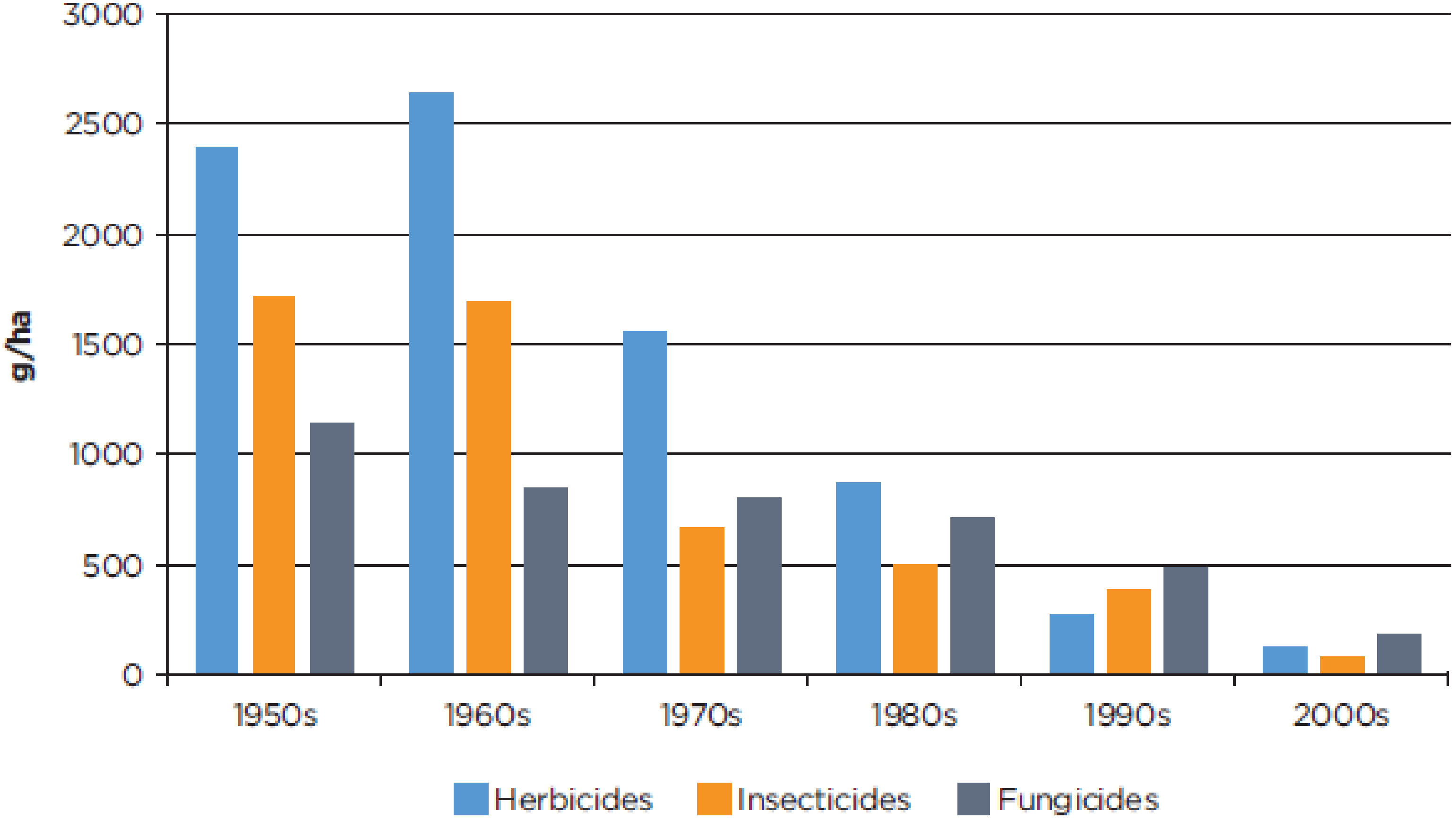
Figure 10: Yield losses with and without crop protection products



Source: Phillips McDougall analysis 2017

# Agrochemical Efficacy

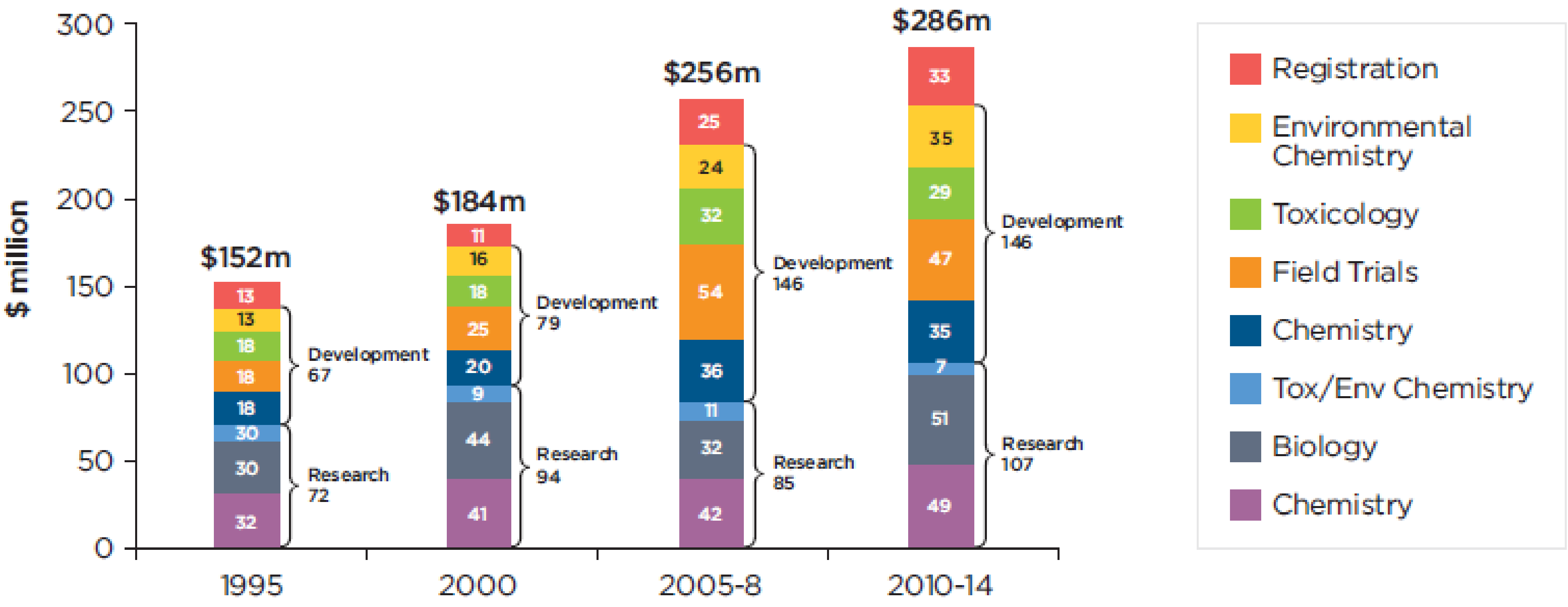
Figure 5: Average active ingredient application rates over time



Source: Phillips McDougall analysis 2017

# How much does it cost to develop a new agrochemical?

Figure 6: Discovery and development costs of a new crop protection product



Source: Phillips McDougall analysis 2017

# How much does it cost to develop a new agrochemical?

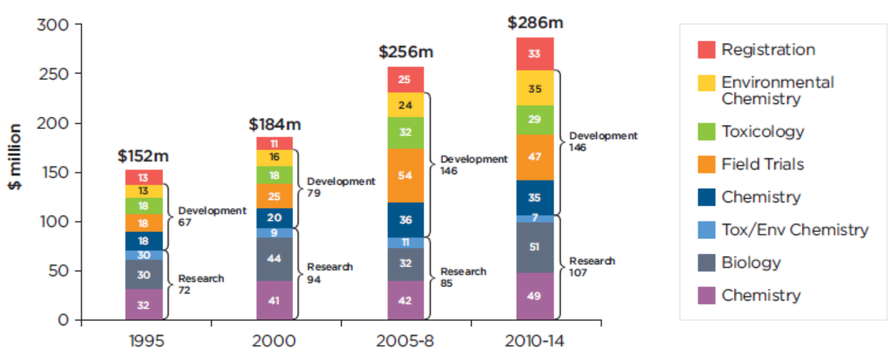


Figure 6: Discovery and development costs of a new crop protection product

High-Level sketch representation of the journey to bring a small molecule to market

Research

Development

Commercialisation

Source: Phillips McDougall analysis 2017

# Sustainable Agriculture

UN: 9 billion people by 2050

UN Food and Agriculture Organization (FAO) estimates that **farmers will have to produce significantly more food by 2050** to meet the needs of the world's population,

Challenge: **Tackle climate change and protecting finite natural resources**.

A 2018 study estimated a 2°C temperature rise in global mean surface temperatures would result in **yield losses** due to insects of 31% for corn, 19% for rice and 46% for wheat.

Source: Phillips McDougall analysis 2017

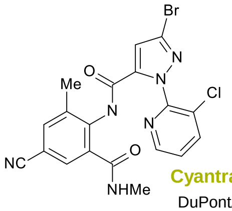
www.menti.com

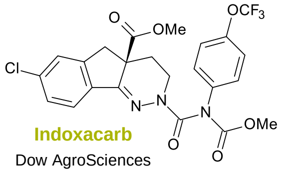
71 95 70 73

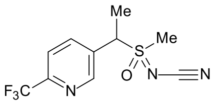
link

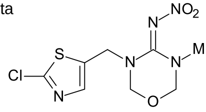
# Examples of recent agrochemicals

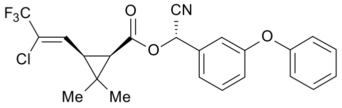
## Insecticides

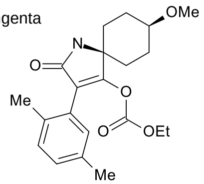

**Cyantraniliprole**
DuPont/Syngenta


**Indoxacarb**
Dow AgroSciences

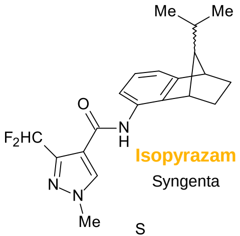

**Sulfoxaflor**
Dow AgroSciences

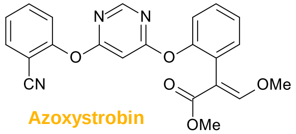

**Thiamethoxam**
Syngenta

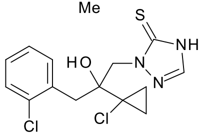

**Lambda-cyhalothrin**
Syngenta

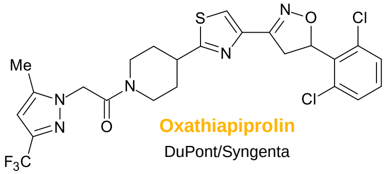

**Spirotetramat**
Bayer CropScience

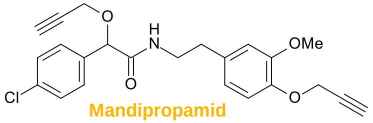
## Fungicides

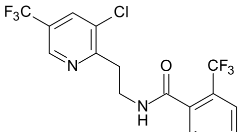

**Isopyrazam**
Syngenta


**Azoxystrobin**
Syngenta

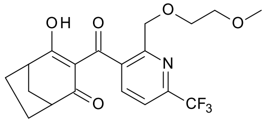

**Prothioconazole**
Bayer CropScience

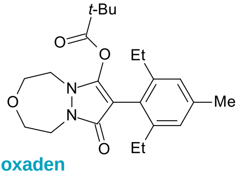

**Oxathiapiprolin**
DuPont/Syngenta

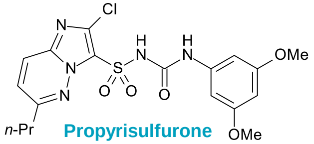

**Mandipropamid**
Syngenta

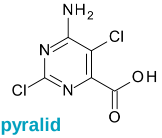

**Fluopyram**
Bayer CropScience

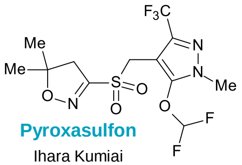
## Herbicides

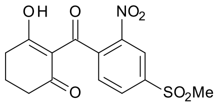

**Bicyclopyrone**
Syngenta


**Pinoxaden**
Syngenta


**Propyrisulfurone**
Sumitomo


**Aminopyralid**
Dow AgroSciences


**Pyroxasulfon**
Ihara Kumiai


**Mesotrione**
Syngenta

- Similar complexity, but much **lower cost** and **higher volume** than pharmaceuticals

Typical Ai cost ($/kg): 10 ↔ 200
scale (ton/year): 100 ↔ >10’000

New trends: ↓Use rate, ↑Selectivity
↑Structure complexity, ↑Chirality

**=> High need for an efficient production route**

# What does a manufacturing process look like?

# The Components of a Manufacturing Process

**Route**

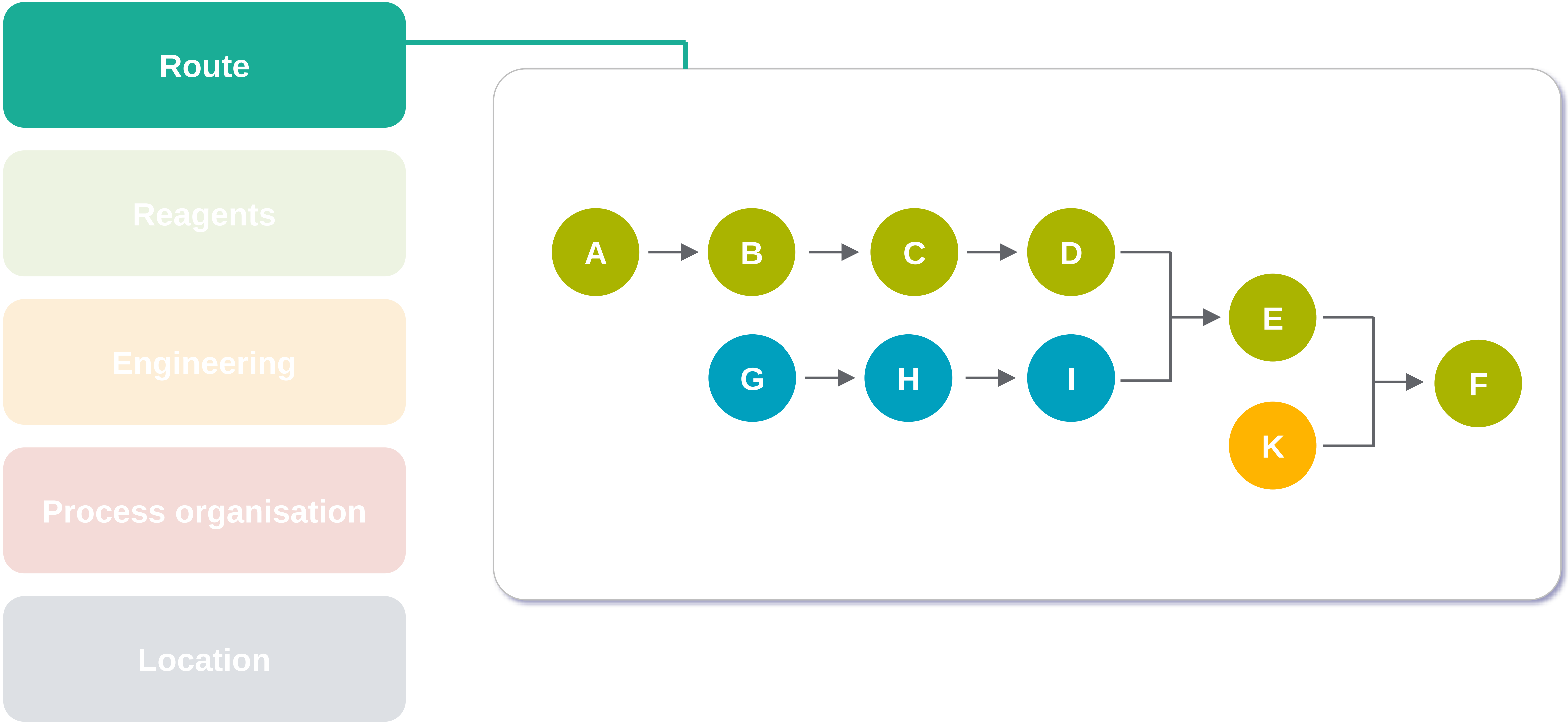
**Reagents**

**Engineering**

**Process organisation**

**Location**

# The Components of a Manufacturing Process



Route

Reagents

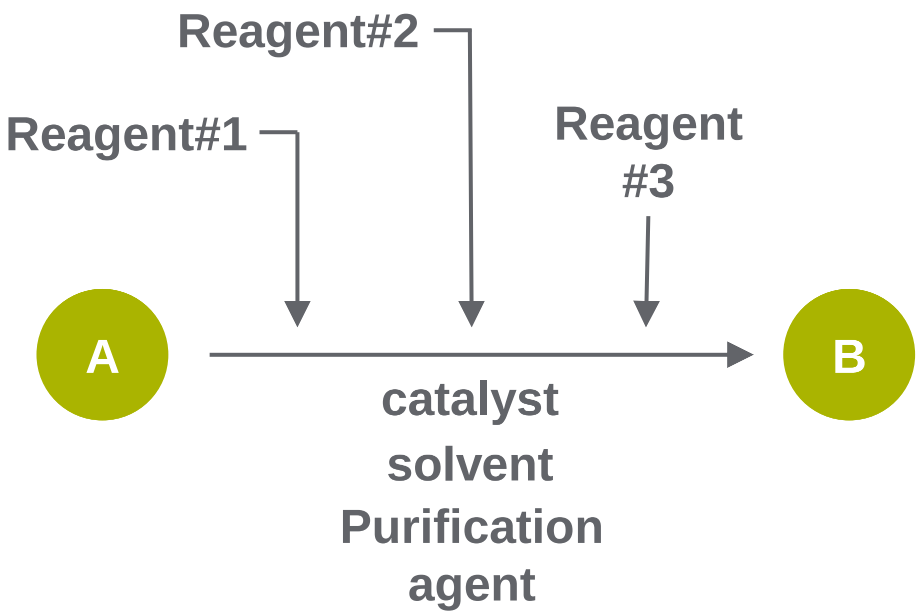
Engineering

Process organisation

Location

# The Components of a Manufacturing Process

- Route
- **Reagents**
- Engineering
- Process organisation
- Location



Reagent#2

Reagent#1

Reagent #3

catalyst

solvent

Purification agent

# The Components of a Manufacturing Process

Route

Reagents

**Engineering**

Process organisation

Location

# The Components of a Manufacturing Process

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# The Components of a Manufacturing Process

Route

Reagents

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**Location**

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# Location – Why do steps externally at all?

Route

Reagents

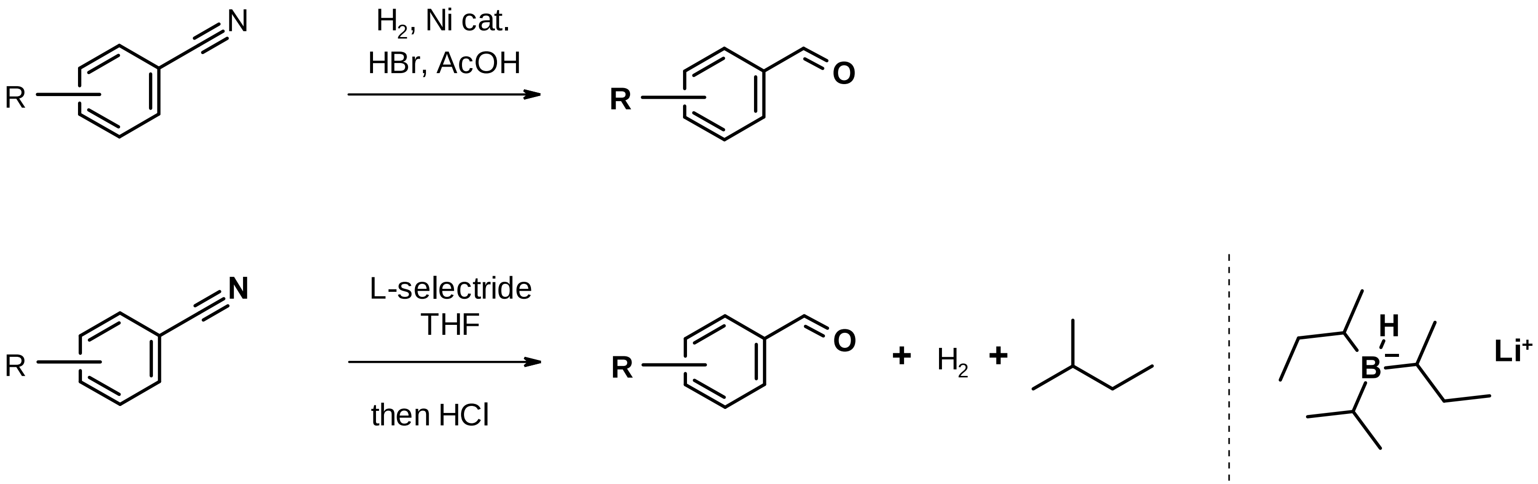
Engineering

**Process organisation**

**Location**

## Need to consider for example

- Assets of each site (available reactors, available technology to perform or deal with the chemistry



# Location – Why do steps externally at all?

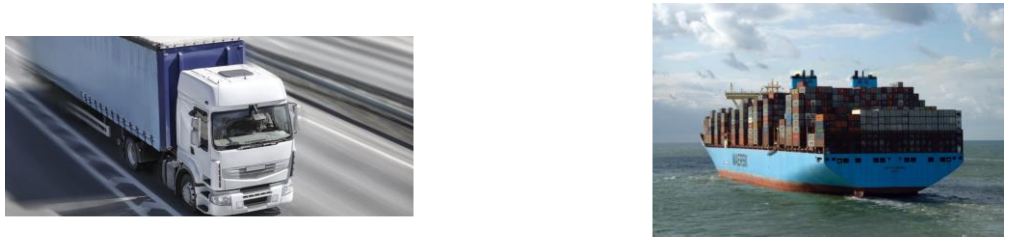
Route

Reagents

Engineering

**Process organisation**

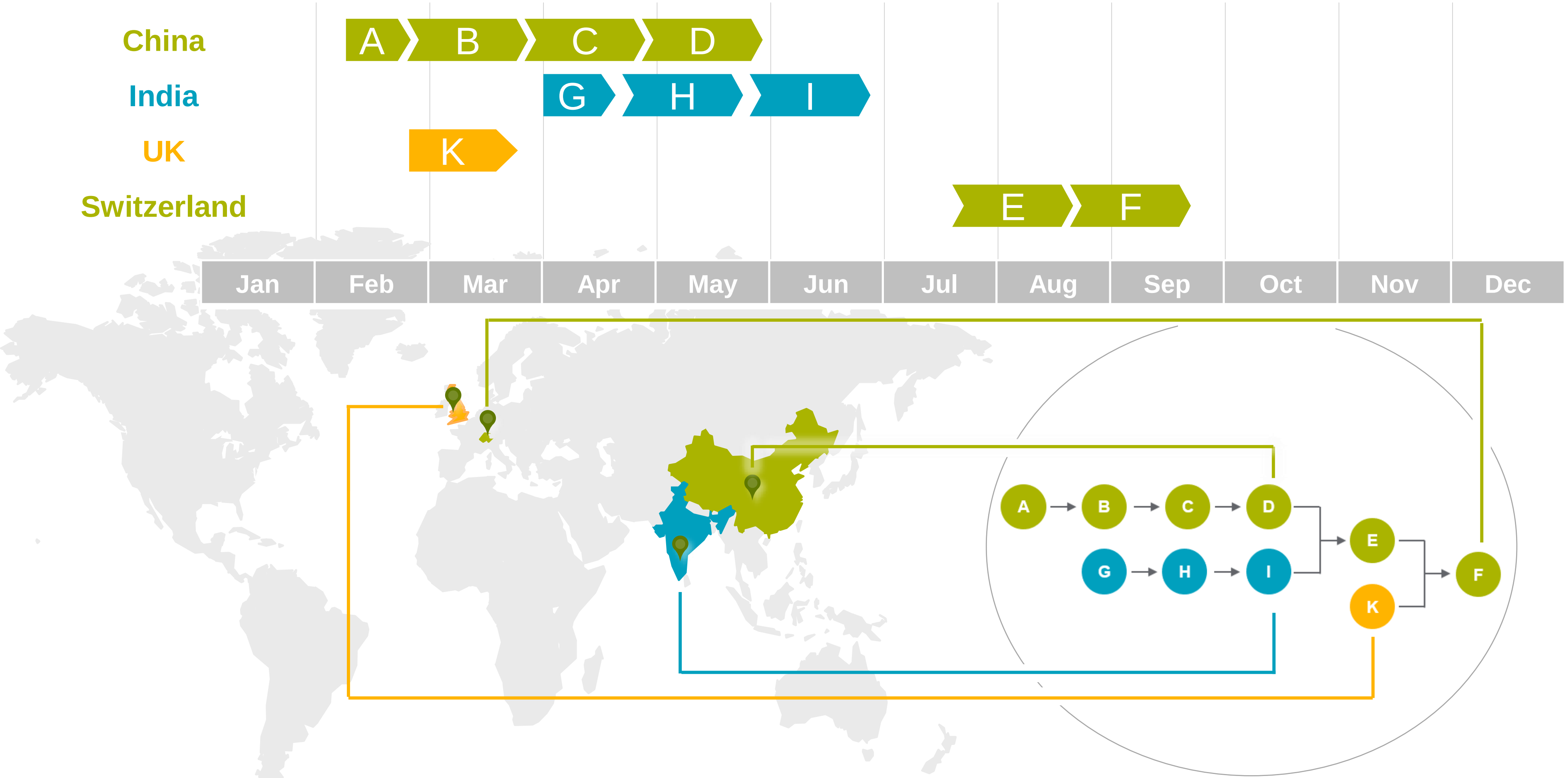
**Location**



**Need to consider for example**

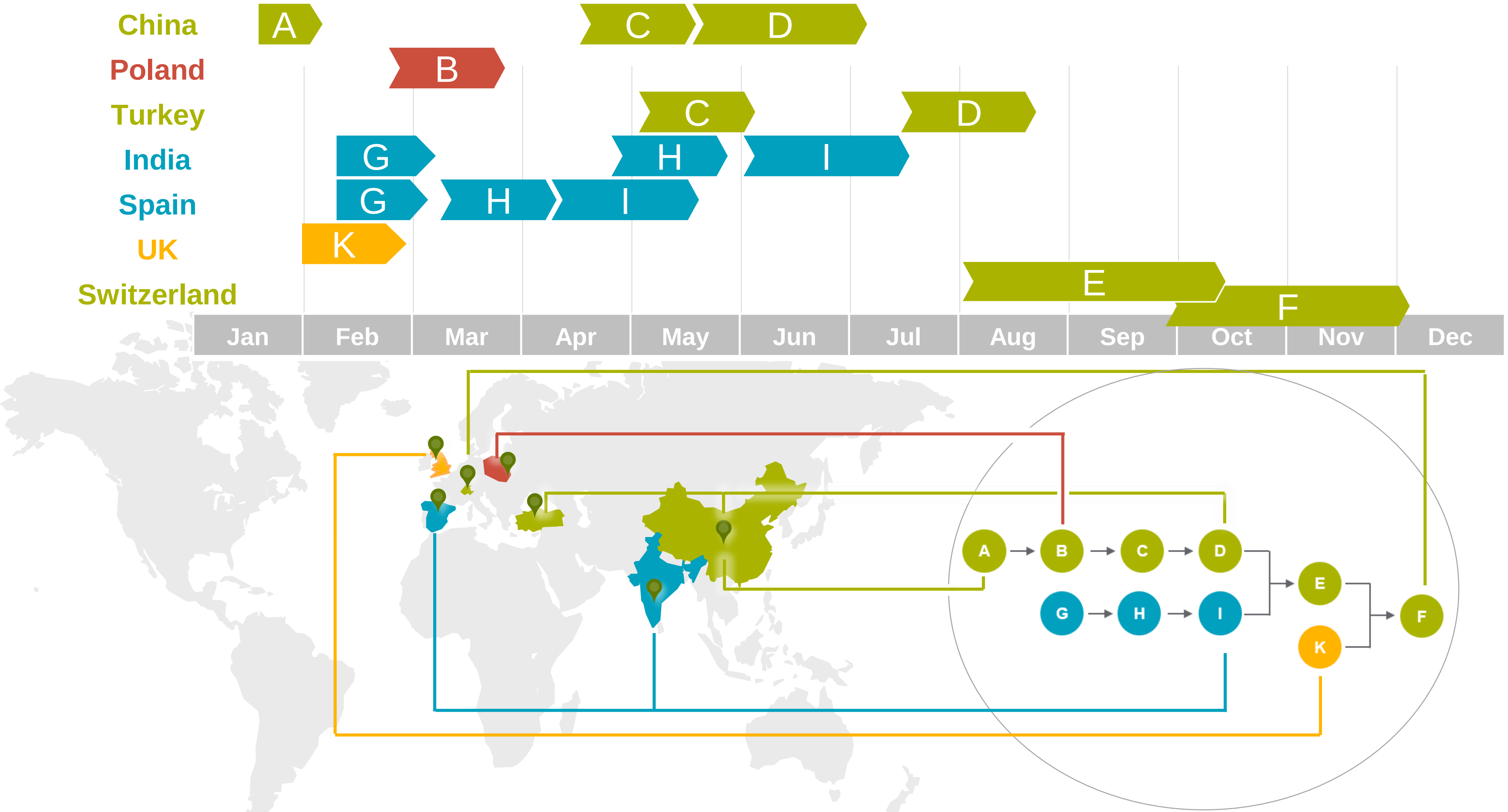
- Assets of each site (available reactors, available technology to perform or deal with the chemistry
- Regulations (use of certain chemicals is sometimes forbidden is some countries)
- Transportation (minimize whenever possible)
- If a toller has not more expertise than you in doing a specific type of chemistry (hydrogenation, F chemistry…)

# Location



- Steps are not necessarily done at the same location

# Location



- Steps are not necessarily done at the same location
- And can become quite a bit more complex…

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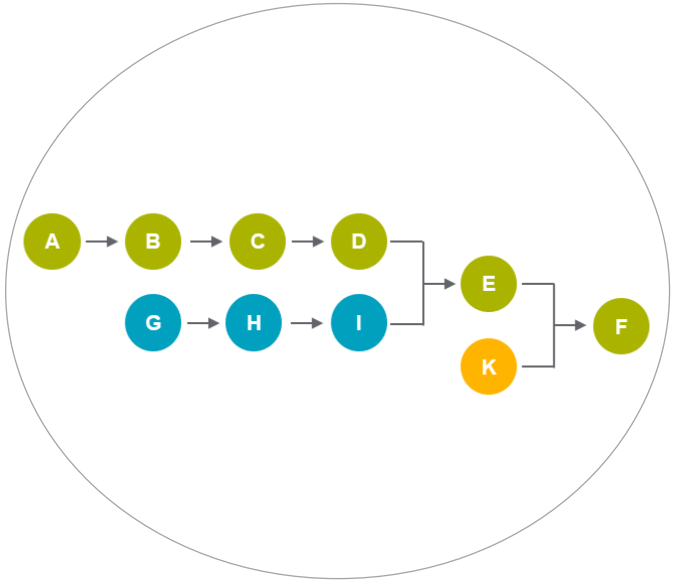
# What does a good manufacturing process look like?

# What is a good synthetic route?

- Route
- Reagents
- Engineering
- Process organisation
- Location



- Low cost
- Few steps
- Stable intermediates
- No regio/stereo selectivity issues
- Cheap readily available raw materials
- Minimised waste
- Safe technology
- Few manufacturing plants
- Easily sited internally or externally
- Flexibility to respond to volume changes
- Patented technology

# What is a good synthetic process?

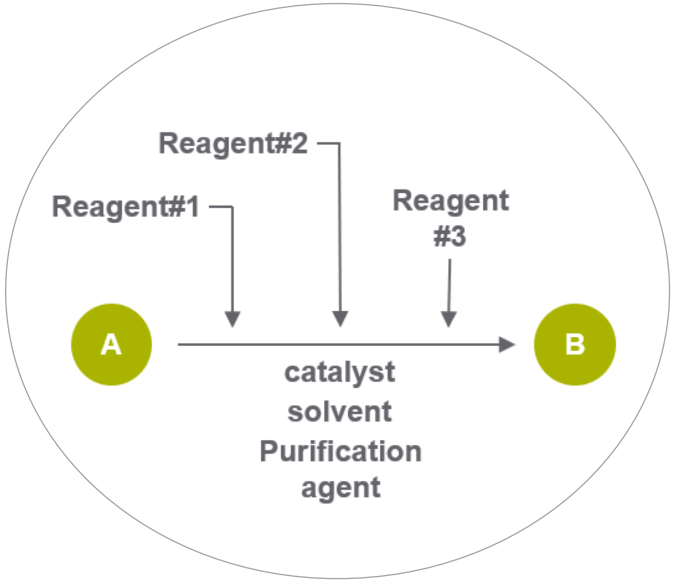
Route

Reagents

Engineering

Process organisation

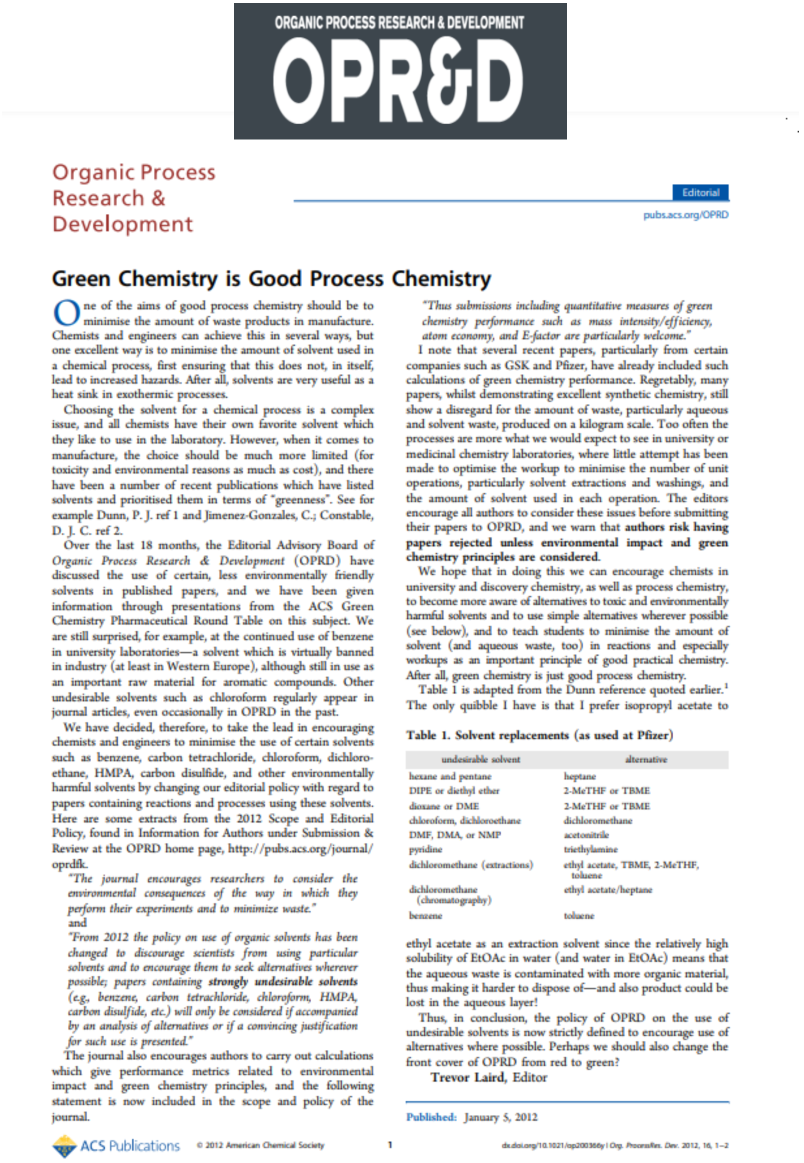
Location



- No auxilliaries
- As little waste as possible
- High space/time productivity
  - → High concentration/no solvent
  - → Fast reactions
- No purification
- Robust operation
- Safe
- Process understanding
- Integrated into the overall route (forward, backward)
- Low cost implementation
- Available technology

# What is Green chemistry?

- Green Chemistry is Good Process Chemistry (T.Laird)
- Greener processes are most often the most cost effective ones



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### Green Chemistry is Good Process Chemistry

One of the aims of good process chemistry should be to minimise the amount of waste products in manufacture. Chemists and engineers can achieve this in several ways, but one excellent way is to minimise the amount of solvent used in a chemical process, first ensuring that this does not, in itself, lead to increased hazards. After all, solvents are very useful as a heat sink in exothermic processes.

Choosing the solvent for a chemical process is a complex issue, and all chemists have their own favorite solvent which they like to use in the laboratory. However, when it comes to manufacture, the choice should be much more limited (for toxicity and environmental reasons as much as cost), and there have been a number of recent publications which have listed solvents and prioritised them in terms of "greenness". See for example Dunn, P. J. ref 1 and Jimenez-Gonzales, C.; Constable, D. J. C. ref 2.

Over the last 18 months, the Editorial Advisory Board of *Organic Process Research & Development* (OPRD) have discussed the use of certain, less environmentally friendly solvents in published papers, and we have been given information through presentations from the ACS Green Chemistry Pharmaceutical Round Table on this subject. We are still surprised, for example, at the continued use of benzene in university laboratories—a solvent which is virtually banned in industry (at least in Western Europe), although still in use as an important raw material for aromatic compounds. Other undesirable solvents such as chloroform regularly appear in journal articles, even occasionally in OPRD in the past.

We have decided, therefore, to take the lead in encouraging chemists and engineers to minimise the use of certain solvents such as benzene, carbon tetrachloride, chloroform, dichloroethane, HMPA, carbon disulfide, and other environmentally harmful solvents by changing our editorial policy with regard to papers containing reactions and processes using these solvents. Here are some extracts from the 2012 Scope and Editorial Policy, found in Information for Authors under Submission & Review at the OPRD home page, http://pubs.acs.org/journal/oprdfk.

> *"The journal encourages researchers to consider the environmental consequences of the way in which they perform their experiments and to minimize waste."*
>
> and
>
> *"From 2012 the policy on use of organic solvents has been changed to discourage scientists from using particular solvents and to encourage them to seek alternatives wherever possible; papers containing* ***strongly undesirable solvents*** *(e.g., benzene, carbon tetrachloride, chloroform, HMPA, carbon disulfide, etc.) will only be considered if accompanied by an analysis of alternatives or if a convincing justification for such use is presented."*

The journal also encourages authors to carry out calculations which give performance metrics related to environmental impact and green chemistry principles, and the following statement is now included in the scope and policy of the journal.

> *"Thus submissions including quantitative measures of green chemistry performance such as mass intensity/efficiency, atom economy, and E-factor are particularly welcome."*

I note that several recent papers, particularly from certain companies such as GSK and Pfizer, have already included such calculations of green chemistry performance. Regretably, many papers, whilst demonstrating excellent synthetic chemistry, still show a disregard for the amount of waste, particularly aqueous and solvent waste, produced on a kilogram scale. Too often the processes are more what we would expect to see in university or medicinal chemistry laboratories, where little attempt has been made to optimise the workup to minimise the number of unit operations, particularly solvent extractions and washings, and the amount of solvent used in each operation. The editors encourage all authors to consider these issues before submitting their papers to OPRD, and we warn that **authors risk having papers rejected unless environmental impact and green chemistry principles are considered**.

We hope that in doing this we can encourage chemists in university and discovery chemistry, as well as process chemistry, to become more aware of alternatives to toxic and environmentally harmful solvents and to use simple alternatives wherever possible (see below), and to teach students to minimise the amount of solvent (and aqueous waste, too) in reactions and especially workups as an important principle of good practical chemistry. After all, green chemistry is just good process chemistry.

Table 1 is adapted from the Dunn reference quoted earlier.[1] The only quibble I have is that I prefer isopropyl acetate to ethyl acetate as an extraction solvent since the relatively high solubility of EtOAc in water (and water in EtOAc) means that the aqueous waste is contaminated with more organic material, thus making it harder to dispose of—and also product could be lost in the aqueous layer!

**Table 1. Solvent replacements (as used at Pfizer)**

| undesirable solvent | alternative |
|---|---|
| hexane and pentane | heptane |
| DIPE or diethyl ether | 2-MeTHF or TBME |
| dioxane or DME | 2-MeTHF or TBME |
| chloroform, dichloroethane | dichloromethane |
| DMF, DMA, or NMP | acetonitrile |
| pyridine | triethylamine |
| dichloromethane (extractions) | ethyl acetate, TBME, 2-MeTHF, toluene |
| dichloromethane (chromatography) | ethyl acetate/heptane |
| benzene | toluene |

Thus, in conclusion, the policy of OPRD on the use of undesirable solvents is now strictly defined to encourage use of alternatives where possible. Perhaps we should also change the front cover of OPRD from red to green?

**Trevor Laird**, Editor

Published: January 5, 2012

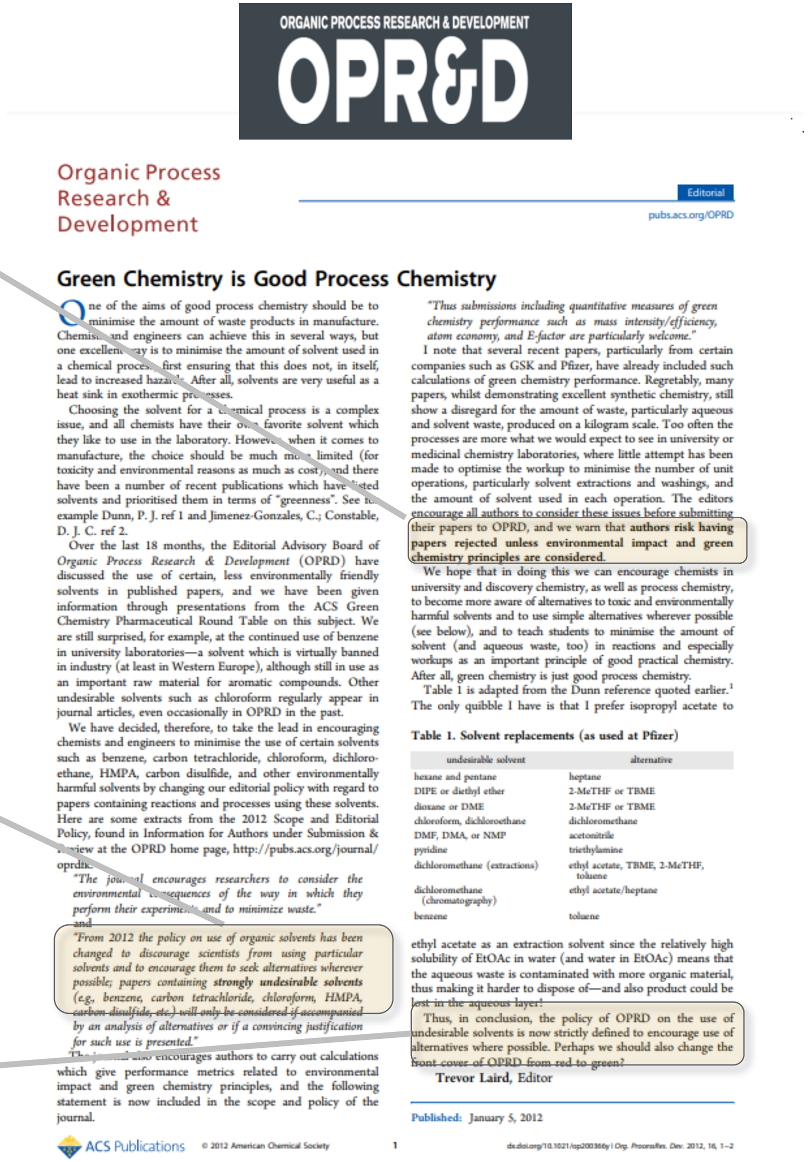
*T. Laird Org. Process Res. Dev.* **2012**, *16*, 1

# What is Green chemistry?

**papers rejected unless** environmental impact and green chemistry principles are considered

**Papers containing strongly undesirable solvents** (e.g., benzene, carbon tetrachloride, chloroform, HMPA, carbon disulfide, etc…) will only be considered if accompanied by an analysis of alternatives or if a convincing justification for such use is presented.”

Our policy […] **discourage scientists from using particular solvents** and encourage them to seek alternatives wherever possible



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The journal also encourages authors to carry out calculations which give performance metrics related to environmental impact and green chemistry principles, and the following statement is now included in the scope and policy of the journal.

> *"Thus submissions including quantitative measures of green chemistry performance such as mass intensity/efficiency, atom economy, and E-factor are particularly welcome."*

I note that several recent papers, particularly from certain companies such as GSK and Pfizer, have already included such calculations of green chemistry performance. Regretably, many papers, whilst demonstrating excellent synthetic chemistry, still show a disregard for the amount of waste, particularly aqueous and solvent waste, produced on a kilogram scale. Too often the processes are more what we would expect to see in university or medicinal chemistry laboratories, where little attempt has been made to optimise the workup to minimise the number of unit operations, particularly solvent extractions and washings, and the amount of solvent used in each operation. The editors encourage all authors to consider these issues before submitting their papers to OPRD, and we warn that **authors risk having papers rejected unless environmental impact and green chemistry principles are considered**.

We hope that in doing this we can encourage chemists in university and discovery chemistry, as well as process chemistry, to become more aware of alternatives to toxic and environmentally harmful solvents and to use simple alternatives wherever possible (see below), and to teach students to minimise the amount of solvent (and aqueous waste, too) in reactions and especially workups as an important principle of good practical chemistry. After all, green chemistry is just good process chemistry.

Table 1 is adapted from the Dunn reference quoted earlier.[1] The only quibble I have is that I prefer isopropyl acetate to ethyl acetate as an extraction solvent since the relatively high solubility of EtOAc in water (and water in EtOAc) means that the aqueous waste is contaminated with more organic material, thus making it harder to dispose of—and also product could be lost in the aqueous layer!

**Table 1. Solvent replacements (as used at Pfizer)**

| undesirable solvent | alternative |
|---|---|
| hexane and pentane | heptane |
| DIPE or diethyl ether | 2-MeTHF or TBME |
| dioxane or DME | 2-MeTHF or TBME |
| chloroform, dichloroethane | dichloromethane |
| DMF, DMA, or NMP | acetonitrile |
| pyridine | triethylamine |
| dichloromethane (extractions) | ethyl acetate, TBME, 2-MeTHF, toluene |
| dichloromethane (chromatography) | ethyl acetate/heptane |
| benzene | toluene |

Thus, in conclusion, the policy of OPRD on the use of undesirable solvents is now strictly defined to encourage use of alternatives where possible. Perhaps we should also change the front cover of OPRD from red to green?

**Trevor Laird**, Editor

Published: January 5, 2012

Classification: PUBLIC

T. Laird *Org. Process Res. Dev.* **2012**, *16*, 1

# 12 Principles of Green and Sustainable Chemistry

J. C. Warner

1. Prevent waste
2. Atom economy
3. Less Hazardous Synthesis
4. Design Benign Chemicals
5. Benign Solvent
6. Energy efficiency
7. Use of renewable feedstocks
8. Reduce derivatives
9. Catalysis
10. Design for degradation
11. Real-time analysis for pollution prevention
12. Safer chemistry for accident prevention

P. T. Anastas

*Green Chemistry: Theory* and *Practice*, Ox. Uni. Press, New York, *1998*

# The 12 principles of Green chemistry

**Dr. David Constable**

*Former Director of ACSGCI*

**Dr. Richard Williams**

*President of the Environmental Science & Green Chemistry Consulting LLC*

1.Prevent waste

2.Atom economy

3.Less Hazardous Synthesis

4.Design Benign Chemicals

5.Benign Solvent

6.Energy efficiency

7. Use of renewable feedstocks

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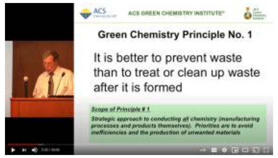


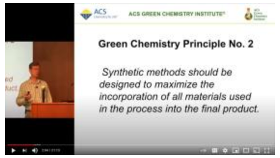
ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 1**

It is better to prevent waste than to treat or clean up waste after it is formed

*Scope of Principle # 1*

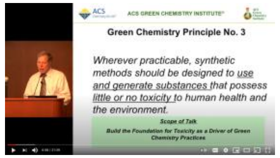
*Strategic approach to conducting all chemistry (manufacturing processes and products themselves). Priorities are to avoid inefficiencies and the production of unwanted materials*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 2**

*Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 3**

*Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.*

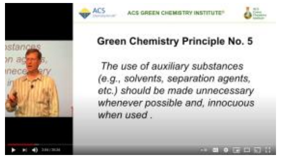
*Scope of Talk*

*Build the Foundation for Toxicity as a Driver of Green Chemistry Practices*

ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 4**

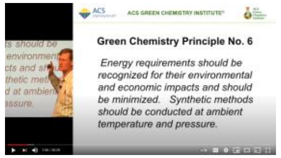
*Chemical products should be designed to affect their desired function while minimizing their toxicity*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 5**

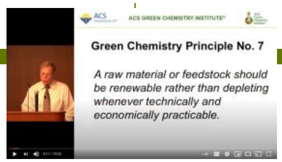
*The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary whenever possible and, innocuous when used .*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 6**

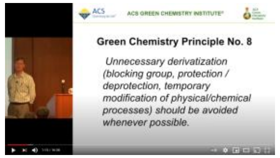
*Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 7**

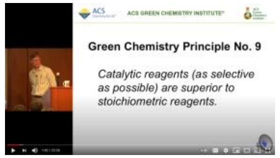
*A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 8**

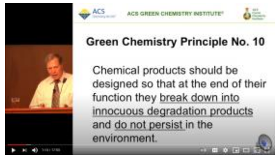
*Unnecessary derivatization (blocking group, protection / deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 9**

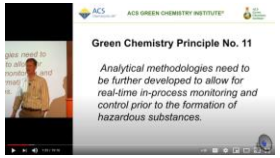
*Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.*



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 10**

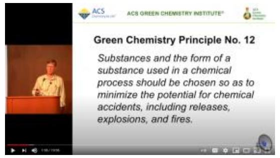
Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.



ACS GREEN CHEMISTRY INSTITUTE®

**Green Chemistry Principle No. 11**

*Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.*



ACS GREEN CHEMISTRY INSTITUTE®

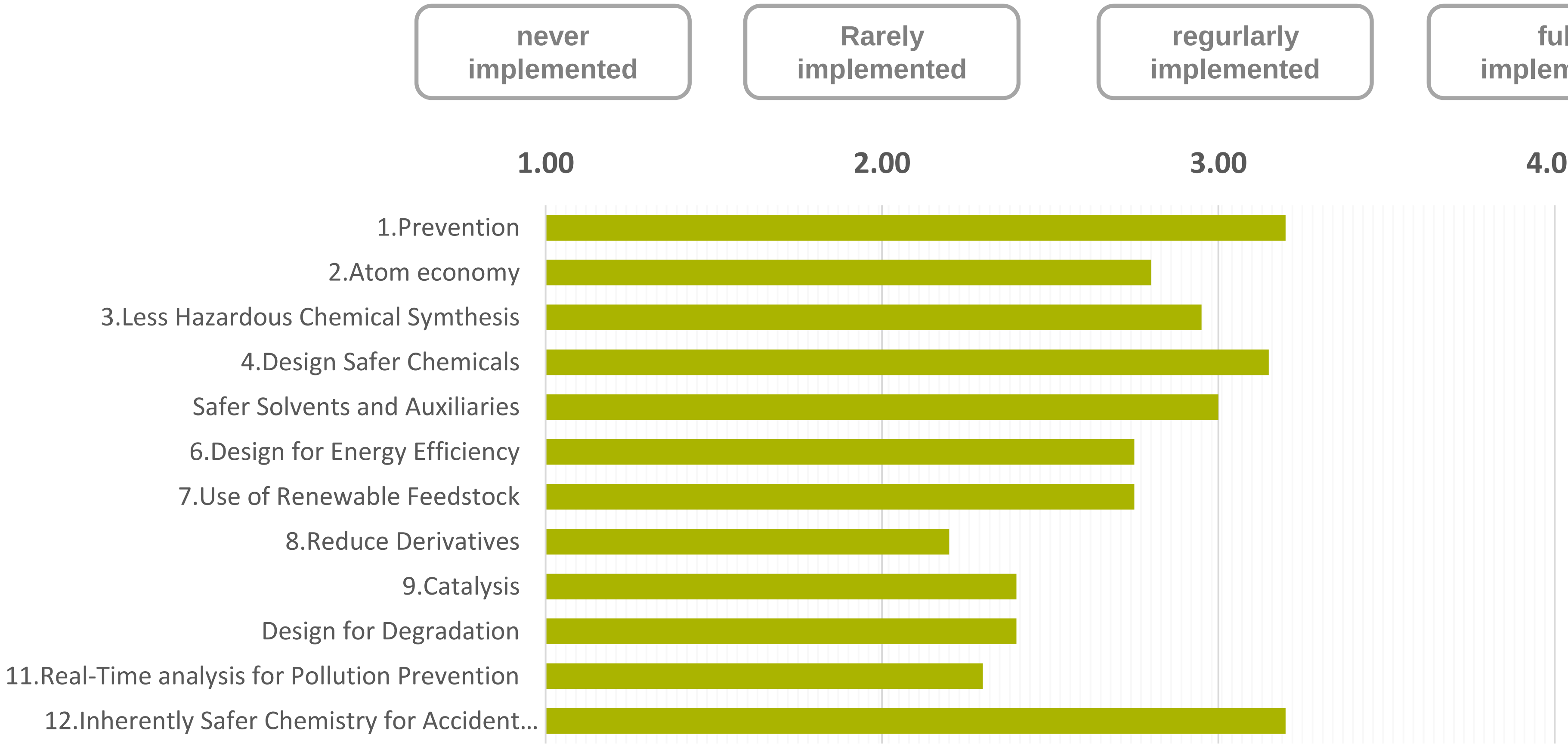
**Green Chemistry Principle No. 12**

*Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.*

GC&E Student Workshop June 17, 2013, ACS headquarters in Washington, D.C

# Current Applications of Green Chemistry in Industry

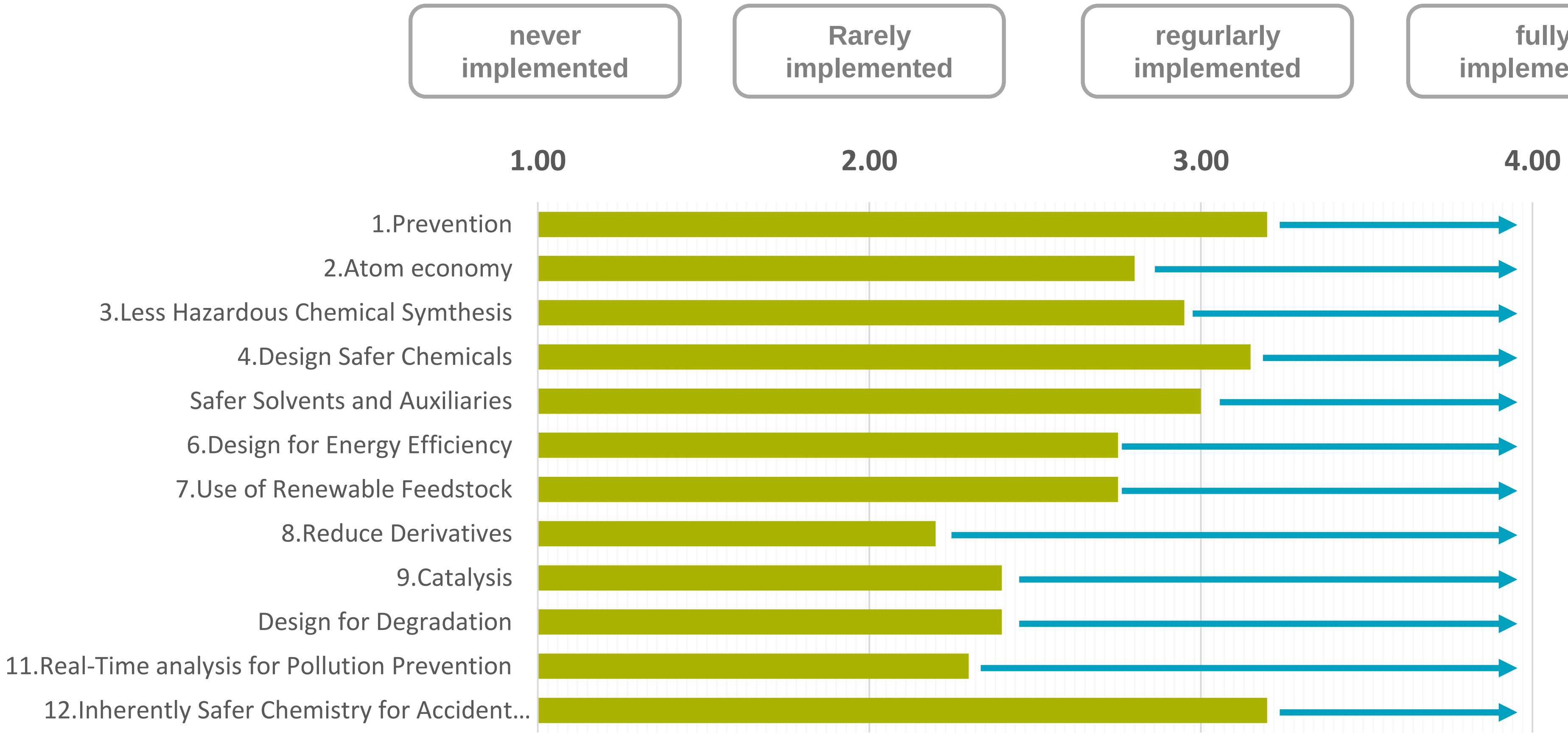
**Survey question: “In your opinion, how frequently does your company implement the following principles of green chemistry?”**



*ACS Sustainable Chemistry & Engineering*, 2014, **2**, 2237

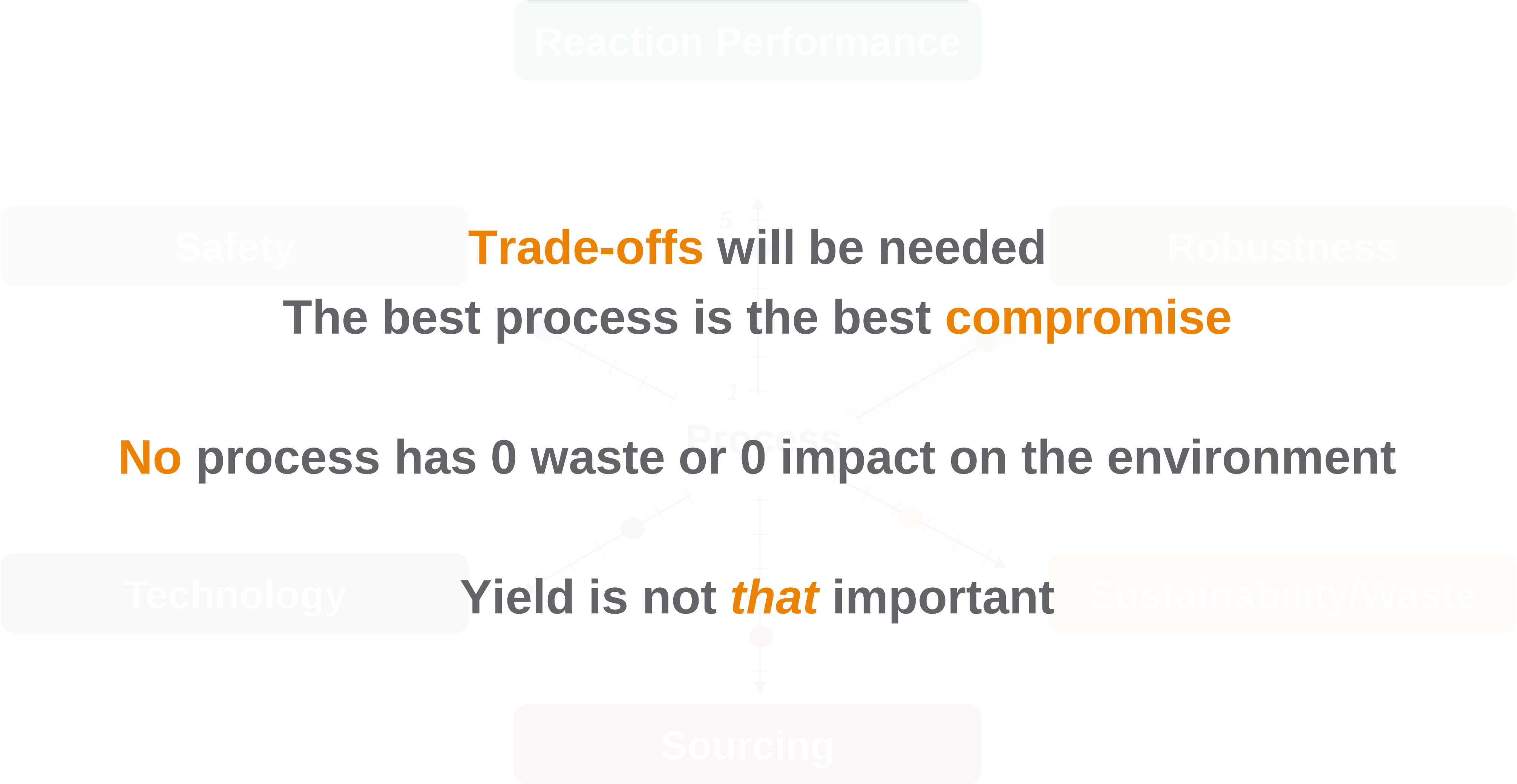
# Current Applications of Green Chemistry in Industry

## Survey question: “In your opinion, how frequently does your company implement the following principles of green chemistry?”



*ACS Sustainable Chemistry & Engineering*, 2014, **2**, 2237

# Holistic Evaluation of a Process



**Trade-offs will be needed**

**The best process is the best compromise**

**No process has 0 waste or 0 impact on the environment**

**Yield is not *that* important**

Classification: PUBLIC

# 12 Principles of Green and Sustainable Chemistry

1.Prevent waste

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3.Less Hazardous Synthesis

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**5.Benign Solvent**

6.Energy efficiency

7. Use of renewable feedstocks

8. Reduce derivatives

9. Catalysis

10. Design for degradation

11. Real-time analysis for pollution prevention

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Classification: PUBLIC

*Green Chemistry: Theory* and *Practice*, Ox. Uni. Press, New York, *1998*

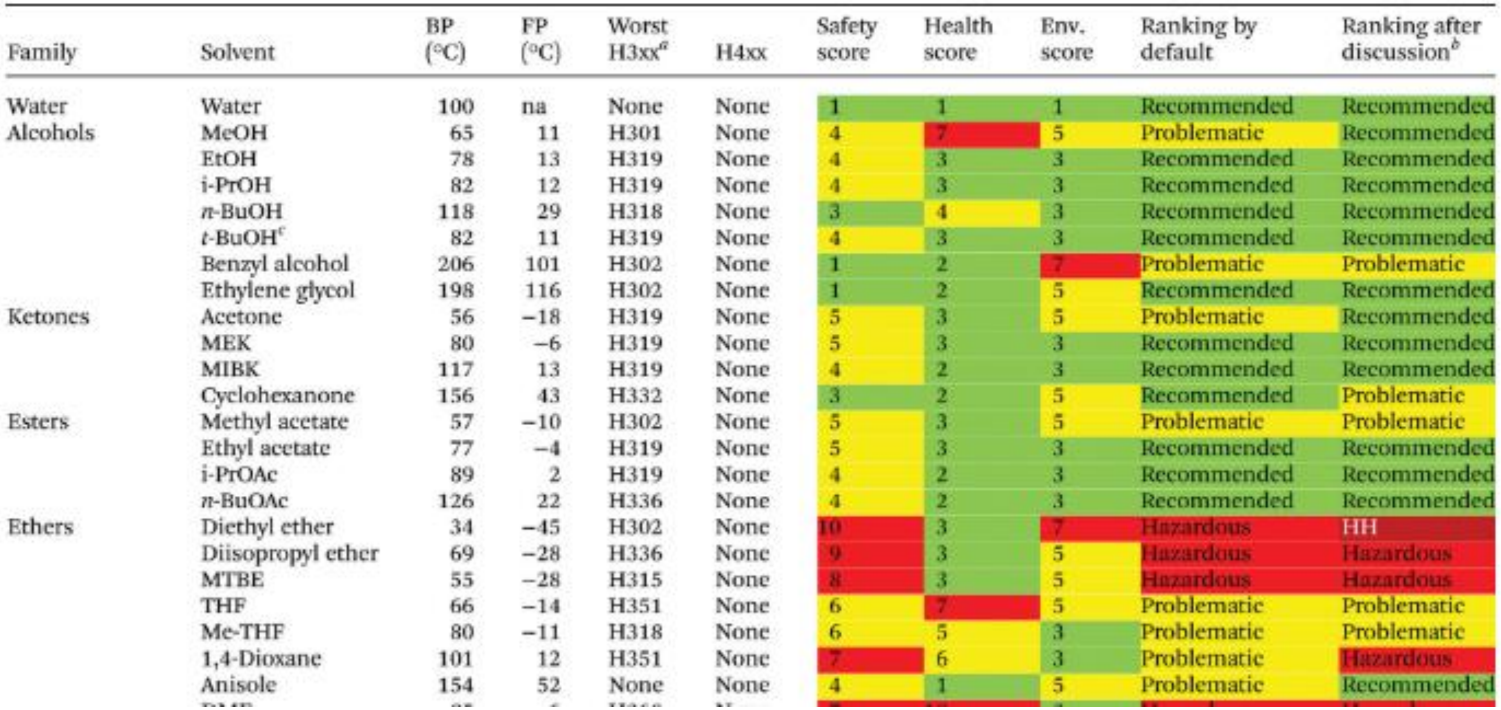
www.menti.com

71 95 70 73

link

# Solvent guides

## There are many many solvent guides



| Family | Solvent | BP (°C) | FP (°C) | Worst H3xx[a] | H4xx | Safety score | Health score | Env. score | Ranking by default | Ranking after discussion[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| Water | Water | 100 | na | None | None | 1 | 1 | 1 | Recommended | Recommended |
| Alcohols | MeOH | 65 | 11 | H301 | None | 4 | 7 | 5 | Problematic | Recommended |
| | EtOH | 78 | 13 | H319 | None | 4 | 3 | 3 | Recommended | Recommended |
| | i-PrOH | 82 | 12 | H319 | None | 4 | 3 | 3 | Recommended | Recommended |
| | *n*-BuOH | 118 | 29 | H318 | None | 3 | 4 | 3 | Recommended | Recommended |
| | *t*-BuOH[c] | 82 | 11 | H319 | None | 4 | 3 | 3 | Recommended | Recommended |
| | Benzyl alcohol | 206 | 101 | H302 | None | 1 | 2 | 7 | Problematic | Problematic |
| | Ethylene glycol | 198 | 116 | H302 | None | 1 | 2 | 5 | Recommended | Recommended |
| Ketones | Acetone | 56 | −18 | H319 | None | 5 | 3 | 5 | Problematic | Recommended |
| | MEK | 80 | −6 | H319 | None | 5 | 3 | 3 | Recommended | Recommended |
| | MIBK | 117 | 13 | H319 | None | 4 | 2 | 3 | Recommended | Recommended |
| | Cyclohexanone | 156 | 43 | H332 | None | 3 | 2 | 5 | Recommended | Problematic |
| Esters | Methyl acetate | 57 | −10 | H302 | None | 5 | 3 | 5 | Problematic | Problematic |
| | Ethyl acetate | 77 | −4 | H319 | None | 5 | 3 | 3 | Recommended | Recommended |
| | i-PrOAc | 89 | 2 | H319 | None | 4 | 2 | 3 | Recommended | Recommended |
| | *n*-BuOAc | 126 | 22 | H336 | None | 4 | 2 | 3 | Recommended | Recommended |
| Ethers | Diethyl ether | 34 | −45 | H302 | None | 10 | 3 | 7 | Hazardous | HH |
| | Diisopropyl ether | 69 | −28 | H336 | None | 9 | 3 | 5 | Hazardous | Hazardous |
| | MTBE | 55 | −28 | H315 | None | 8 | 3 | 5 | Hazardous | Hazardous |
| | THF | 66 | −14 | H351 | None | 6 | 7 | 5 | Problematic | Problematic |
| | Me-THF | 80 | −11 | H318 | None | 6 | 5 | 3 | Problematic | Problematic |
| | 1,4-Dioxane | 101 | 12 | H351 | None | 7 | 6 | 3 | Problematic | Hazardous |
| | Anisole | 154 | 52 | None | None | 4 | 1 | 5 | Problematic | Recommended |

Green Chemistry 2016, 18, 288

# Solvents : how are solvents classified ?

- GSK classification methodology:

## waste score

**incineration score**

Water solubilty
Combustion enthalpy

**recycling score**

Is solvent easily recycled
Water azeotrope
Boiling point
Flammability, explosivity

**VOC emissions score**

Low vapor pressure, low bp
Losses on storage, transport

**biotreatment score**

Problematic solvent when present in aqueous phases

## environmental impact score

**aqueous score**

photochemical ozone creation potential
odour

**air score**

Acute environmental toxicity
Chronic environmental toxicity
Biodegradation

## health score

**exposure potential score**

occupational exposure limits (OELs) - human health hazard
calculation of saturation concentration

**health hazard score**

European Union risk phrases
GHS Hazard and Precautionary (H&P) risk phrases

## safety score

**flammability & explosion potential score**

Boiling point; Flash point; Auto ignition temperature
Electrical conductivity,
Vapour pressure

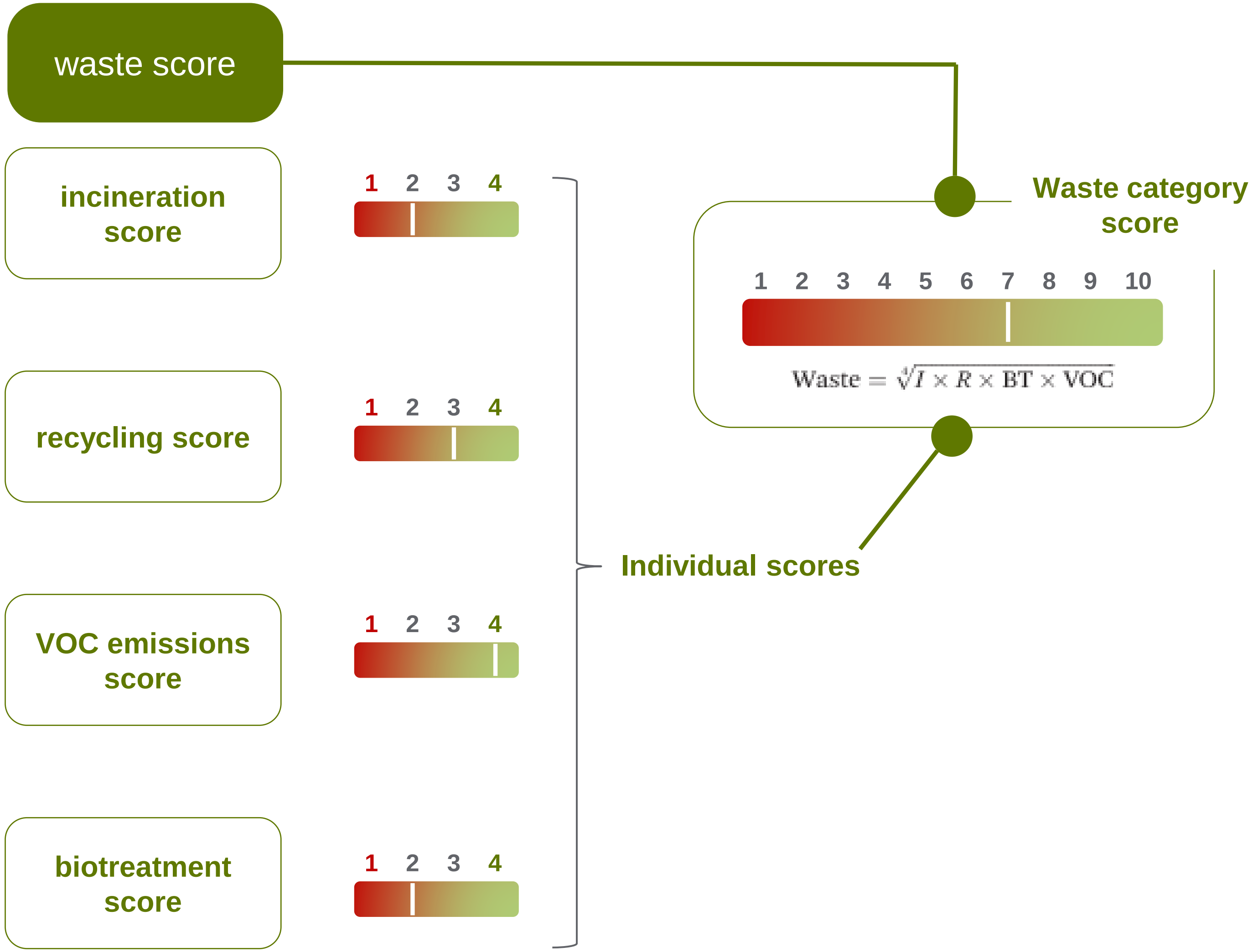
**reactivity & stability score**

Peroxide formation
Potential for self-reaction
Acidity/Basicity
Special hazards (pyrophoric or shock sensitive solvents)

Green Chem., 2016, 18, 3879−3890

# Solvents : how are solvents classified ?

- GSK classification methodology: 4 categories to characterize solvents

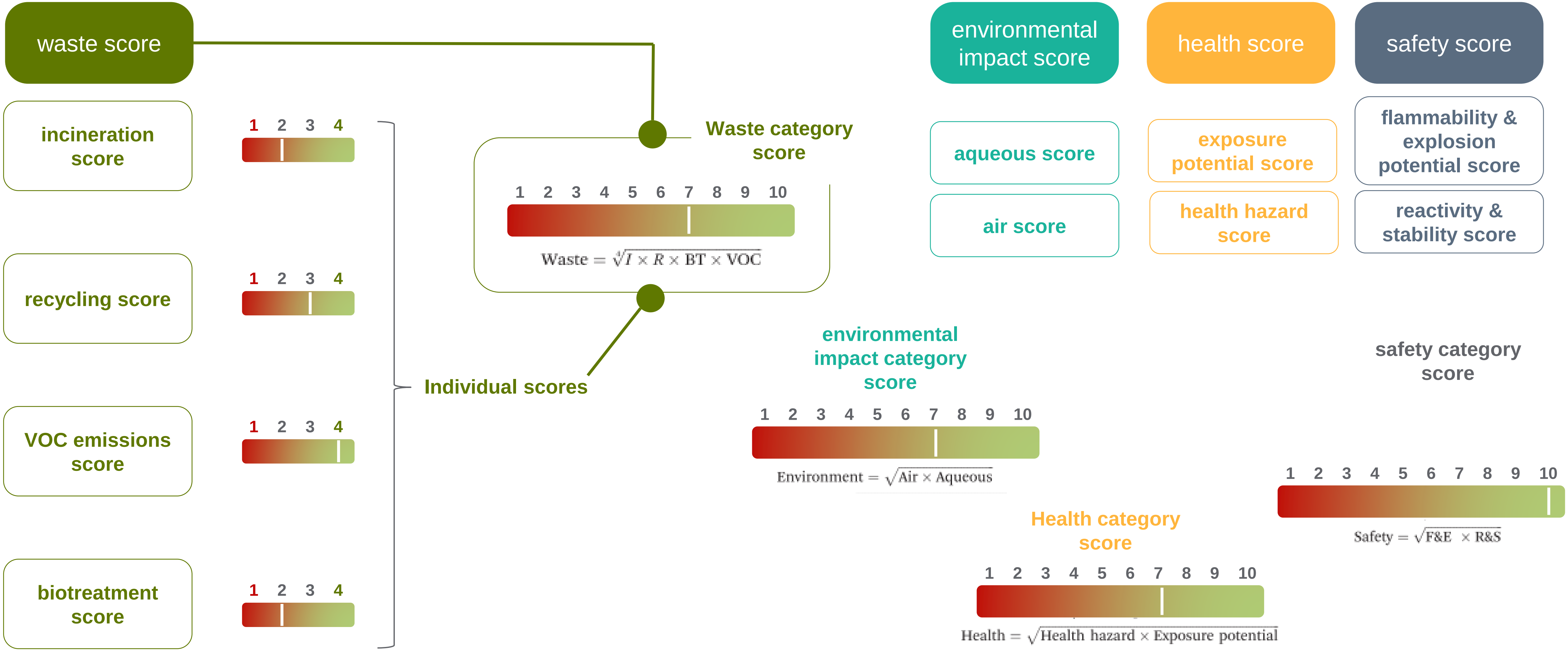


$$\text{Waste} = \sqrt[4]{I \times R \times \text{BT} \times \text{VOC}}$$

Green Chem., 2016, 18, 3879–3890

# Solvents : how are solvents classified ?

- GSK classification methodology: 4 categories to characterize solvents



**waste score**

**incineration score**

**recycling score**

**VOC emissions score**

**biotreatment score**

**Individual scores**

**Waste category score**

Waste = $\sqrt[4]{I \times R \times BT \times VOC}$

environmental impact score

**aqueous score**

**air score**

**environmental impact category score**

Environment = $\sqrt{\text{Air} \times \text{Aqueous}}$

health score

**exposure potential score**

**health hazard score**

**Health category score**

Health = $\sqrt{\text{Health hazard} \times \text{Exposure potential}}$

safety score

**flammability & explosion potential score**

**reactivity & stability score**

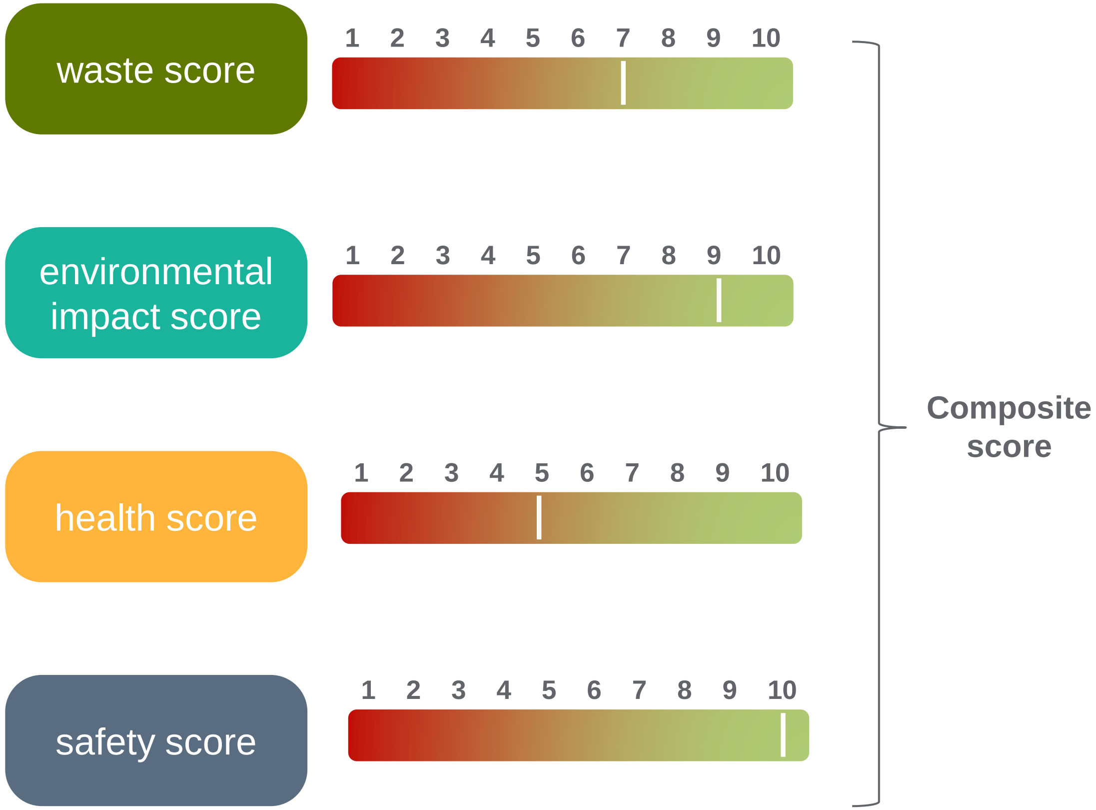
safety category score

Safety = $\sqrt{\text{F\&E} \times \text{R\&S}}$

Green Chem., 2016, 18, 3879–3890

# Solvents : how are solvents classified ?

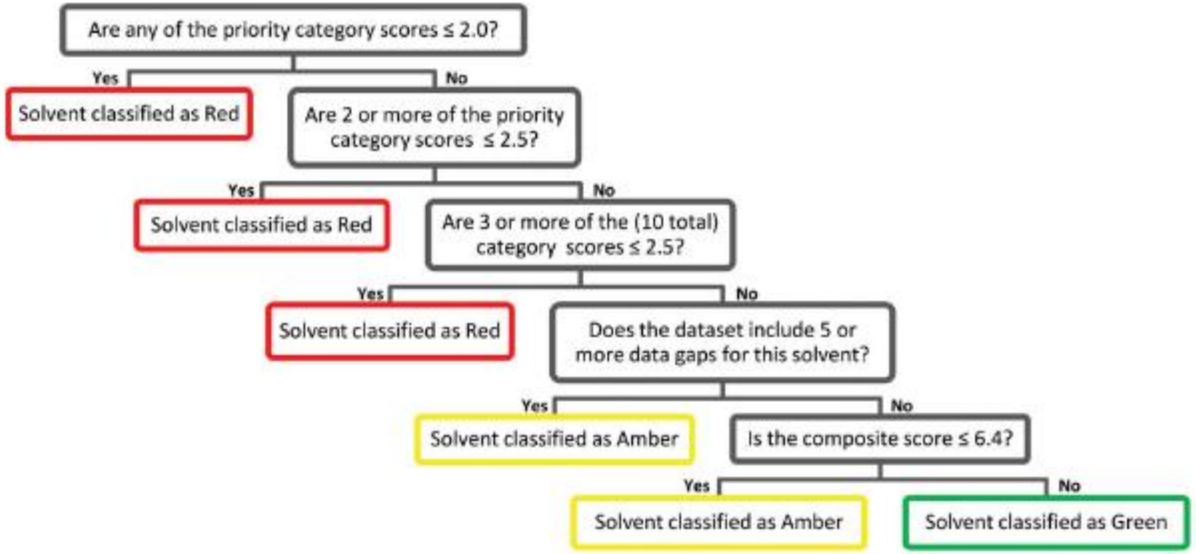
- GSK classification methodology: 4 categories to characterize solvents



🟥 Score ≥ 7.5

🟨 7.5 > Score ≥ 3.5

🟩 3.5 > Score

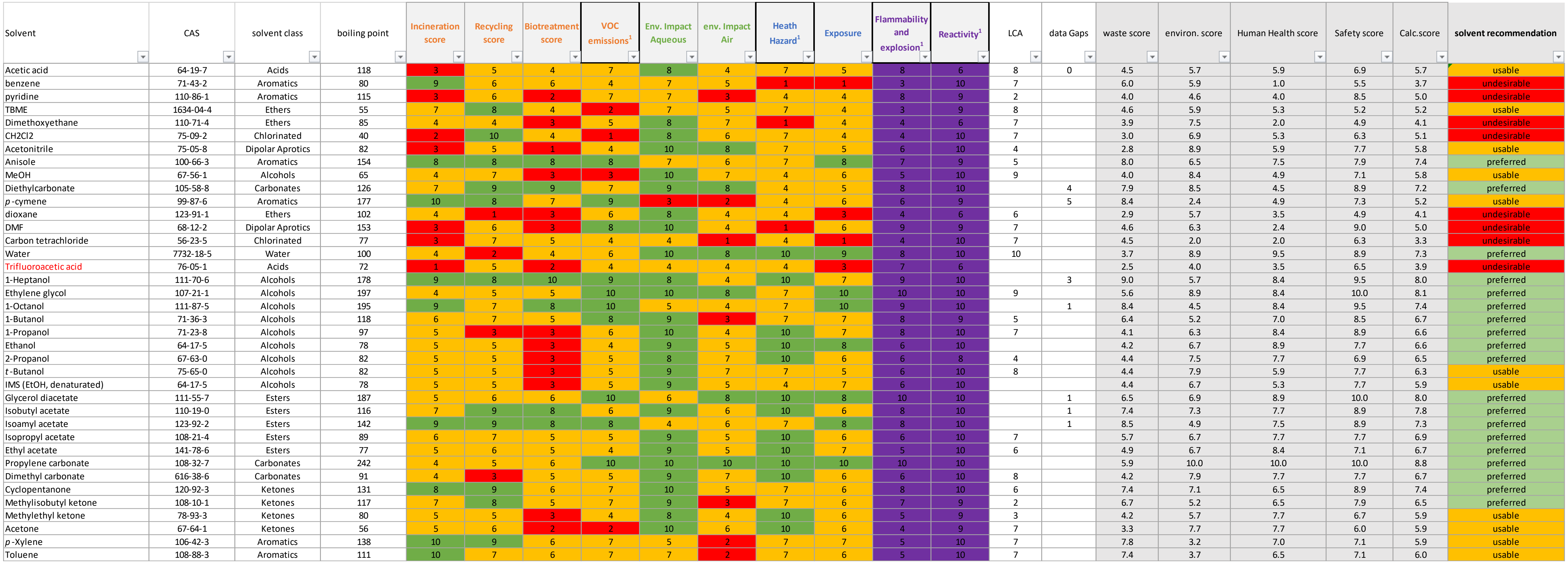


$$\text{Composite} = \sqrt[4]{\text{Waste} \times \text{Environment} \times \text{Health} \times \text{Safety}}$$

Green Chem., 2016, 18, 3879–3890

# Solvents : how are solvents classified ?

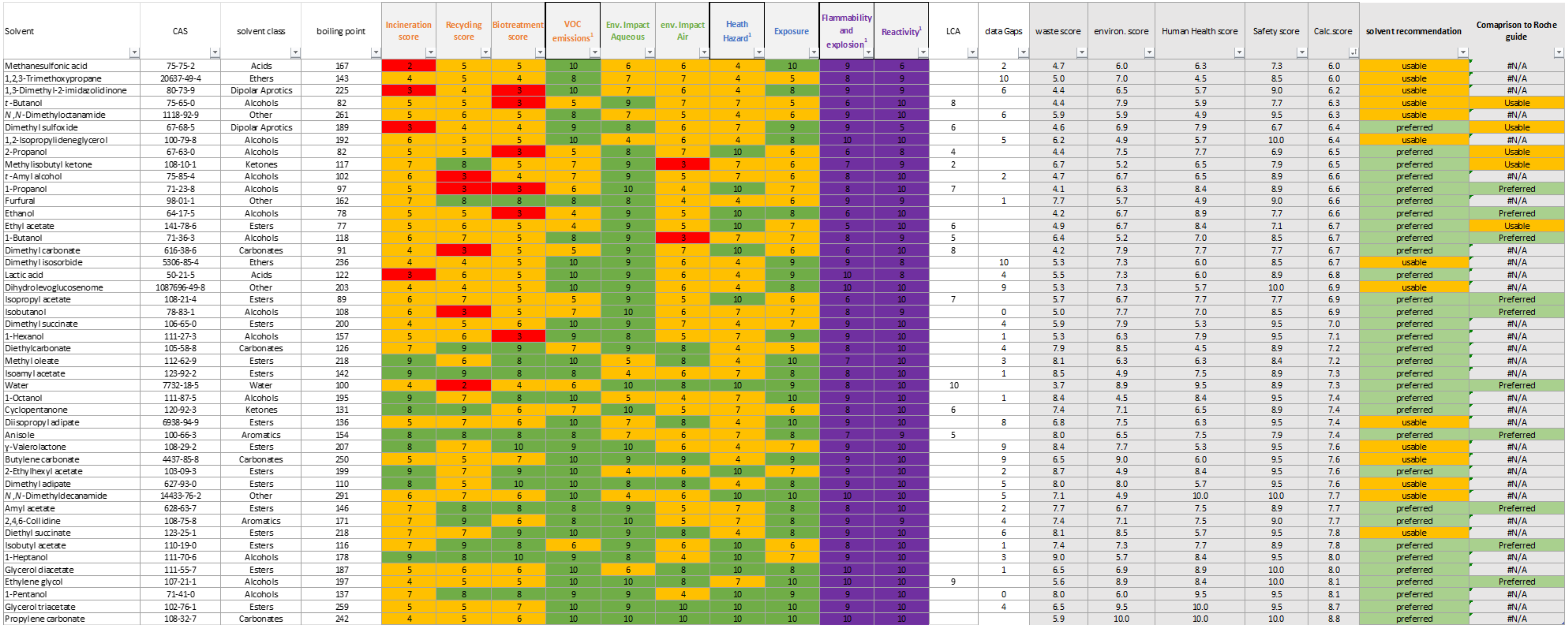
- GSK classification methodology: 4 categories to characterize solvents



| Solvent | CAS | solvent class | boiling point | Incineration score | Recycling score | Biotreatment score | VOC emissions$^1$ | Env. Impact Aqueous | env. Impact Air | Heath Hazard$^1$ | Exposure | Flammability and explosion$^1$ | Reactivity$^1$ | LCA | data Gaps | waste score | environ. score | Human Health score | Safety score | Calc.score | solvent recommendation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetic acid | 64-19-7 | Acids | 118 | 3 | 5 | 4 | 7 | 8 | 4 | 7 | 5 | 8 | 6 | 8 | 0 | 4.5 | 5.7 | 5.9 | 6.9 | 5.7 | usable |
| benzene | 71-43-2 | Aromatics | 80 | 9 | 6 | 6 | 4 | 7 | 5 | 1 | 1 | 3 | 10 | 7 |  | 6.0 | 5.9 | 1.0 | 5.5 | 3.7 | undesirable |
| pyridine | 110-86-1 | Aromatics | 115 | 3 | 6 | 2 | 7 | 7 | 3 | 4 | 4 | 8 | 9 | 2 |  | 4.0 | 4.6 | 4.0 | 8.5 | 5.0 | undesirable |
| TBME | 1634-04-4 | Ethers | 55 | 7 | 8 | 4 | 2 | 7 | 5 | 7 | 4 | 3 | 9 | 8 |  | 4.6 | 5.9 | 5.3 | 5.2 | 5.2 | usable |
| Dimethoxyethane | 110-71-4 | Ethers | 85 | 4 | 4 | 3 | 5 | 8 | 7 | 1 | 4 | 4 | 6 | 7 |  | 3.9 | 7.5 | 2.0 | 4.9 | 4.1 | undesirable |
| CH2Cl2 | 75-09-2 | Chlorinated | 40 | 2 | 10 | 4 | 1 | 8 | 6 | 7 | 4 | 4 | 10 | 7 |  | 3.0 | 6.9 | 5.3 | 6.3 | 5.1 | undesirable |
| Acetonitrile | 75-05-8 | Dipolar Aprotics | 82 | 3 | 5 | 1 | 4 | 10 | 8 | 7 | 5 | 6 | 10 | 4 |  | 2.8 | 8.9 | 5.9 | 7.7 | 5.8 | usable |
| Anisole | 100-66-3 | Aromatics | 154 | 8 | 8 | 8 | 8 | 7 | 6 | 7 | 8 | 7 | 9 | 5 |  | 8.0 | 6.5 | 7.5 | 7.9 | 7.4 | preferred |
| MeOH | 67-56-1 | Alcohols | 65 | 4 | 7 | 3 | 3 | 10 | 7 | 4 | 6 | 5 | 10 | 9 |  | 4.0 | 8.4 | 4.9 | 7.1 | 5.8 | usable |
| Diethylcarbonate | 105-58-8 | Carbonates | 126 | 7 | 9 | 9 | 7 | 9 | 8 | 4 | 5 | 8 | 10 |  | 4 | 7.9 | 8.5 | 4.5 | 8.9 | 7.2 | preferred |
| *p*-cymene | 99-87-6 | Aromatics | 177 | 10 | 8 | 7 | 9 | 3 | 2 | 4 | 6 | 6 | 9 |  | 5 | 8.4 | 2.4 | 4.9 | 7.3 | 5.2 | usable |
| dioxane | 123-91-1 | Ethers | 102 | 4 | 1 | 3 | 6 | 8 | 4 | 4 | 3 | 4 | 6 | 6 |  | 2.9 | 5.7 | 3.5 | 4.9 | 4.1 | undesirable |
| DMF | 68-12-2 | Dipolar Aprotics | 153 | 3 | 6 | 3 | 8 | 10 | 4 | 1 | 6 | 9 | 9 | 7 |  | 4.6 | 6.3 | 2.4 | 9.0 | 5.0 | undesirable |
| Carbon tetrachloride | 56-23-5 | Chlorinated | 77 | 3 | 7 | 5 | 4 | 4 | 1 | 4 | 1 | 4 | 10 | 7 |  | 4.5 | 2.0 | 2.0 | 6.3 | 3.3 | undesirable |
| Water | 7732-18-5 | Water | 100 | 4 | 2 | 4 | 6 | 10 | 8 | 10 | 9 | 8 | 10 | 10 |  | 3.7 | 8.9 | 9.5 | 8.9 | 7.3 | preferred |
| Trifluoroacetic acid | 76-05-1 | Acids | 72 | 1 | 5 | 2 | 4 | 4 | 4 | 4 | 3 | 7 | 6 |  |  | 2.5 | 4.0 | 3.5 | 6.5 | 3.9 | undesirable |
| 1-Heptanol | 111-70-6 | Alcohols | 178 | 9 | 8 | 10 | 9 | 8 | 4 | 10 | 7 | 9 | 10 |  | 3 | 9.0 | 5.7 | 8.4 | 9.5 | 8.0 | preferred |
| Ethylene glycol | 107-21-1 | Alcohols | 197 | 4 | 5 | 5 | 10 | 10 | 8 | 7 | 10 | 10 | 10 | 9 |  | 5.6 | 8.9 | 8.4 | 10.0 | 8.1 | preferred |
| 1-Octanol | 111-87-5 | Alcohols | 195 | 9 | 7 | 8 | 10 | 5 | 4 | 7 | 10 | 9 | 10 |  | 1 | 8.4 | 4.5 | 8.4 | 9.5 | 7.4 | preferred |
| 1-Butanol | 71-36-3 | Alcohols | 118 | 6 | 7 | 5 | 8 | 9 | 3 | 7 | 7 | 8 | 9 | 5 |  | 6.4 | 5.2 | 7.0 | 8.5 | 6.7 | preferred |
| 1-Propanol | 71-23-8 | Alcohols | 97 | 5 | 3 | 3 | 6 | 10 | 4 | 10 | 7 | 8 | 10 | 7 |  | 4.1 | 6.3 | 8.4 | 8.9 | 6.6 | preferred |
| Ethanol | 64-17-5 | Alcohols | 78 | 5 | 5 | 3 | 4 | 9 | 5 | 10 | 8 | 6 | 10 |  |  | 4.2 | 6.7 | 8.9 | 7.7 | 6.6 | preferred |
| 2-Propanol | 67-63-0 | Alcohols | 82 | 5 | 5 | 3 | 5 | 8 | 7 | 10 | 6 | 6 | 8 | 4 |  | 4.4 | 7.5 | 7.7 | 6.9 | 6.5 | preferred |
| *t*-Butanol | 75-65-0 | Alcohols | 82 | 5 | 5 | 3 | 5 | 9 | 7 | 7 | 5 | 6 | 10 | 8 |  | 4.4 | 7.9 | 5.9 | 7.7 | 6.3 | usable |
| IMS (EtOH, denaturated) | 64-17-5 | Alcohols | 78 | 5 | 5 | 3 | 5 | 9 | 5 | 4 | 7 | 6 | 10 |  |  | 4.4 | 6.7 | 5.3 | 7.7 | 5.9 | usable |
| Glycerol diacetate | 111-55-7 | Esters | 187 | 5 | 6 | 6 | 10 | 6 | 8 | 10 | 8 | 10 | 10 |  | 1 | 6.5 | 6.9 | 8.9 | 10.0 | 8.0 | preferred |
| Isobutyl acetate | 110-19-0 | Esters | 116 | 7 | 9 | 8 | 6 | 9 | 6 | 10 | 6 | 8 | 10 |  | 1 | 7.4 | 7.3 | 7.7 | 8.9 | 7.8 | preferred |
| Isoamyl acetate | 123-92-2 | Esters | 142 | 9 | 9 | 8 | 8 | 4 | 6 | 7 | 8 | 8 | 10 |  | 1 | 8.5 | 4.9 | 7.5 | 8.9 | 7.3 | preferred |
| Isopropyl acetate | 108-21-4 | Esters | 89 | 6 | 7 | 5 | 5 | 9 | 5 | 10 | 6 | 6 | 10 | 7 |  | 5.7 | 6.7 | 7.7 | 7.7 | 6.9 | preferred |
| Ethyl acetate | 141-78-6 | Esters | 77 | 5 | 6 | 5 | 4 | 9 | 5 | 10 | 7 | 5 | 10 | 6 |  | 4.9 | 6.7 | 8.4 | 7.1 | 6.7 | preferred |
| Propylene carbonate | 108-32-7 | Carbonates | 242 | 4 | 5 | 6 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |  |  | 5.9 | 10.0 | 10.0 | 10.0 | 8.8 | preferred |
| Dimethyl carbonate | 616-38-6 | Carbonates | 91 | 4 | 3 | 5 | 5 | 9 | 7 | 10 | 6 | 6 | 10 | 8 |  | 4.2 | 7.9 | 7.7 | 7.7 | 6.7 | preferred |
| Cyclopentanone | 120-92-3 | Ketones | 131 | 8 | 9 | 6 | 7 | 10 | 5 | 7 | 6 | 8 | 10 | 6 |  | 7.4 | 7.1 | 6.5 | 8.9 | 7.4 | preferred |
| Methylisobutyl ketone | 108-10-1 | Ketones | 117 | 7 | 8 | 5 | 7 | 9 | 3 | 7 | 6 | 7 | 9 | 2 |  | 6.7 | 5.2 | 6.5 | 7.9 | 6.5 | preferred |
| Methylethyl ketone | 78-93-3 | Ketones | 80 | 5 | 5 | 3 | 4 | 8 | 4 | 10 | 6 | 5 | 9 | 3 |  | 4.2 | 5.7 | 7.7 | 6.7 | 5.9 | usable |
| Acetone | 67-64-1 | Ketones | 56 | 5 | 6 | 2 | 2 | 10 | 6 | 10 | 6 | 4 | 9 | 7 |  | 3.3 | 7.7 | 7.7 | 6.0 | 5.9 | usable |
| *p*-Xylene | 106-42-3 | Aromatics | 138 | 10 | 9 | 6 | 7 | 5 | 2 | 7 | 7 | 5 | 10 | 7 |  | 7.8 | 3.2 | 7.0 | 7.1 | 5.9 | usable |
| Toluene | 108-88-3 | Aromatics | 111 | 10 | 7 | 6 | 7 | 7 | 2 | 7 | 6 | 5 | 10 | 7 |  | 7.4 | 3.7 | 6.5 | 7.1 | 6.0 | usable |

Green Chem., 2016, 18, 3879–3890

# Solvents : how are solvents classified part 2



| Solvent | CAS | solvent class | boiling point | Incineration score | Recyding score | Biotreatment score | VOC emissions[1] | Env. Impact Aqueous | env. Impact Air | Heath Hazard[1] | Exposure | Flammability and explosion[1] | Reactivity[1] | LCA | data Gaps | waste score | environ. score | Human Health score | Safety score | Calc. score | solvent recommendation | Comaprison to Roche guide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Methanesulfonic acid | 75-75-2 | Acids | 167 | 2 | 5 | 5 | 10 | 6 | 6 | 4 | 10 | 9 | 6 |  | 2 | 4.7 | 6.0 | 6.3 | 7.3 | 6.0 | usable | #N/A |
| 1,2,3-Trimethoxypropane | 20637-49-4 | Ethers | 143 | 4 | 5 | 4 | 8 | 7 | 7 | 4 | 5 | 8 | 9 |  | 10 | 5.0 | 7.0 | 4.5 | 8.5 | 6.0 | usable | #N/A |
| 1,3-Dimethyl-2-imidazolidinone | 80-73-9 | Dipolar Aprotics | 225 | 3 | 4 | 3 | 10 | 7 | 6 | 4 | 8 | 9 | 9 |  | 6 | 4.4 | 6.5 | 5.7 | 9.0 | 6.2 | usable | #N/A |
| *t*-Butanol | 75-65-0 | Alcohols | 82 | 5 | 5 | 3 | 5 | 9 | 7 | 7 | 5 | 6 | 10 | 8 |  | 4.4 | 7.9 | 5.9 | 7.7 | 6.3 | usable | Usable |
| *N*,*N*-Dimethyloctanamide | 1118-92-9 | Other | 261 | 5 | 6 | 5 | 8 | 7 | 5 | 4 | 6 | 9 | 10 |  | 6 | 5.9 | 5.9 | 4.9 | 9.5 | 6.3 | usable | #N/A |
| Dimethyl sulfoxide | 67-68-5 | Dipolar Aprotics | 189 | 3 | 4 | 4 | 9 | 8 | 6 | 7 | 9 | 9 | 5 | 6 |  | 4.6 | 6.9 | 7.9 | 6.7 | 6.4 | preferred | Usable |
| 1,2-Isopropylideneglycerol | 100-79-8 | Alcohols | 192 | 6 | 5 | 5 | 10 | 4 | 6 | 4 | 8 | 10 | 10 |  | 5 | 6.2 | 4.9 | 5.7 | 10.0 | 6.4 | usable | #N/A |
| 2-Propanol | 67-63-0 | Alcohols | 82 | 5 | 5 | 3 | 5 | 8 | 7 | 10 | 6 | 6 | 8 | 4 |  | 4.4 | 7.5 | 7.7 | 6.9 | 6.5 | preferred | Usable |
| Methylisobutyl ketone | 108-10-1 | Ketones | 117 | 7 | 8 | 5 | 7 | 9 | 3 | 7 | 6 | 7 | 9 | 2 |  | 6.7 | 5.2 | 6.5 | 7.9 | 6.5 | preferred | Usable |
| *t*-Amyl alcohol | 75-85-4 | Alcohols | 102 | 6 | 3 | 4 | 7 | 9 | 5 | 7 | 6 | 8 | 10 |  | 2 | 4.7 | 6.7 | 6.5 | 8.9 | 6.6 | preferred | #N/A |
| 1-Propanol | 71-23-8 | Alcohols | 97 | 5 | 3 | 3 | 6 | 10 | 4 | 10 | 7 | 8 | 10 | 7 |  | 4.1 | 6.3 | 8.4 | 8.9 | 6.6 | preferred | Preferred |
| Furfural | 98-01-1 | Other | 162 | 7 | 8 | 8 | 8 | 8 | 4 | 4 | 6 | 9 | 9 |  | 1 | 7.7 | 5.7 | 4.9 | 9.0 | 6.6 | preferred | #N/A |
| Ethanol | 64-17-5 | Alcohols | 78 | 5 | 5 | 3 | 4 | 9 | 5 | 10 | 8 | 6 | 10 |  |  | 4.2 | 6.7 | 8.9 | 7.7 | 6.6 | preferred | Preferred |
| Ethyl acetate | 141-78-6 | Esters | 77 | 5 | 6 | 5 | 4 | 9 | 5 | 10 | 7 | 5 | 10 | 6 |  | 4.9 | 6.7 | 8.4 | 7.1 | 6.7 | preferred | Usable |
| 1-Butanol | 71-36-3 | Alcohols | 118 | 6 | 7 | 5 | 8 | 9 | 3 | 7 | 7 | 8 | 9 | 5 |  | 6.4 | 5.2 | 7.0 | 8.5 | 6.7 | preferred | Preferred |
| Dimethyl carbonate | 616-38-6 | Carbonates | 91 | 4 | 3 | 5 | 5 | 9 | 7 | 10 | 6 | 6 | 10 | 8 |  | 4.2 | 7.9 | 7.7 | 7.7 | 6.7 | preferred | #N/A |
| Dimethyl isosorbide | 5306-85-4 | Ethers | 236 | 4 | 4 | 5 | 10 | 9 | 6 | 4 | 9 | 9 | 8 |  | 10 | 5.3 | 7.3 | 6.0 | 8.5 | 6.7 | usable | #N/A |
| Lactic acid | 50-21-5 | Acids | 122 | 3 | 6 | 5 | 10 | 9 | 6 | 4 | 9 | 10 | 8 |  | 4 | 5.5 | 7.3 | 6.0 | 8.9 | 6.8 | preferred | #N/A |
| Dihydrolevoglucosenome | 1087696-49-8 | Other | 203 | 4 | 4 | 5 | 10 | 9 | 6 | 4 | 8 | 10 | 10 |  | 9 | 5.3 | 7.3 | 5.7 | 10.0 | 6.9 | usable | #N/A |
| Isopropyl acetate | 108-21-4 | Esters | 89 | 6 | 7 | 5 | 5 | 9 | 5 | 10 | 6 | 6 | 10 | 7 |  | 5.7 | 6.7 | 7.7 | 7.7 | 6.9 | preferred | Preferred |
| Isobutanol | 78-83-1 | Alcohols | 108 | 6 | 3 | 5 | 7 | 10 | 6 | 7 | 7 | 8 | 9 |  | 0 | 5.0 | 7.7 | 7.0 | 8.5 | 6.9 | preferred | Preferred |
| Dimethyl succinate | 106-65-0 | Esters | 200 | 4 | 5 | 6 | 10 | 9 | 7 | 4 | 7 | 9 | 10 |  | 4 | 5.9 | 7.9 | 5.3 | 9.5 | 7.0 | preferred | #N/A |
| 1-Hexanol | 111-27-3 | Alcohols | 157 | 5 | 6 | 3 | 9 | 8 | 5 | 7 | 9 | 9 | 10 |  | 1 | 5.3 | 6.3 | 7.9 | 9.5 | 7.1 | preferred | #N/A |
| Diethylcarbonate | 105-58-8 | Carbonates | 126 | 7 | 9 | 9 | 7 | 9 | 8 | 4 | 5 | 8 | 10 |  | 4 | 7.9 | 8.5 | 4.5 | 8.9 | 7.2 | preferred | #N/A |
| Methyl oleate | 112-62-9 | Esters | 218 | 9 | 6 | 8 | 10 | 5 | 8 | 4 | 10 | 7 | 10 |  | 3 | 8.1 | 6.3 | 6.3 | 8.4 | 7.2 | preferred | #N/A |
| Isoamyl acetate | 123-92-2 | Esters | 142 | 9 | 9 | 8 | 8 | 4 | 6 | 7 | 8 | 8 | 10 |  | 1 | 8.5 | 4.9 | 7.5 | 8.9 | 7.3 | preferred | #N/A |
| Water | 7732-18-5 | Water | 100 | 4 | 2 | 4 | 6 | 10 | 8 | 10 | 9 | 8 | 10 | 10 |  | 3.7 | 8.9 | 9.5 | 8.9 | 7.3 | preferred | Preferred |
| 1-Octanol | 111-87-5 | Alcohols | 195 | 9 | 7 | 8 | 10 | 5 | 4 | 7 | 10 | 9 | 10 |  | 1 | 8.4 | 4.5 | 8.4 | 9.5 | 7.4 | preferred | #N/A |
| Cyclopentanone | 120-92-3 | Ketones | 131 | 8 | 9 | 6 | 7 | 10 | 5 | 7 | 6 | 8 | 10 | 6 |  | 7.4 | 7.1 | 6.5 | 8.9 | 7.4 | preferred | #N/A |
| Diisopropyl adipate | 6938-94-9 | Esters | 136 | 5 | 7 | 6 | 10 | 7 | 8 | 4 | 10 | 9 | 10 |  | 8 | 6.8 | 7.5 | 6.3 | 9.5 | 7.4 | usable | #N/A |
| Anisole | 100-66-3 | Aromatics | 154 | 8 | 8 | 8 | 8 | 7 | 6 | 7 | 8 | 7 | 9 | 5 |  | 8.0 | 6.5 | 7.5 | 7.9 | 7.4 | preferred | Preferred |
| γ-Valerolactone | 108-29-2 | Esters | 207 | 8 | 7 | 10 | 9 | 10 | 6 | 4 | 7 | 9 | 10 |  | 9 | 8.4 | 7.7 | 5.3 | 9.5 | 7.6 | usable | #N/A |
| Butylene carbonate | 4437-85-8 | Carbonates | 250 | 5 | 5 | 7 | 10 | 9 | 9 | 4 | 9 | 9 | 10 |  | 9 | 6.5 | 9.0 | 6.0 | 9.5 | 7.6 | usable | #N/A |
| 2-Ethylhexyl acetate | 103-09-3 | Esters | 199 | 9 | 7 | 9 | 10 | 4 | 6 | 10 | 7 | 9 | 10 |  | 2 | 8.7 | 4.9 | 8.4 | 9.5 | 7.6 | preferred | #N/A |
| Dimethyl adipate | 627-93-0 | Esters | 110 | 8 | 5 | 10 | 10 | 8 | 8 | 4 | 8 | 9 | 10 |  | 5 | 8.0 | 8.0 | 5.7 | 9.5 | 7.6 | usable | #N/A |
| *N*,*N*-Dimethyldecanamide | 14433-76-2 | Other | 291 | 6 | 7 | 6 | 10 | 4 | 6 | 10 | 10 | 10 | 10 |  | 5 | 7.1 | 4.9 | 10.0 | 10.0 | 7.7 | usable | #N/A |
| Amyl acetate | 628-63-7 | Esters | 146 | 7 | 8 | 8 | 8 | 9 | 5 | 7 | 8 | 8 | 10 |  | 2 | 7.7 | 6.7 | 7.5 | 8.9 | 7.7 | preferred | Preferred |
| 2,4,6-Collidine | 108-75-8 | Aromatics | 171 | 7 | 9 | 6 | 8 | 10 | 5 | 7 | 8 | 9 | 9 |  | 4 | 7.4 | 7.1 | 7.5 | 9.0 | 7.7 | preferred | #N/A |
| Diethyl succinate | 123-25-1 | Esters | 218 | 7 | 7 | 9 | 10 | 9 | 8 | 4 | 8 | 9 | 10 |  | 6 | 8.1 | 8.5 | 5.7 | 9.5 | 7.8 | usable | #N/A |
| Isobutyl acetate | 110-19-0 | Esters | 116 | 7 | 9 | 8 | 6 | 9 | 6 | 10 | 6 | 8 | 10 |  | 1 | 7.4 | 7.3 | 7.7 | 8.9 | 7.8 | preferred | Preferred |
| 1-Heptanol | 111-70-6 | Alcohols | 178 | 9 | 8 | 10 | 9 | 8 | 4 | 10 | 7 | 9 | 10 |  | 3 | 9.0 | 5.7 | 8.4 | 9.5 | 8.0 | preferred | #N/A |
| Glycerol diacetate | 111-55-7 | Esters | 187 | 5 | 6 | 6 | 10 | 6 | 8 | 10 | 8 | 10 | 10 |  | 1 | 6.5 | 6.9 | 8.9 | 10.0 | 8.0 | preferred | #N/A |
| Ethylene glycol | 107-21-1 | Alcohols | 197 | 4 | 5 | 5 | 10 | 10 | 8 | 7 | 10 | 10 | 10 | 9 |  | 5.6 | 8.9 | 8.4 | 10.0 | 8.1 | preferred | Preferred |
| 1-Pentanol | 71-41-0 | Alcohols | 137 | 7 | 8 | 8 | 9 | 9 | 4 | 10 | 9 | 9 | 10 |  | 0 | 8.0 | 6.0 | 9.5 | 9.5 | 8.1 | preferred | #N/A |
| Glycerol triacetate | 102-76-1 | Esters | 259 | 5 | 5 | 7 | 10 | 9 | 10 | 10 | 10 | 9 | 10 |  | 4 | 6.5 | 9.5 | 10.0 | 9.5 | 8.7 | preferred | #N/A |
| Propylene carbonate | 108-32-7 | Carbonates | 242 | 4 | 5 | 6 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |  |  | 5.9 | 10.0 | 10.0 | 10.0 | 8.8 | preferred | #N/A |

Green Chem., 2016, 18, 3879–3890

# Solvents: why do we need a solvent?

The best solvent is… **no solvent at all**. In industry, it is frequent to run reaction neat.

Advantages:

- Increased reaction efficiency/rates
- Reduced environmental impact

Disadvantages:

- solubility (of reactants into each other)
- Potential lack of reaction control (selectivity, safety)
- Reduced heat transfer
- purification

Selection of useful solvents attributes

- Solubilize reactants
- Offer great control of the reaction
- Act as heat sink to dissipate energy
- Act as heat transfer to homogeneously distribute the energy a reaction might need to proceed
- Facilitate product isolation/purification

*Chem. Rev.* **2021**, 121, 1582

# Solvents

Academia and Industry R&D

- Usually, chemists use the «literature» conditions as is (ex: Suzuki, Buchwald): dioxane
- keep using solvent which industry cannot use on scale ($CH_2Cl_2$, $CHCl_3$, $Et_2O$, dioxane, DCE...)

→ *Means process needs to be re-designed. Doing right/green first time?*

- First time reactions are usually run **very very diluted**
- **solvent mixtures**: much more complicated to recycle
- Work-up, purifications are usually **high consuming** operations
- Water is green solvent **only if** the waste water generated can be sent to the waste water treatment plant

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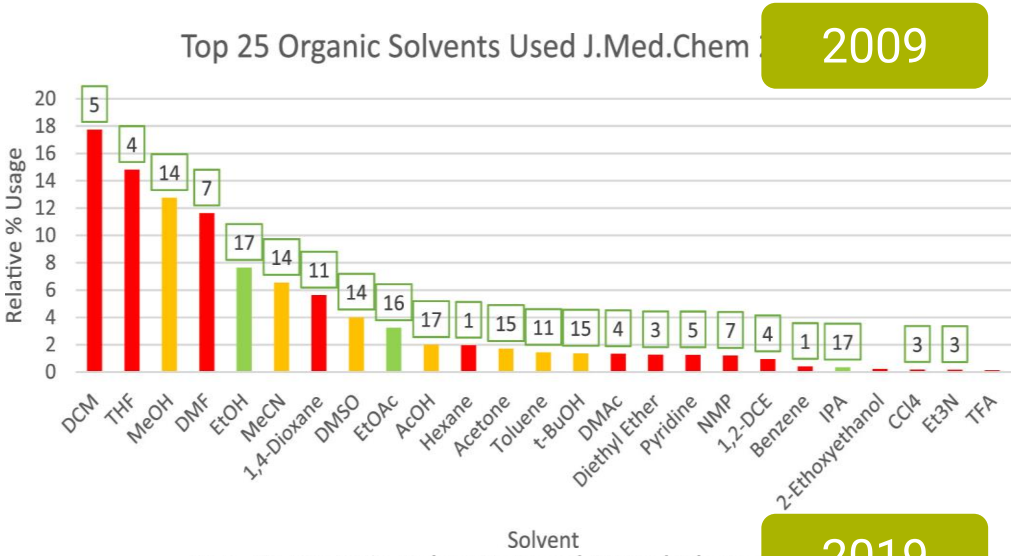

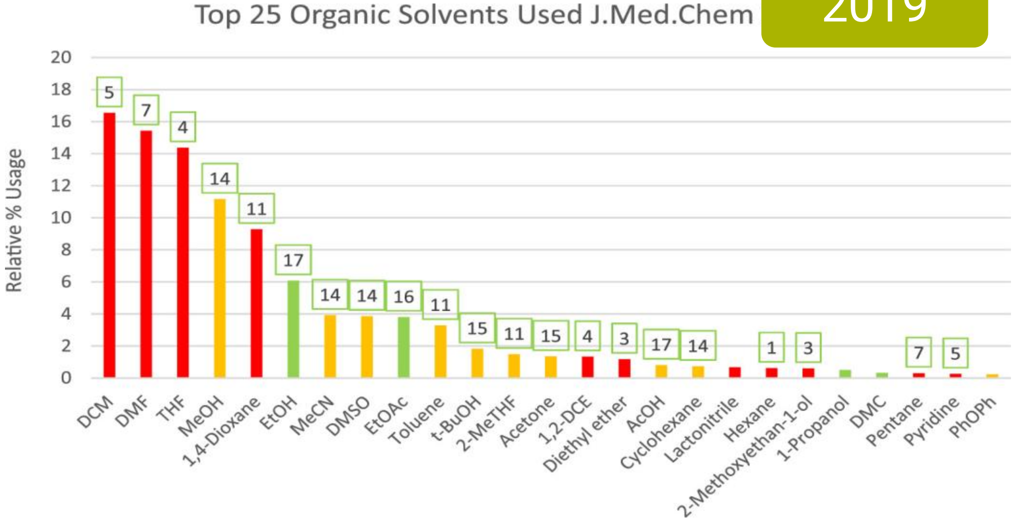

**Shift mindset is hard**

*Chem. Rev.* **2021**, 121, 1582

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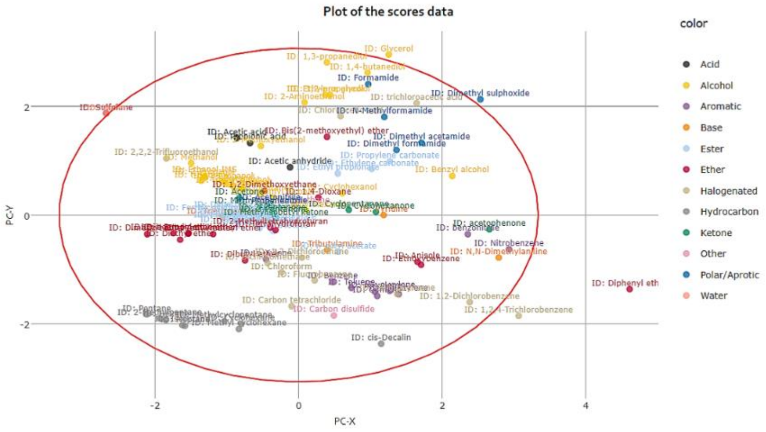
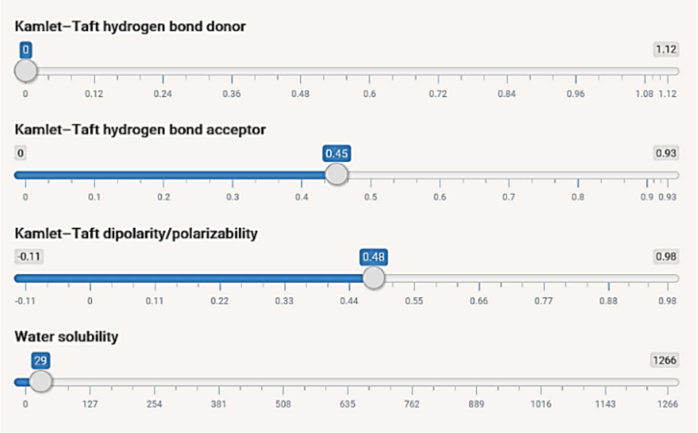
## On Ag scale > 1000 tons per annum

- solvents are almost always **recycled**
  - cost loss (need to buy new solvent)
  - cost disposal (incineration)
  - Capacity (incineration)
  - Large volumes: air emission ($CO_2$) would be high
- On pharma scale,solvent waste are mostly **burned**
  - Lower volumes but still results $CO_2$ emissions
  - Required GMP quality solvent Re-qualifying recycled solvent often does not compete vs buying new

# Solvent Selection Resources

- Internal platform and Database




**Kamlet–Taft hydrogen bond donor**: 0 (range 0–1.12)

**Kamlet–Taft hydrogen bond acceptor**: 0.45 (range 0–0.93)

**Kamlet–Taft dipolarity/polarizability**: 0.48 (range -0.11–0.98)

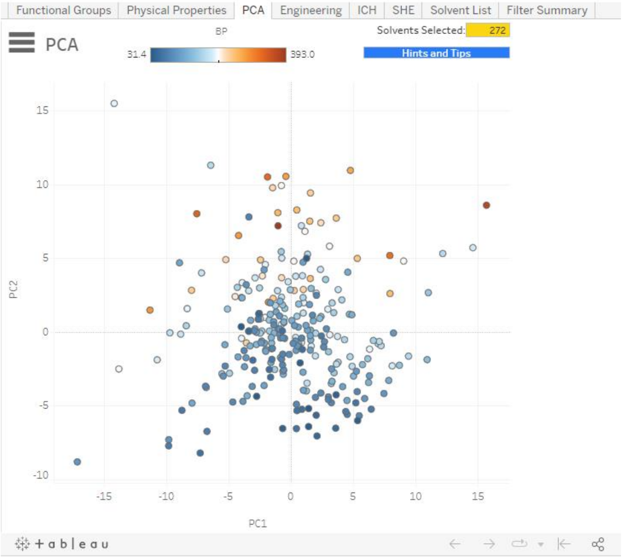
**Water solubility**: 29 (range 0–1266)

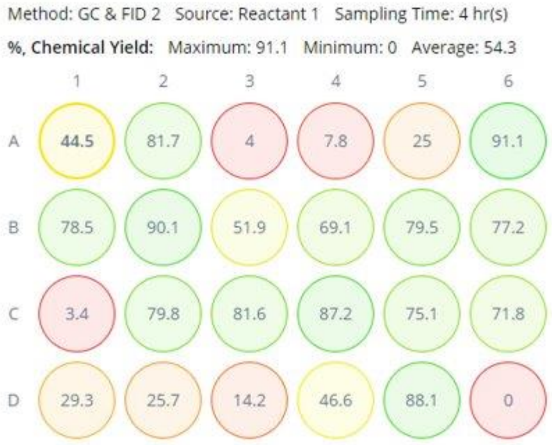
| name | parameters |
|---|---|
| solvency, Kamlet–Taft only | Kamlet–Taft hydrogen-bond donor |
| | Kamlet–Taft hydrogen-bond acceptor |
| | Kamlet–Taft dipolarity/polarizability |
| solvency for reactions, solvatochromic equation | Abraham's polarizability dipolarity *S* |
| | Abraham's hydrogen-bond acidity *A* |
| | Abraham's hydrogen-bond basicity *B* |
| | Polarizability correction term $\delta$ |
| | Hildebrand solubility $\delta_H{}^2$ |
| Solvency for gas–liquid reactions, Abraham's-*L* | Abraham's excessive molar refractivity *E* |
| | Abraham's polarizability dipolarity *S* |
| | Abraham's hydrogen-bond acidity *A* |
| | Abraham's hydrogen-bond basicity *B* |
| | Abraham's gas hexadecane partition coefficient *L* |
| solvency for condensed phase reactions, Abraham's-*V* | Abraham's excessive molar refractivity *E* |
| | Abraham's polarizability dipolarity *S* |
| | Abraham's hydrogen-bond acidity *A* |
| | Abraham's hydrogen-bond basicity *B* |
| | Abraham's McGowan volume *V* |
| solvency, Kamlet–Taft and other general parameters | Dimroth–Reichardt Et Parameter |
| | acity |
| | basity |
| | Kamlet–Taft hydrogen-bond donor |
| | Kamlet–Taft hydrogen-bond acceptor |
| | Kamlet–Taft dipolarity/polarizability |
| | elutropic series |
| | dipole moment |
| | dielectric constant |
| | Hansen parameter - dispersive ($\delta_d$) |
| | Hansen parameter - polar ($\delta_p$) |
| | Hansen parameter - hydrogen bonding ($\delta_h$) |
| polarity descriptors | dipole moment |
| | dielectric constant |
| solubility Parameters (gE models, regular solution theory) | Hansen parameter - dispersive ($\delta_d$) |
| | Hansen parameter - polar ($\delta_p$) |
| | Hansen parameter - hydrogen bonding ($\delta_h$) |
| | Hildebrand solubility $\delta_H{}^2$ |
| | Hildebrand solubility, calculated |
| general physical properties | molecular mass |
| | density |
| | flash point |
| | vapor pressure |
| | melting point |
| | boiling point |
| | water solubility |
| | dipole moment |
| | dielectric constant |
| | vaporization enthalpy |
| GSK HSE descriptors | GSK guide: waste |
| | GSK guide: environmental impact |
| | GSK guide: health |
| | GSK guide: flammability and explosion |
| | GSK guide: stability |

*OPRD* 2019, 23, 5, 998

# Solvent screening

- PCA (principal component analysis) mapping solvents
- This approach only optimizes the **reaction performance and not other criterias** (ease of work-up, recyclability…)





Method: GC & FID 2 Source: Reactant 1 Sampling Time: 4 hr(s)

**%, Chemical Yield:** Maximum: 91.1 Minimum: 0 Average: 54.3

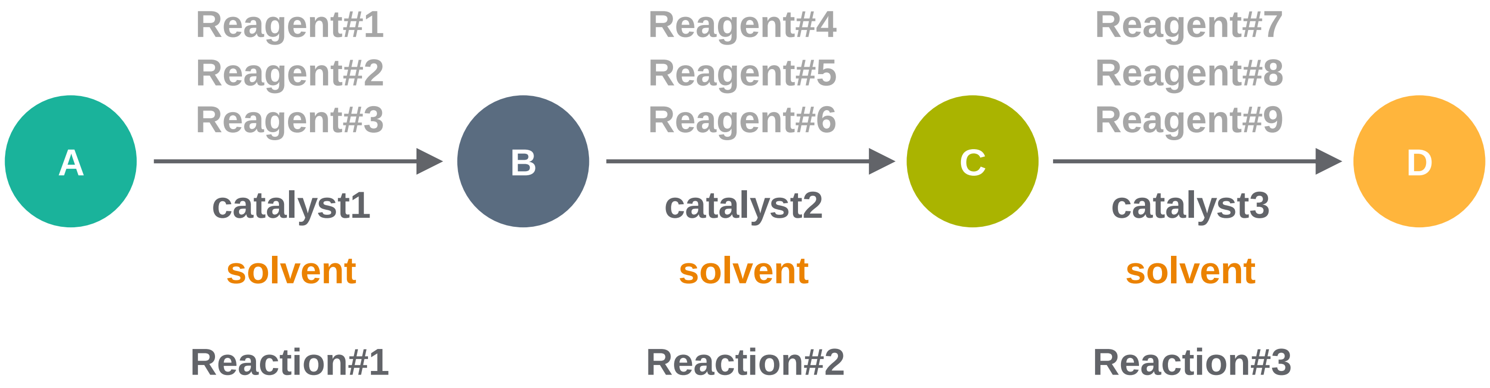
|   | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| A | 44.5 | 81.7 | 4 | 7.8 | 25 | 91.1 |
| B | 78.5 | 90.1 | 51.9 | 69.1 | 79.5 | 77.2 |
| C | 3.4 | 79.8 | 81.6 | 87.2 | 75.1 | 71.8 |
| D | 29.3 | 25.7 | 14.2 | 46.6 | 88.1 | 0 |

*Org. Process Res. Dev.* **2016,** *20*, 760-773

# Solvents : for a process how do choose the solvent

Most Important criterias for selecting a solvent. Here for Reaction#2

- What is the solvent of the step done before Reaction 2 ? After Reaction 2?
- Is residual solvent important/impacting the next step?
- Are the impurities from step 2 and formed in Solvent2, easily purged in Step 3 or later
- If D is the final product: how much (ppm) will remain in the product? Is it a significant problem?
- **Can I run the reactions 1; 2 and 3 in the same solvent and eliminate isolation of intermediates B and/or C for example**



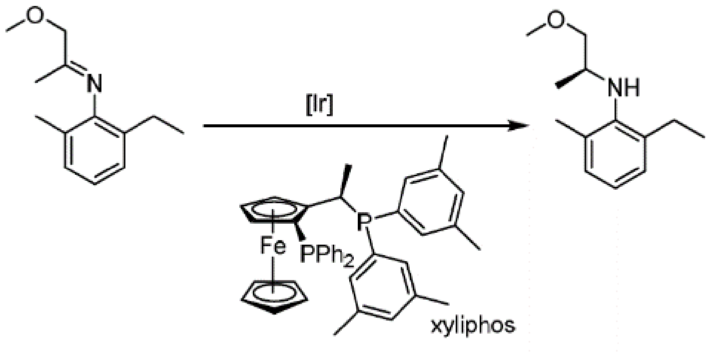
*Chem. Rev.* **2021**, 121, 1582

# Solvent Recycling

Most Important criterias for solvent selection: **is cheap**

- Solvents = 80-90% of total mass in a given chemical reaction
- Cost is $1-10/kg for common solvents but need 1000s of tons/year !
- Very often solvent costs often exceed raw material costs
- Waste disposal also costly
- Regulatory: Solvent emissions limits (VOC regulations)
- When recycled, amortization of solvent cost is possible
- Of course impossible to recycle 100%. 90% is usually a good threshold.

**Cannot throw it away !**



Metolachlor - Solvent Recovery

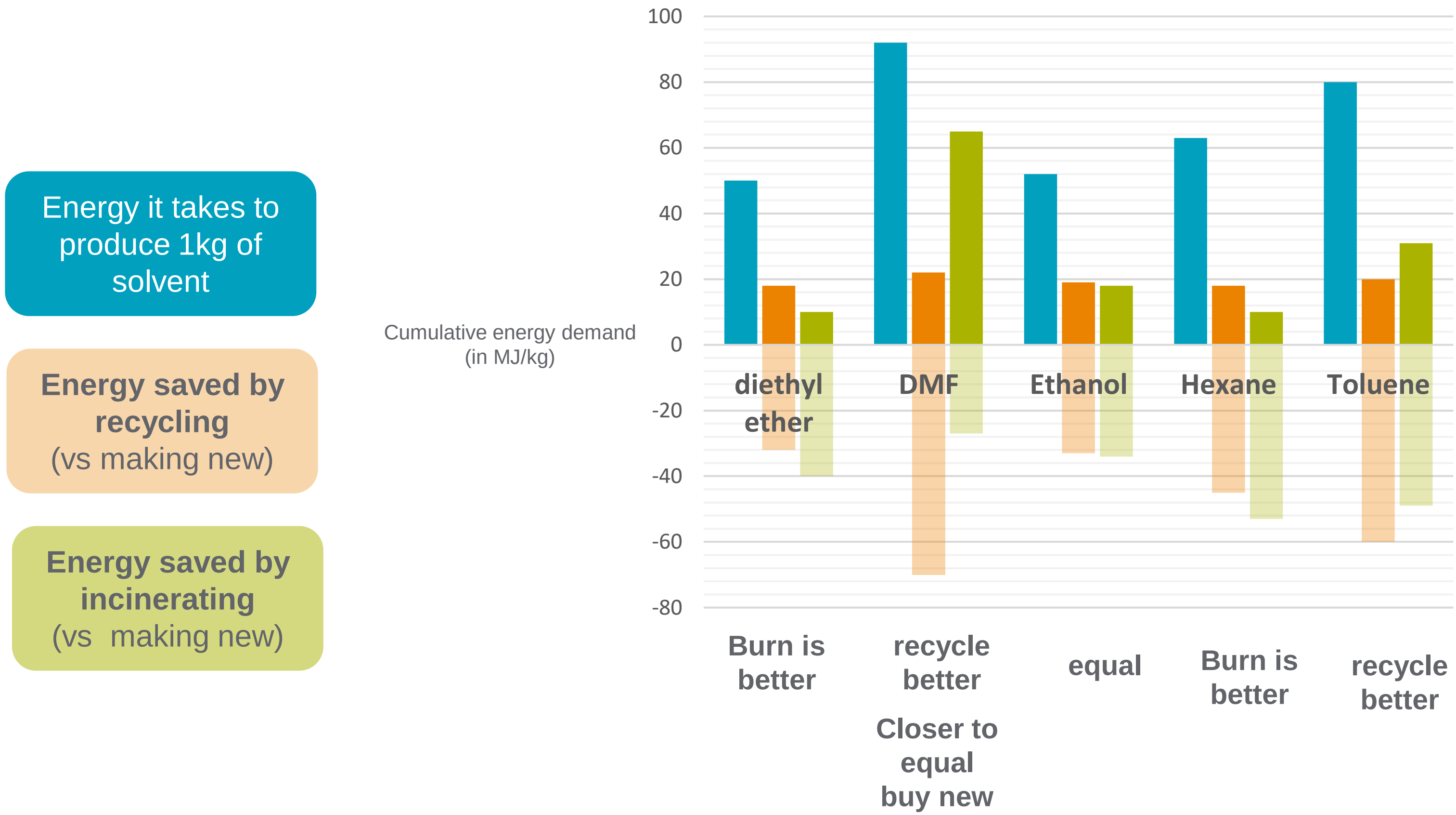
- Two-stage distillation system
- Stage 1: Atmospheric distillation (removes volatiles)
- Stage 2: Vacuum distillation (final purification)
- Carbon filtration to remove trace metals
- Recovery rate: 92-95%
- Reuse: Up to 6 cycles before purge
- Toluene cost savings: ~$1.8M/year

*Chemical Communications*, 2007,44, 4637-4650.

# Solvents Recycling

If a solvent is not recycled, it is «burned» to generate energy back

The energy needed to recyle the solvent to reusable quality **needs to make sense** (don’t spend more energy/money recycling than making it new)



**Burn is better**

**recycle better**

**Closer to equal buy new**

**equal**

**Burn is better**

**recycle better**

*Green Chemistry*, 2007, **9**, 927

# Solvent Recycling: Exercise

Consider the following process:

- Uses 1000 kg DMA per batch
- WE do 50 batches per year
- DMA costs 3.0 $/kg on bulk scale.
- Cost of DMA disposal = 1.5$/kg
- The industrial distillation unit costs 500’000 $
- It enable to recover 90% DMA

**What's the payback period?**

**After amortization of installation, what’s the cost of DMA per batch**

Good or Bad ? And why?

*Use slide 43-44*

**DMSO**

**Dichloromethane**

**Heptane**

**Toluene**

**Isopropanol**

**Diethyl ether**

**Pyridine**

*Green Chemistry*, 2007, **9**, 927

# Solvents : Summary

Most Important criterias for selecting a solvent

- Is cheap
- Is recyclable and reusable. Energy needed to reuse the solvent needs to make sense (don’t spend more enegy/money recycling than making it new)
- Is dried easily if needed
- Is affording an optimal reaction peformance:
  - yield
  - Selectivity (vs by and side-products)
  - Fast kinetics
  - Easy isolation
- is safe (OEL), flash point
- Operationnaly safe (product does not heavily precipitate and break the stirrer, no crust formation to prevent heat dissipation etc…)

| solvents often used on large scale | Solvent rarely used on large scale |
|---|---|
| Toluene | Dichloromethane |
| Methanol | DMSO |
| Ethanol | Diethyl Ether |
| Acetic Acid | 1,2 DCE |
| Ethyl acetate | Pyridine |
| chlorobenzene | benzene |

*Chem. Rev.* **2021**, 121, 1582

# Catalysis

1.Prevent waste

2.Atom economy

3.Less Hazardous Synthesis

4.Design Benign Chemicals

5.Benign Solvent

6.Energy efficiency

7. Use of renewable feedstocks

8. Reduce derivatives

9. Catalysis

10. Design for degradation

11. Real-time analysis for pollution prevention

12. Safer chemistry for accident prevention

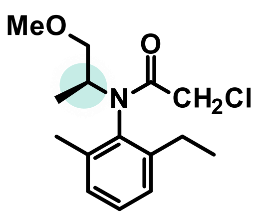
*Green Chemistry: Theory* and *Practice*, Ox. Uni. Press, New York, *1998*

www.menti.com

71 95 70 73

link

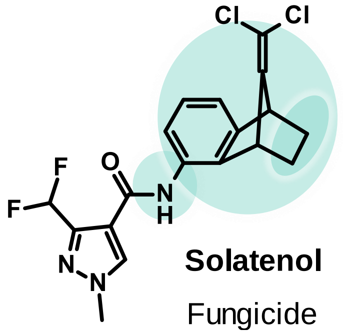
# Selected Syngenta active ingredients derived by catalytic transformations



**S-Metolachlor**

Selective Herbicide

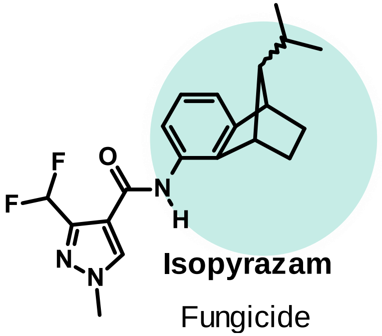
- Enantioselective Ir-catalyzed imine hydrogenation
- air Cu-catalyzed alcohol oxidation (gas-phase)



**Solatenol**

Fungicide

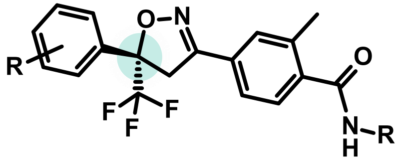
- Cu-Catalyzed Kharash addition
- Al-Catalyzed Diels-Alder reaction
- Rh-Catalyzed alkene hydrogenation
- Ru-Ctalyzed ketone hydrogenation



**Isopyrazam**

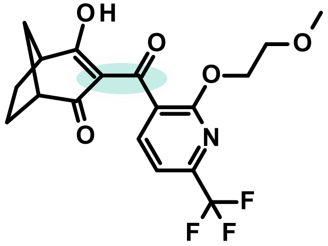
Fungicide

- Buchwald-Hartwig amination
- Hydrogenolysis of benzylamine
-Pd-catalyzed hydrogenation



New inceticide
(in development)

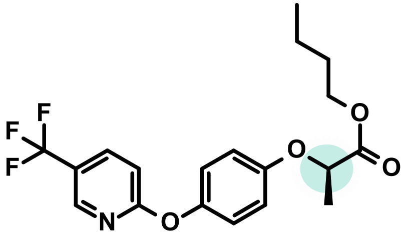
Enantioselective organocatalytic formation of 4,5-dihydroisoxazole



**Bicyclopyrone**

Selective Herbicide

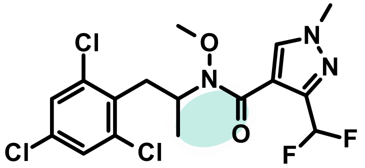
- TEMPO-catalyzed oxidation of alcohol
- Cyanide-catalyzed rearrangement of O-acylated to C-acylated 1,3-diketone



**Fluazifop-Butyl**

Selective Herbicide

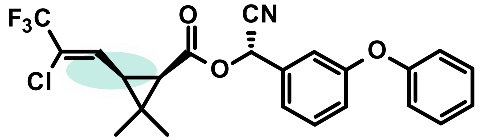
High-temperature gas phase chlorination/Halex on a fluidized bed catalyst



**Adepidin**

Fungicide

Pt-ctalyzed *O*-methyloxime hydrogenation



**Lambda-Cyhalothrin**

Insecticide

Fe-Catalyzed Kharash addition

# Technical, economical and environmental aspects of a catalytic transformation

## Catalytic Reaction

TON - Catalyst loading
TOF - Reaction rate
Volumetric productivity
Catalyst deactivation
Quality of starting materials / catalyst
Heat and mass transfer
Supply chain security
Freedom to operate (FTO)
IP protection
Process safety
Material of construction
Operation mode (i.e. batch/continuous) and reactor design
Process robustness
Process operating window
Catalyst cost and availability on scale
Pressures metals price volatility

## Work-up and Product isolation

Actual isolated yield
Product specification (purity, impurity profile, physical form)
Contamination with heavy metals

## Waste treatment and disposal

Amount of waste generated (environmental and financial aspects)
Presence of heavy metals in aqueous effluents

## Catalyst recovery

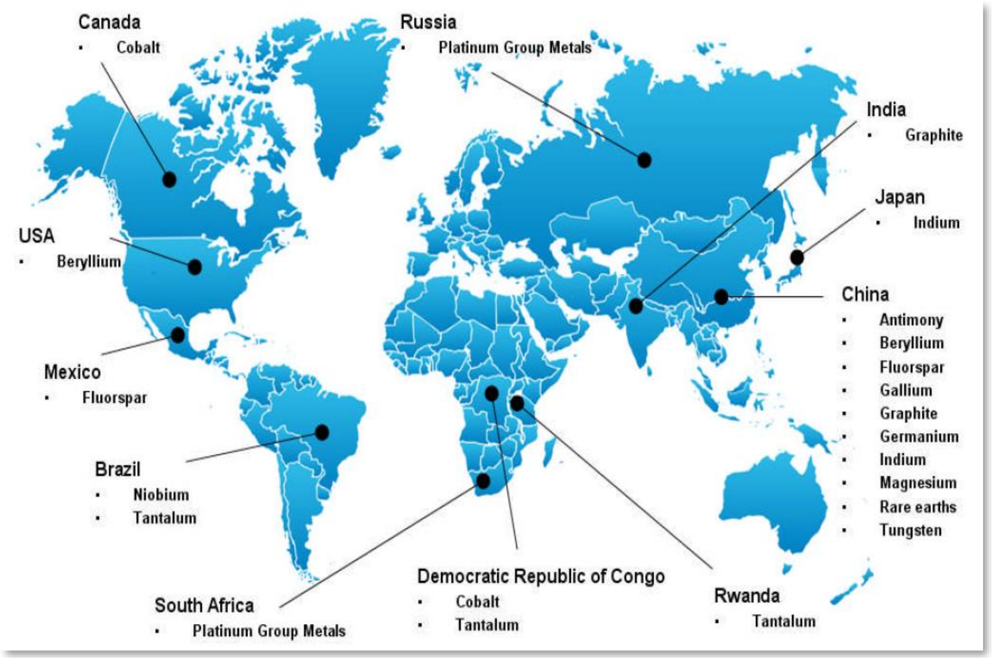
Metal recycling efficiency
Metal leaching
Cost of regeneration / re-synthesis (for homogeneous catalysts)

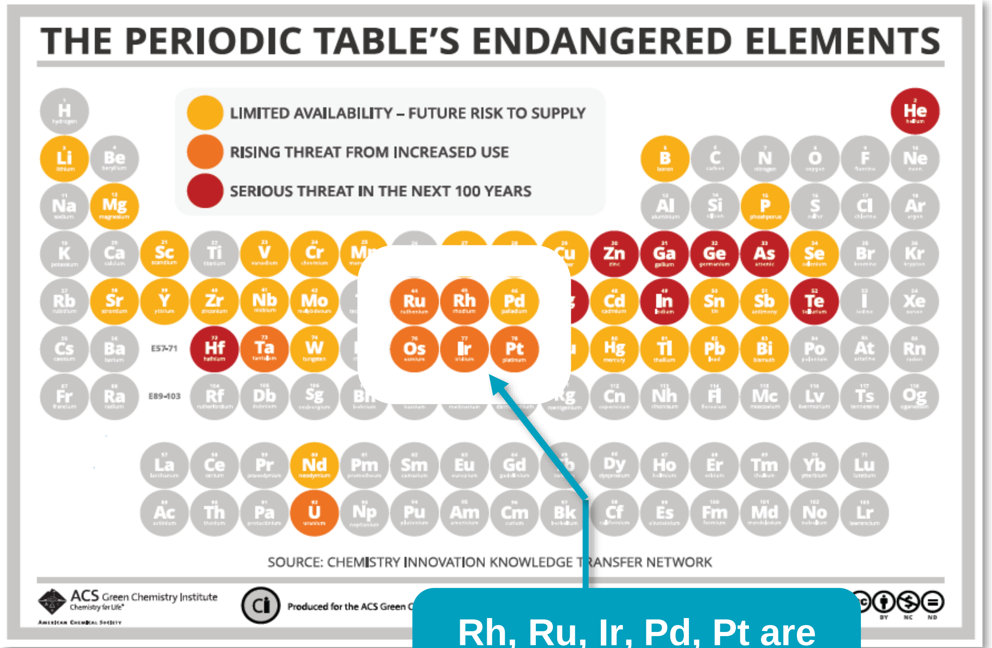
## Solvent recovery

Recovery rate
Quality

# Catalysis: Nobels Metals

- Are scarce and a finite resource
- Are in some cases subject to ethical & geopolitical concerns





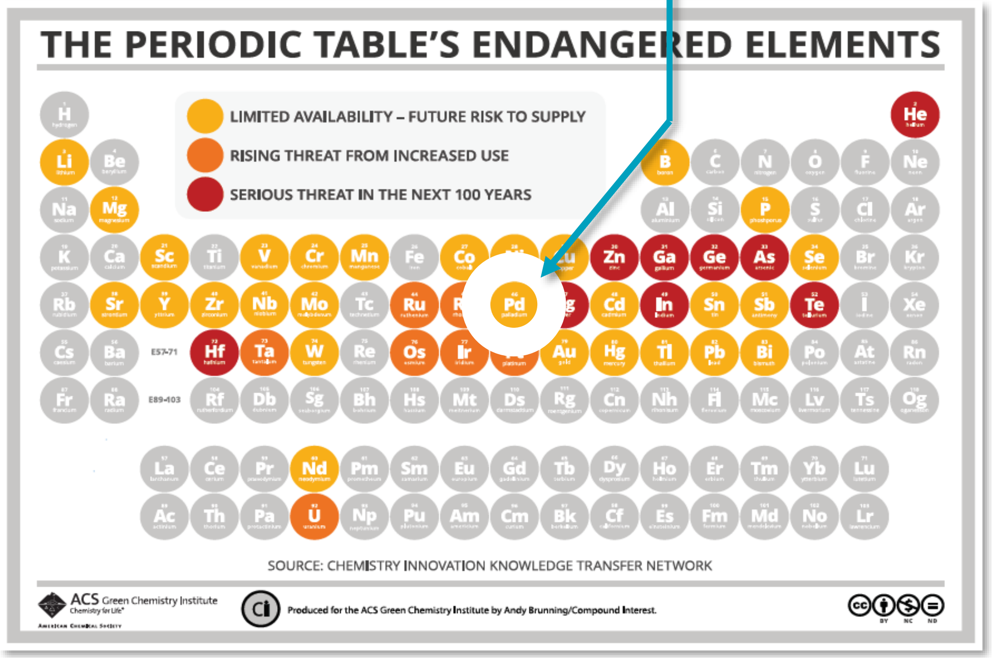
**Rh, Ru, Ir, Pd, Pt are scare resources**

https://www.acs.org/content/acs/en/greenchemistry.html

# Catalysis: Nobels Metals

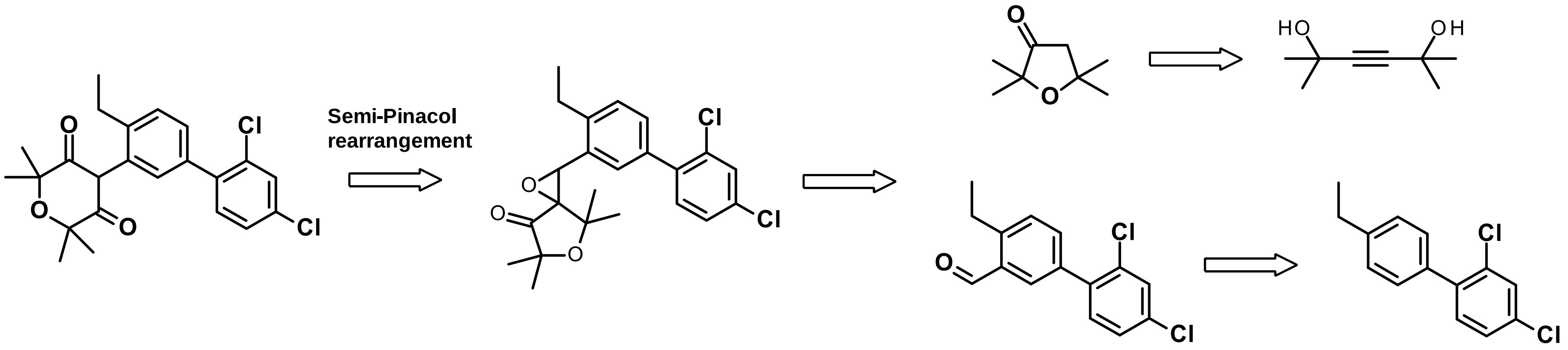
- Are scarce and a finite resource
- Are in some cases subject to ethical & geopolitical concerns
- Have heavily fluctuating (generally updwards)

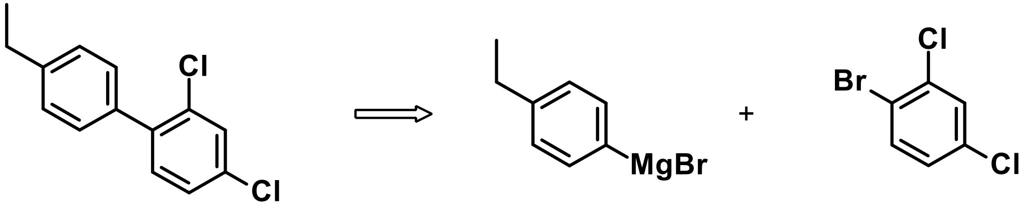
Pd heavily used, price rising



https://www.heraeus.com/en/group/home/home.html ; http://www.acsgci.org

# Herbicide Synthesis





Pros

| Metal | $/kg | $/mol |
|---|---|---|
| Nickel | 12 | **0.7** |
| Palladium | 33000 | **3500** |

Cons

Nickel - carcinogenic heavy metal, must be well managed

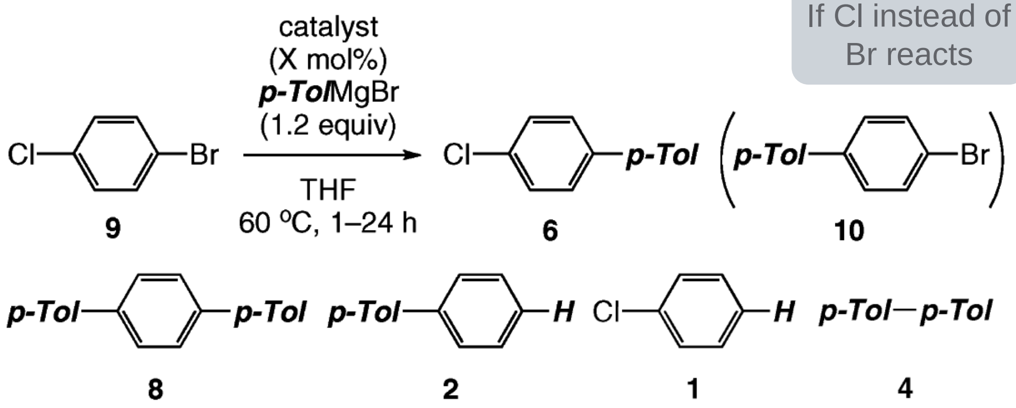
M.Zeller, unpublished, D.Gribkov, DIAC-Novartis Symposium November 2022. D.Gribkov, ACS. Chicago, Aug 2022

# Nickel catalyzed Kumada-Tamao-Corriu Coupling

**Original article:** M. Nakamura et al. *J. Am. Chem. Soc.* **2009**, *131*, 11949-11963; Tosoh Corp. and Kyoto University WO2009/008447A1

**Needed to be achieved:**

- High Cl/Br Selectivity
- No Cross-/ Homo-coupling by-products
- Low catalyst loading (<= 0.5 mol%)

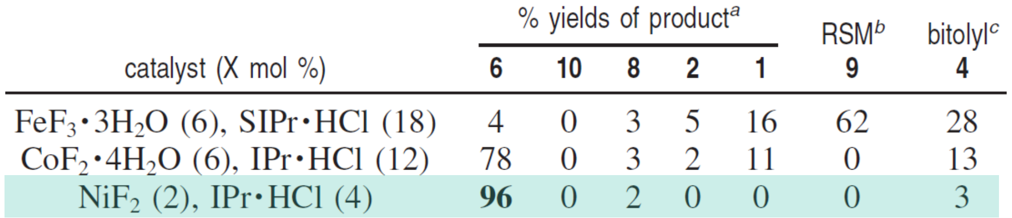


If Cl instead of Br reacts

Coupling with Cl and Br

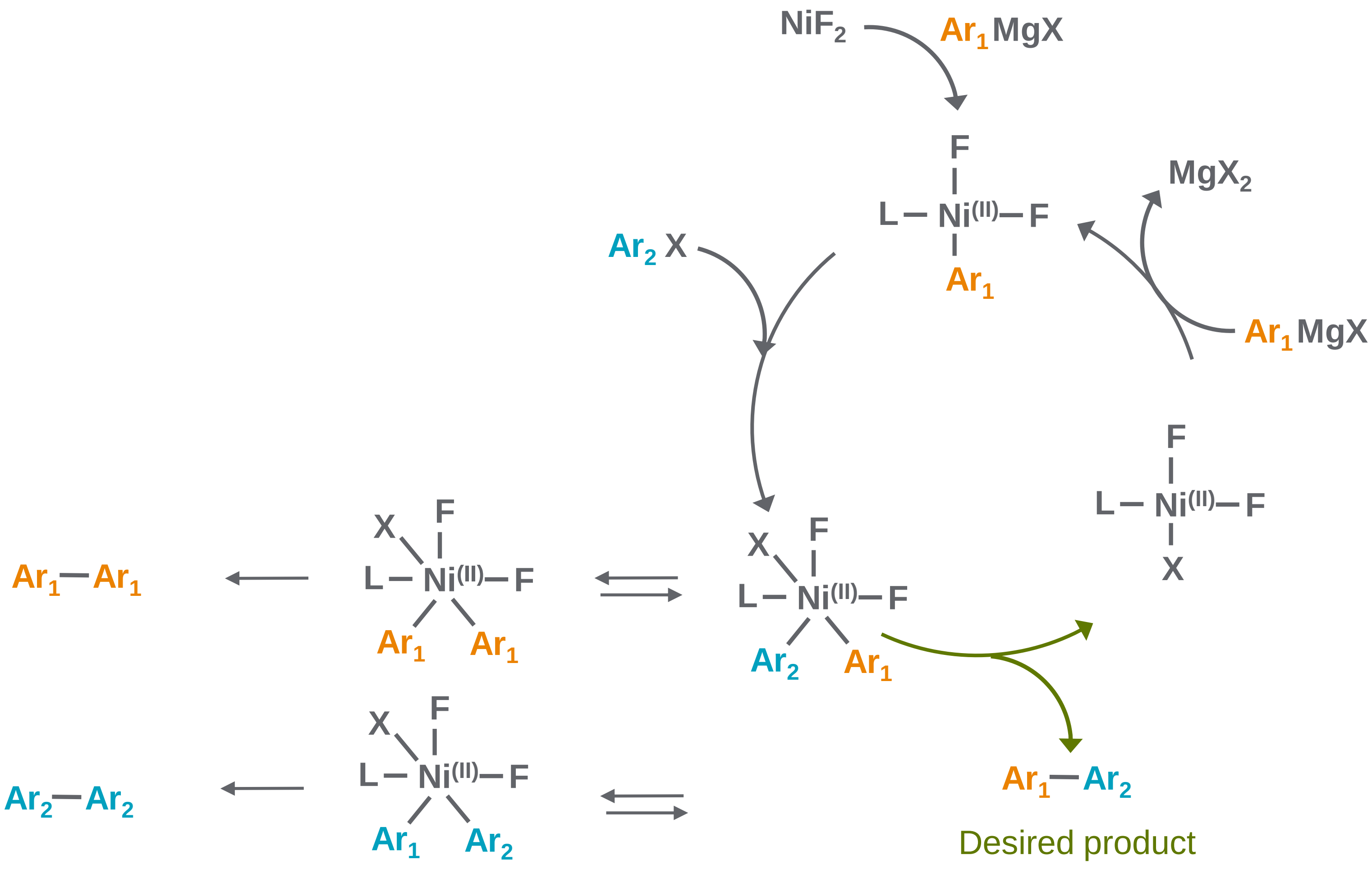
Coupling, second transmet. quench

Wurtz type homocoupling



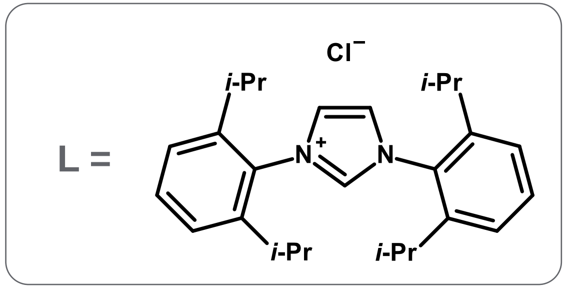
| catalyst (X mol %) | % yields of product[a] 6 | 10 | 8 | 2 | 1 | RSM[b] 9 | bitolyl[c] 4 |
|---|---|---|---|---|---|---|---|
| $FeF_3 \cdot 3H_2O$ (6), SIPr·HCl (18) | 4 | 0 | 3 | 5 | 16 | 62 | 28 |
| $CoF_2 \cdot 4H_2O$ (6), IPr·HCl (12) | 78 | 0 | 3 | 2 | 11 | 0 | 13 |
| $NiF_2$ (2), IPr·HCl (4) | **96** | 0 | 2 | 0 | 0 | 0 | 3 |

# Nickel catalyzed Kumada-Tamao-Corriu Coupling: postulated mechanism



Desired product

Undesired products

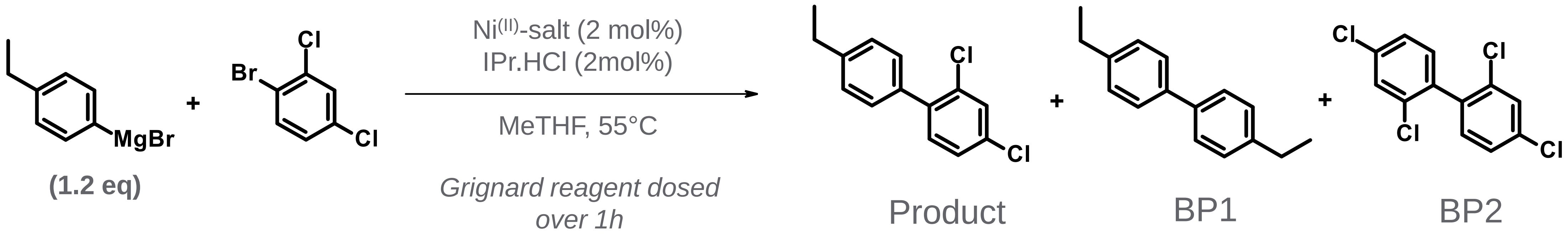


Reductive elimination is fast that Transmetallation required for aryl scrambling is prevented

Classification: PUBLIC

*J. Am. Chem. Soc.* **2009**, *131*, 11949-11963

# [Ni] precursor screening



$Ni^{(II)}$-salt (2 mol%)
IPr.HCl (2mol%)

MeTHF, 55°C

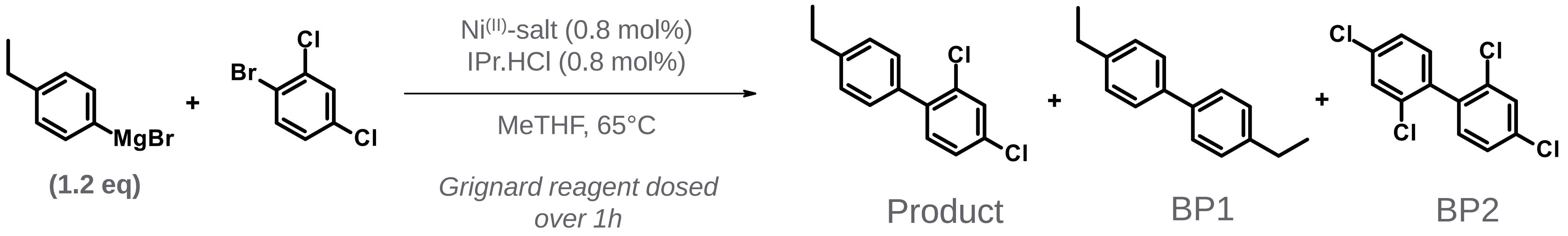
*Grignard reagent dosed over 1h*

| Entry | Ni(II)- salt | Product | BP1 | BP2 |
|---|---|---|---|---|
| 1 | **$NiF_2$** | **88** | 0.7 | 0.5 |
| 2 | $NiCl_2$ | 83 | 2.7 | 0.8 |
| 3 | **Ni(oxalate). $2H_2O$** | **89** | 0.7 | 0.4 |
| 4 | **$Ni(OH)_2$** | **86** | 0.8 | 0.4 |
| 5 | **$NiSO_4$. $6H_2O$** | **88** | 0.9 | 0.4 |
| 6 | NiO | 71 | 0.8 | 0.4 |
| 7 | $NiBr_2$ | 79 | 3.2 | 1.2 |
| 8 | $Ni(OAc)_2$ | 78 | 4.7 | 1.7 |
| 9 | $Ni(acac)_2$ | 79 | 5.6 | 1.6 |

***$NiF_2$ is not the exclusive Ni precatalyst***

M.Zeller, unpublished, D.Gribkov, DIAC-Novartis Symposium November 2022. D.Gribkov, ACS. Chicago, Aug 2022

# Process Robustness



(1.2 eq)

Ni$^{(II)}$-salt (0.8 mol%)
IPr.HCl (0.8 mol%)

MeTHF, 65°C

*Grignard reagent dosed over 1h*

Product

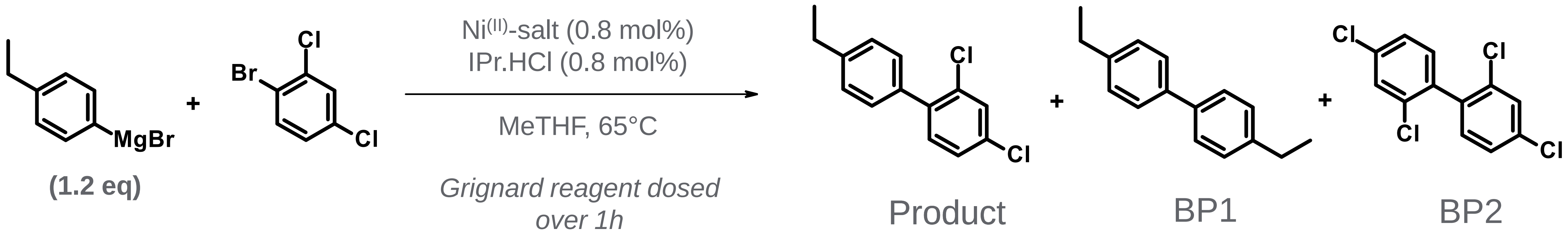
BP1

BP2

| Entry | Ni(II)- salt | supplier | Product | BP1 | BP2 |
|---|---|---|---|---|---|
| 1 | $NiSO_4$. $6H_2O$ | **Aldrich** | **92** | 0.9 | 0.7 |
| 2 | $NiSO_4$. $6H_2O$ | (Nickelhütte Aue) | **53** | **6.3** | **3.2** |
| 3 | $NiSO_4$. $6H_2O$ | (Aldrich grinded) | **48** | **8.2** | **5.2** |

M.Zeller, unpublished, D.Gribkov, DIAC-Novartis Symposium November 2022. D.Gribkov, ACS. Chicago, Aug 2022

# Process Robustness



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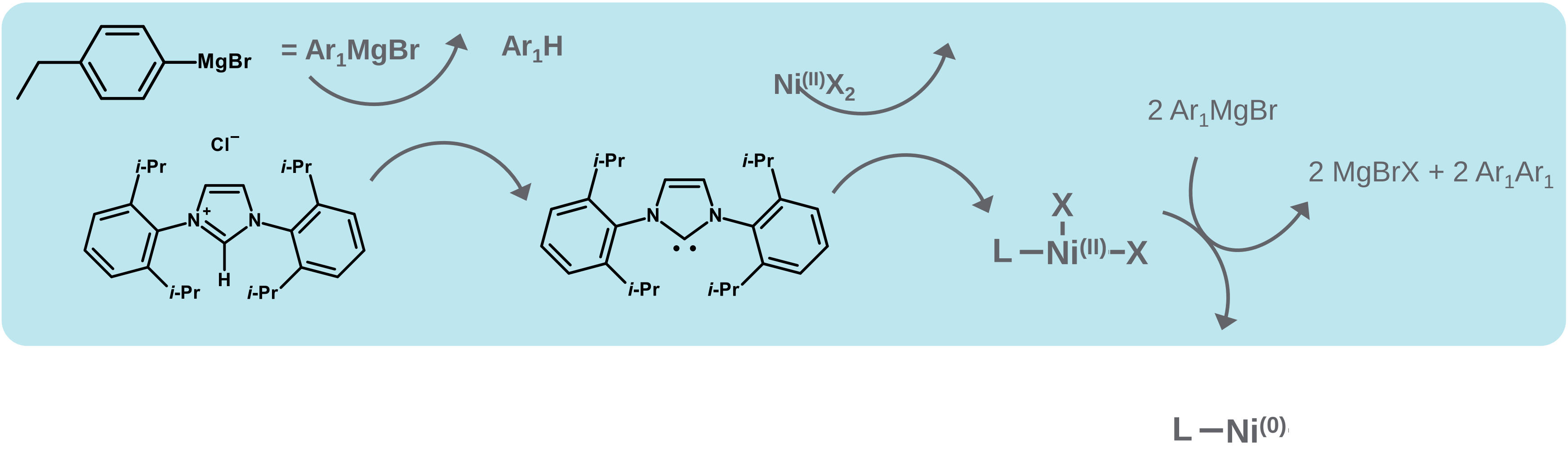
| 2 | $NiSO_4.\ 6H_2O$ | (Nickelhütte Aue) | 53 | 6.3 | 3.2 |
| 3 | $NiSO_4.\ 6H_2O$ | (Aldrich grinded) | 48 | 8.2 | 5.2 |
| 4 | $NiSO_4.\ 6H_2O$ | **(Aldrich)** | **74** | **3.5** | **2.2** |

**Grignard dosing interrupted for 1h**

**Lack of robustness**

M.Zeller, unpublished, D.Gribkov, DIAC-Novartis Symposium November 2022. D.Gribkov, ACS. Chicago, Aug 2022

# Mechanistic considerations help to improve the process



= $Ar_1MgBr$

$Ar_1H$

$Ni^{(II)}X_2$

2 $Ar_1MgBr$

2 MgBrX + 2 $Ar_1Ar_1$

$$L-\overset{X}{Ni^{(II)}}-X$$

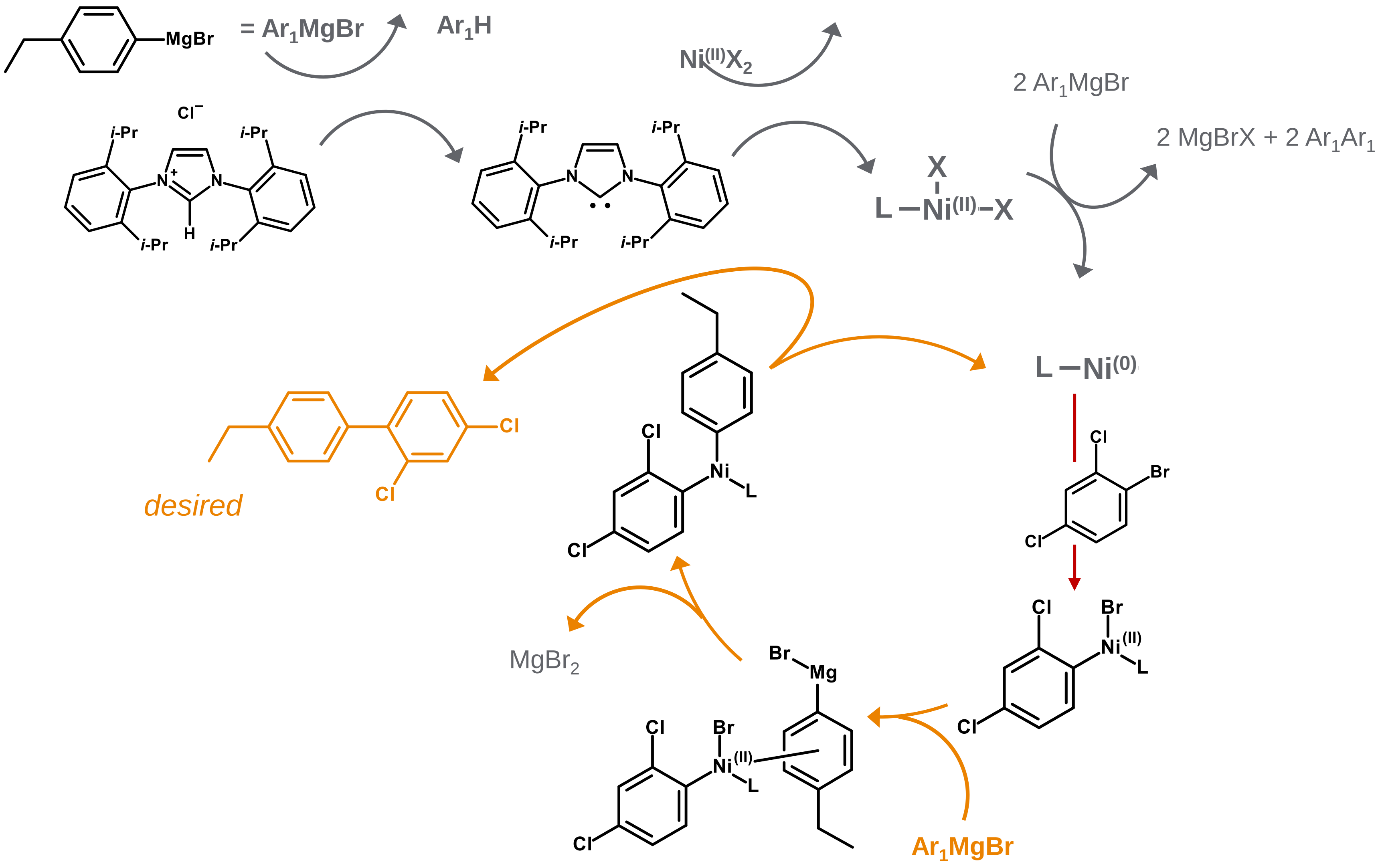
$L-Ni^{(0)}$

**Catalyst formation** (dissolution kinetics difficult to control)

M.Zeller, unpublished

Catalytic cycle adapted and simplified from: S. Tasler, B.H. Lipshutz; J. Org. Chem. 2003, 68, 1190

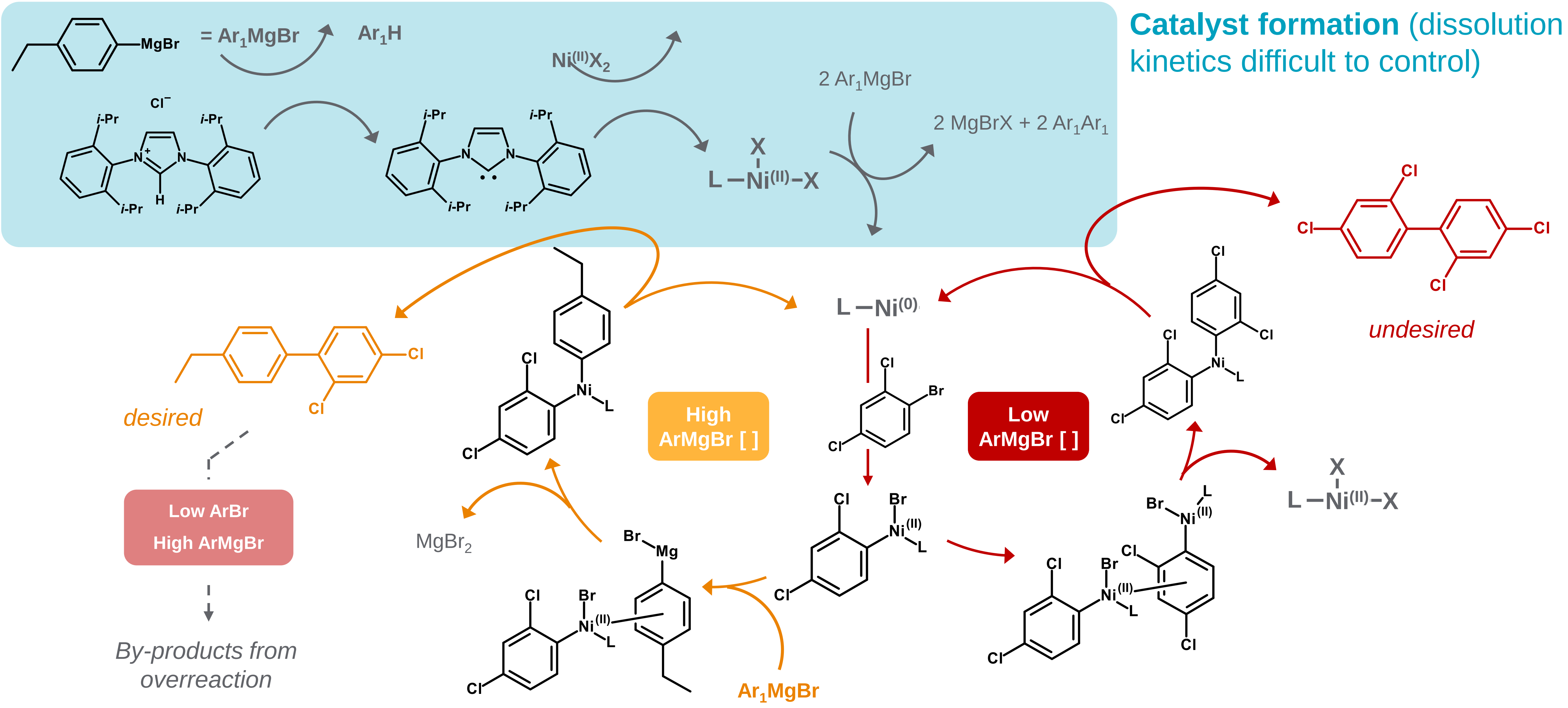
# Mechanistic considerations



M.Zeller, unpublished

Catalytic cycle adapted and simplified from: S. Tasler, B.H. Lipshutz; J. Org. Chem. 2003, 68, 1190

# Mechanistic considerations



**Catalyst formation** (dissolution kinetics difficult to control)

*desired*

*undesired*

**High ArMgBr [ ]**

**Low ArMgBr [ ]**

**Low ArBr**
**High ArMgBr**

*By-products from overreaction*

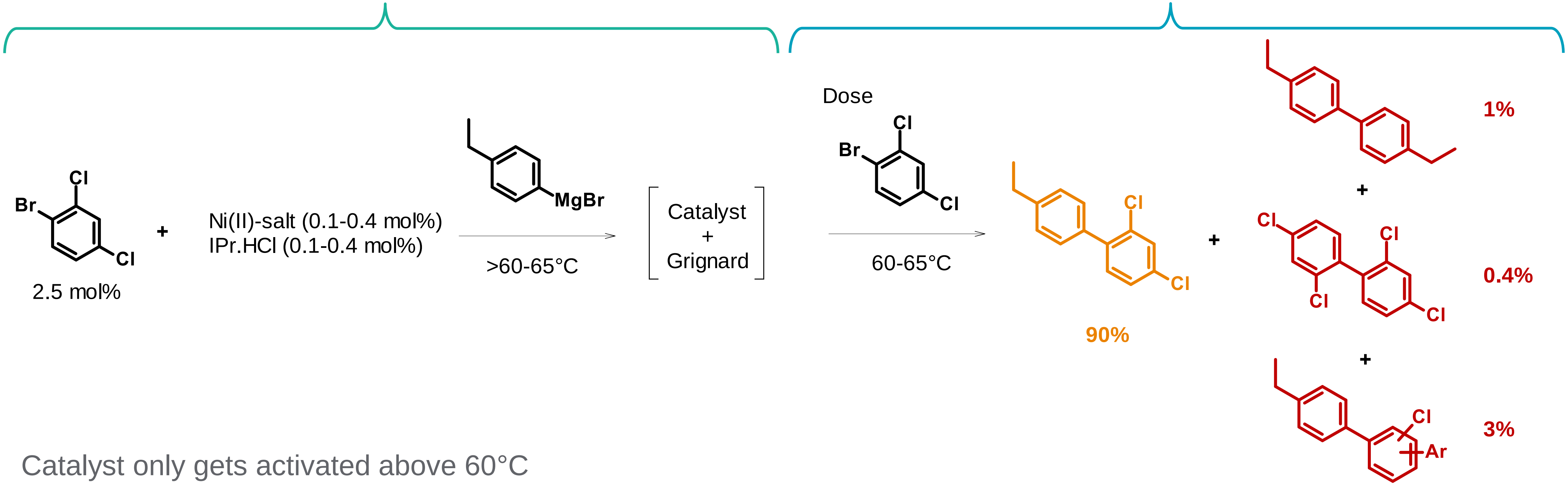
M.Zeller, unpublished

Catalytic cycle adapted and simplified from: S. Tasler, B.H. Lipshutz; J. Org. Chem. 2003, 68, 1190

# Development of a scalable procedure

**Activate the catalyst**

**Perform the coupling at high ArMgBr [ ] vs the catalyst**

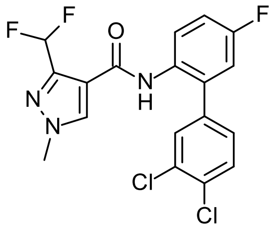


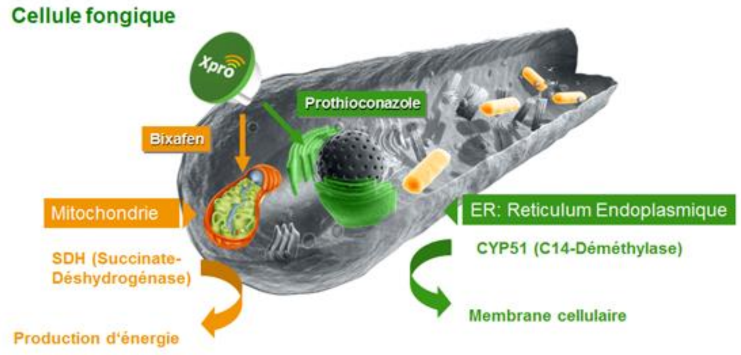
- Catalyst only gets activated above 60°C
- Most [Ni] removed during acidic work up
- Ni content after product distillation <1ppm
- PCB-47 0.4% reduced to <80ppm after distillation (not sufficient , needed<1ppm limit)

M.Zeller, unpublished, D.Gribkov, DIAC-Novartis Symposium November 2022. D.Gribkov, ACS. Chicago, Aug 2022

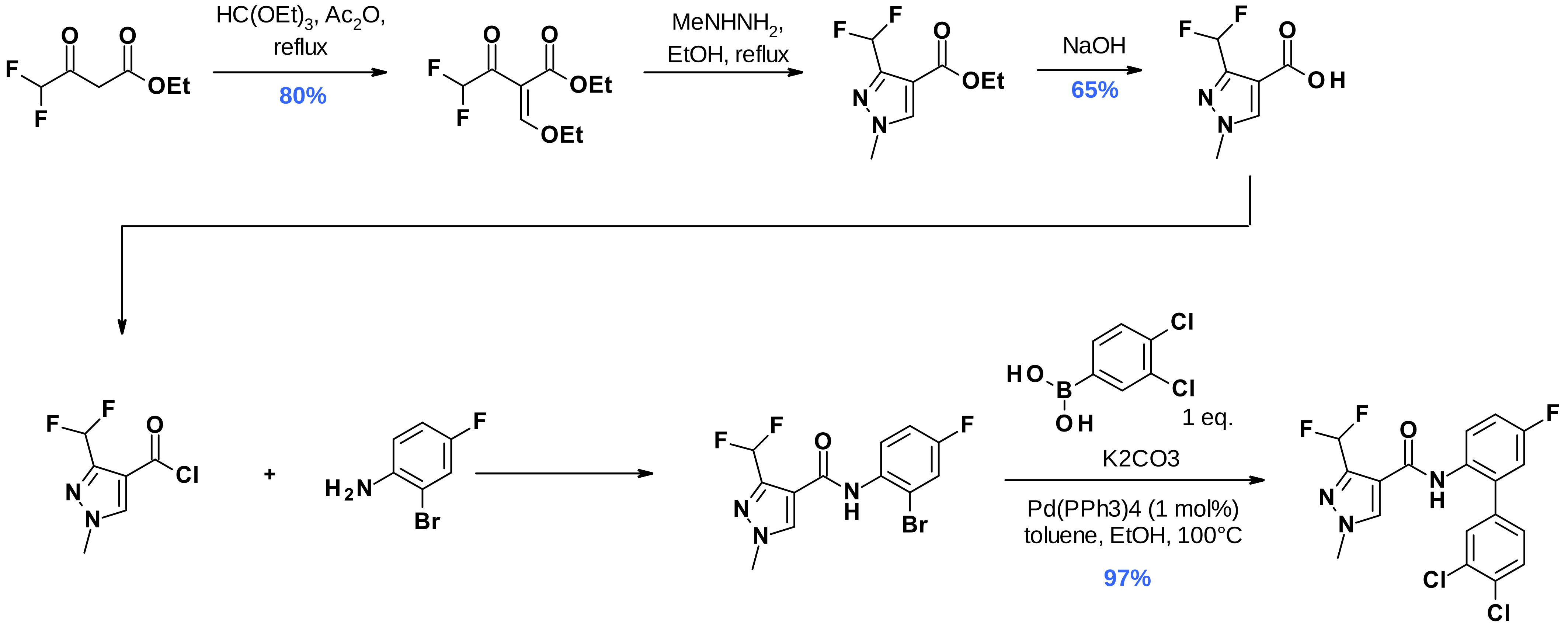
# Bixafen

- Bayer CropScience’s leading SDHI. Introduced in 2011
- Bixafen is a succinate dehydrogenase (SDH) inhibitor specifically for foliar application to control important cereal dieases such as septoria leaf blotch (Septoria tritici) in intensive cereal growing regions.
- Marketed under the brand names Aviator 235 Xpro and Siltra Xpro for the 2011 growing season.



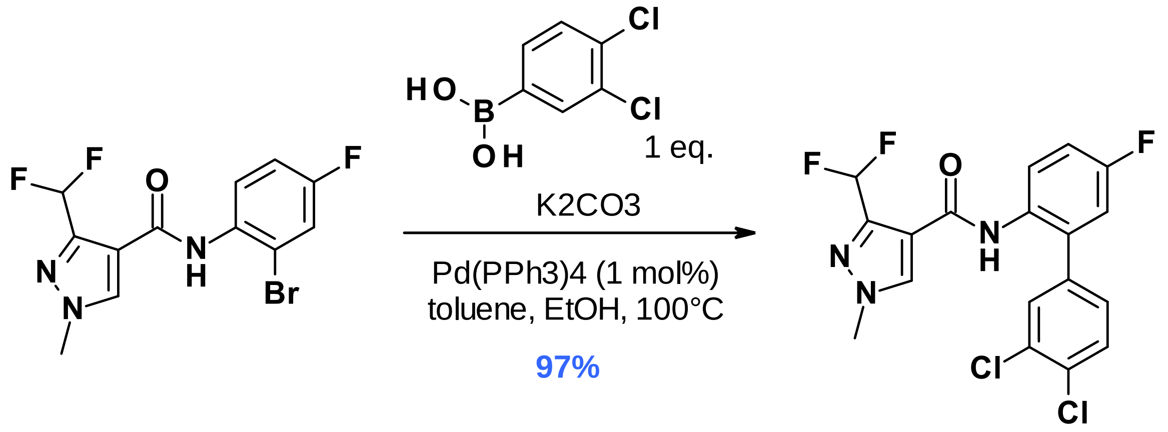


# Bixafen



- Very efficient Suzuki used in the last step. Very attractive.
- How is the boronic acid prepared ?

# Suzuki cross-coupling



Why are Suzuki cross coupling rarely used on scale?

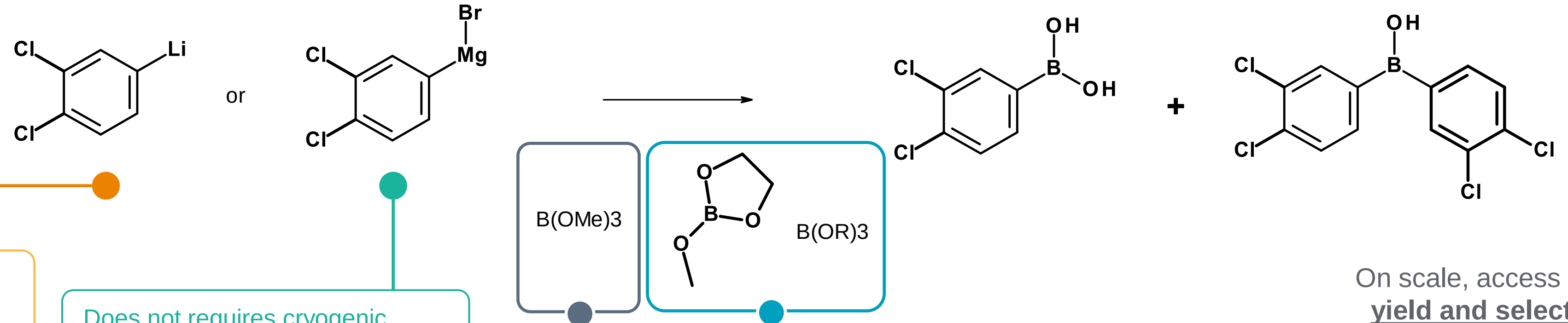
# Suzuki cross-coupling

## Suzuki reactions are routinely used on small scale

- Boronic acids are very verstile intermediates. Often crystalline, stable.
- Suzuki cross coupling is very robust reaction, works reliably, scope extremely large. Reaction conditions are convenient (no need to dry solvent etc…). Dump & steer reaction.
- Very useful and efficient reaction for discovery scale, automation and libraries production

## Why is it so seldom used on very large scale?

- How are boronic acid most often prepared ?
- Catalytic reactions using $R_2B\text{-}BR_2$ reagents. These are typically very expensive reagents



Often gives good selectivity for the monoarylated product
But:
- Requires cryogenic conditions
- Requires expensive nBuLi

Does not requires cryogenic conditions
Prepared from inexpensive Mg(0)
But
Often gives poor selectivity

Cheap but not very selective

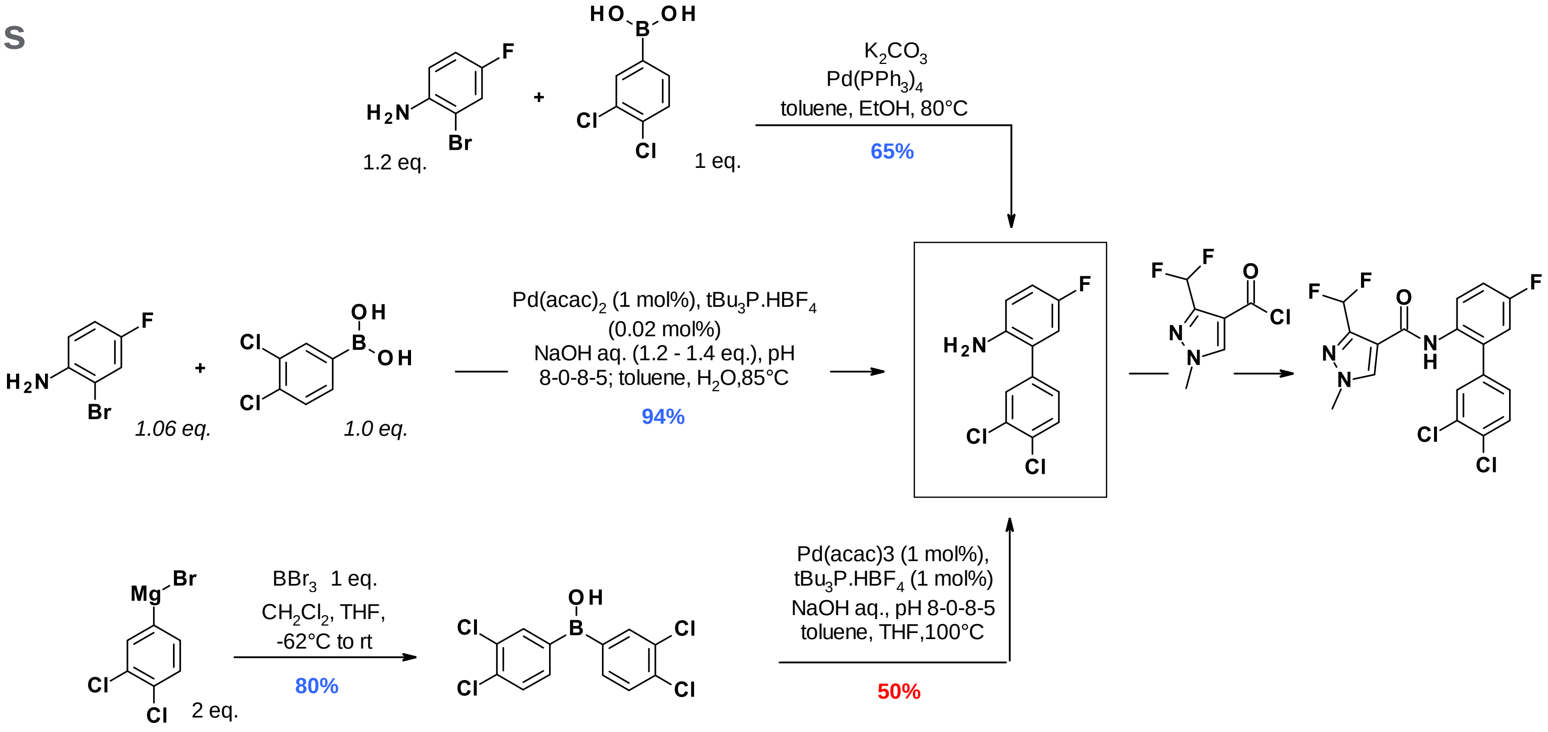
Good selectivity with Grignard
But expensive materials

On scale, access to boronic acid n **high yield and selectivity** likely to require significant development and engineering work

# Bixafen - Biphenyl synthesis via Suzuki cross coupling

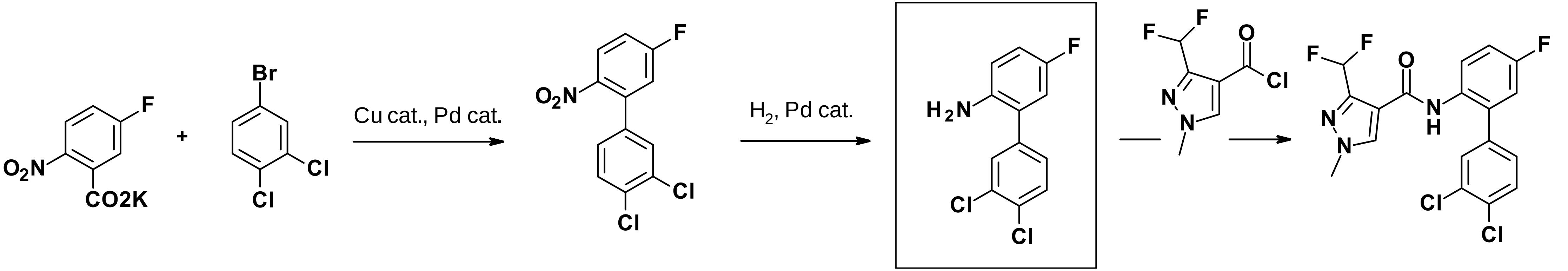
- Can’t we use both the boronic and the borinic acids? Yes but…
- On scale, working with mixture is almost always not wished. Among some of the problems:
  - **different kinetics**
  - **different impurity profiles**
  - **different optimal reaction conditions**

- **Nightmare for a development/plant chemist. Very rarely done.**



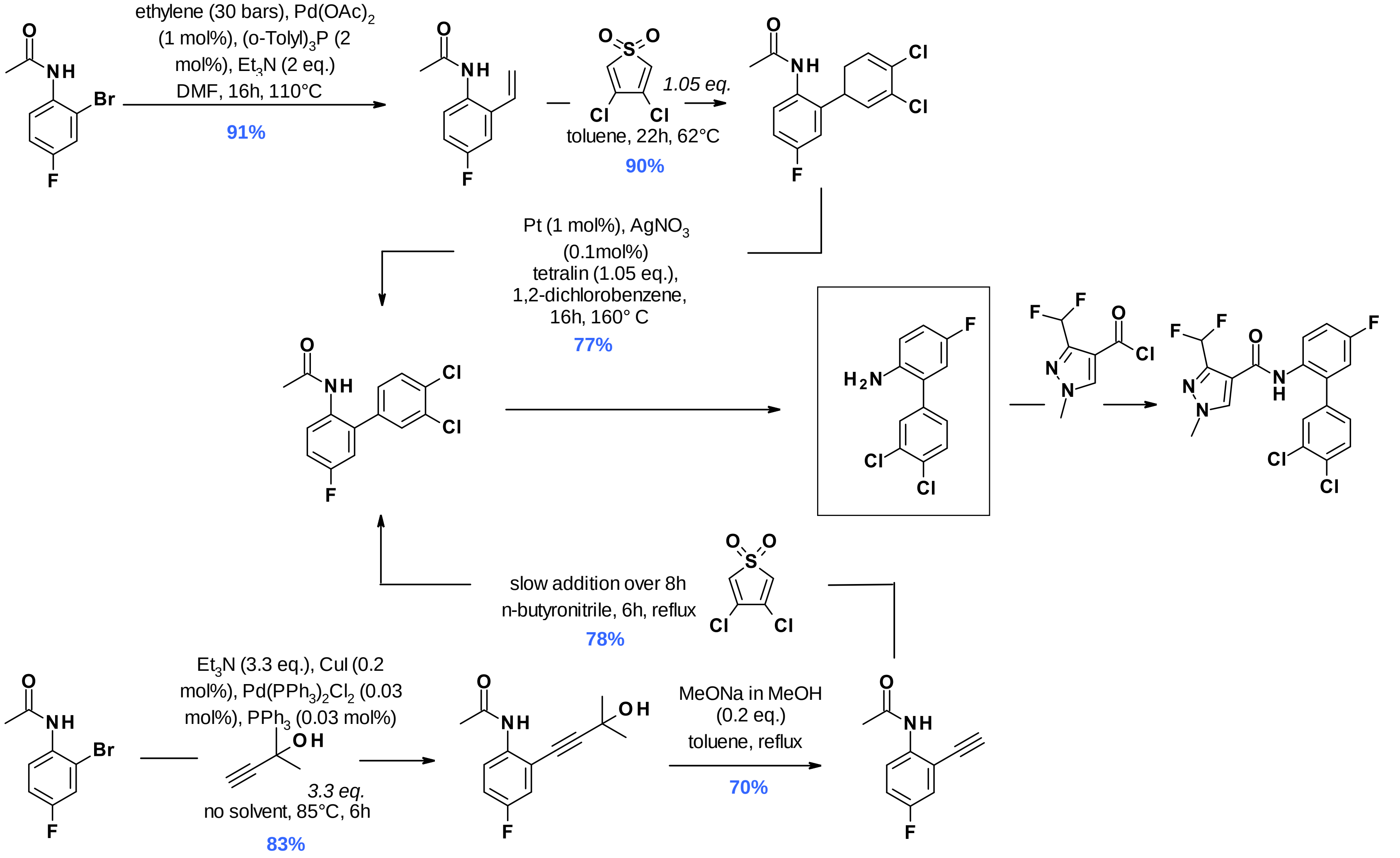
# Bixafen - Alternative to Suzuki #1

- Decarboxylative cross coupling



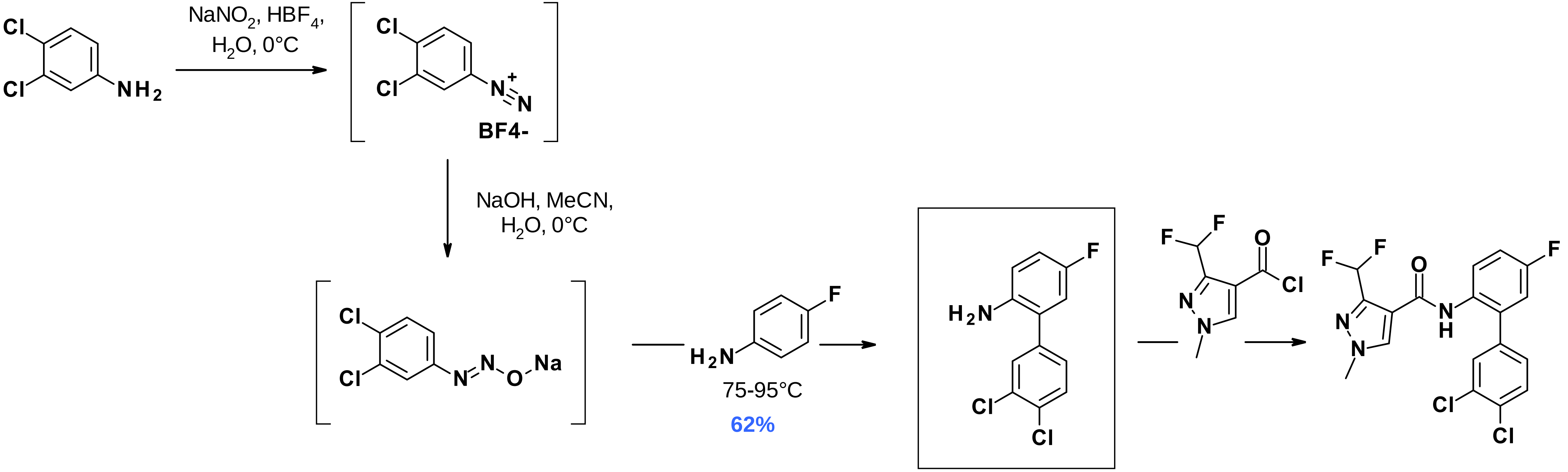
# Bixafen - Alternative to Suzuki #2

- Diels-Alder / Cheletropic SO2 extrusion



# Bixafen - Biphenyl synthesis, a third alternative to Suzuki

- Is catalysis needed at all? Gomberg Bachmann radical cross coupling.



Gomberg.Bachmann

# Metolachlor

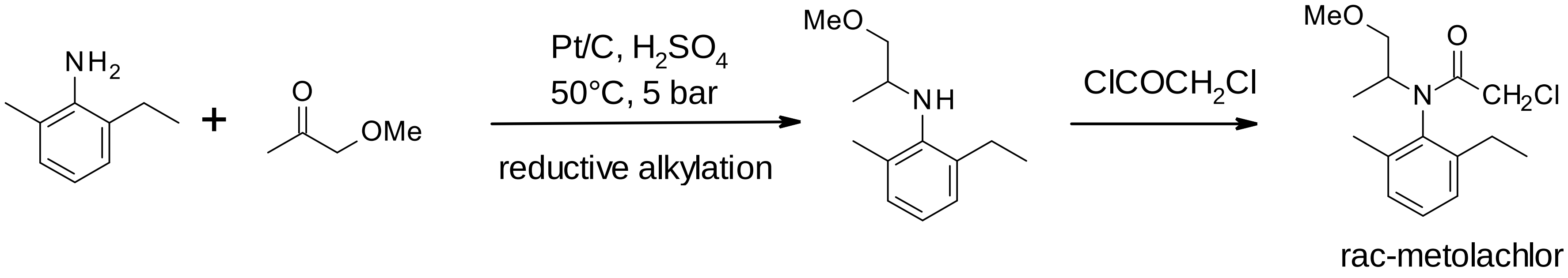
Control various broadleaf weeds and grasses

Metolachlor acts by inhibiting the germination and growth of weeds, primarily by disrupting the synthesis of certain lipids, proteins, and carotenoids

Commonly used in pre-emergence applications, (before weeds emerge)

Used in various crops, including corn, soybeans, cotton, peanuts, and certain vegetables

Industrial production of racemic Metolachlor

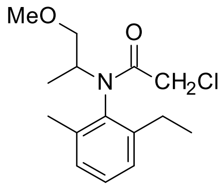


- Low price / high volume process

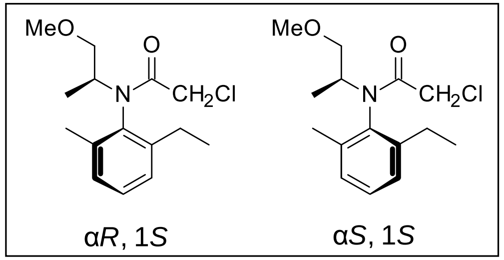
# **Chloracetanilide Herbicides:** Metolachlor and (S)-metolachlor

**Metolachlor**, herbicide Dual®, 1974 Ciba-Geigy (now Syngenta)

**50 : 50**

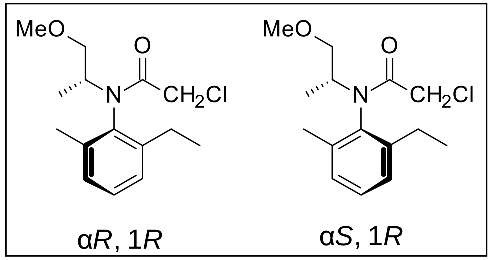


metolachlor



α*R*, 1*S* α*S*, 1*S*

the active stereoisomers



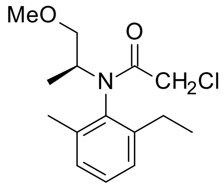
α*R*, 1*R* α*S*, 1*R*

the inactive stereoisomers

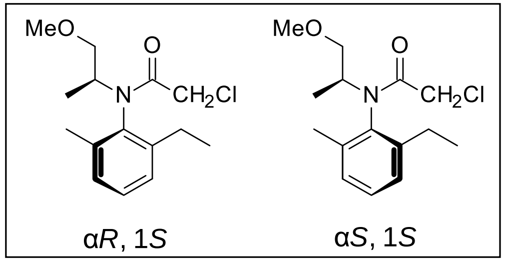
1993/19944 rac-MOC patents expired -> **Successful chiral switch ->**

- **(*S*)-Metolachlor**, herbicide Dual Magnum®, 1997 Novartis (now Syngenta)

**>88 : 12**

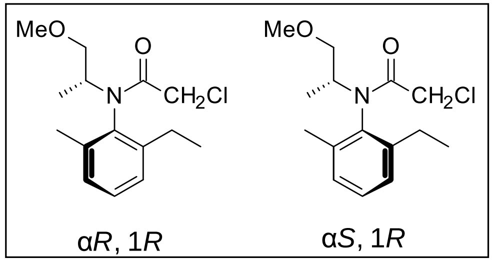


S-metolachlor



α*R*, 1*S* α*S*, 1*S*

the active stereoisomers



α*R*, 1*R* α*S*, 1*R*

the inactive stereoisomers

- ➢ **Reduction of use rates by approx. 40%:**

=> Less environmental load, smaller production units, less energy consumption, less waste, less transportation and storage costs,..

- ➢ **IP protection and technological advantage over generics**

# Catalysis KPIs

- Turnover Number

$$\text{TON} = \frac{\text{Moles of Product formed}}{\text{Moles of Catalyst or Active Sites used}}$$

- Turnover frequency

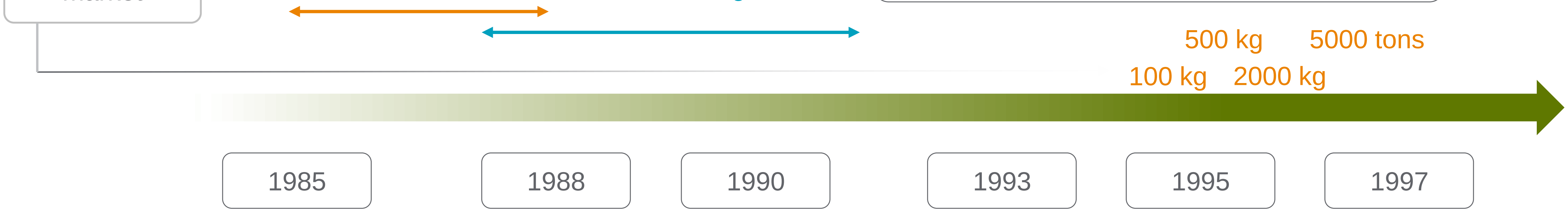
$$\text{TOF} = \frac{\text{TON}}{\text{Reaction time}}$$

- Metolachlor application

Requirements for a technical process:
≥80% ee
TON = 40,000, **<8 h**

*Chimia* **1996**, *50*, 86; Asymmetric Catalysis on Industrial Scale, Eds. (Wiley-VCH, Weinheim, Germany, 2004), 55; *Adv. Synth. Catal.* **2002**, *334*, 17; Acc. *Chem. Res.* **2007**, *40*, 1240

# Enantioenriched Metolachlor – An brief historical summary



Racemic metolachlor on market

S enantiomers 10x more active than R

Route scouting & catalyst screening

**Process Development**
- Metolachlor imine **unstable**
- **Catalyst** Moisture-sensitive, air-sensitive
- **Hydrogen Pressure** Safety concerns at high pressure
- **Catalyst poisoning** by some impurities (pre-purification step required)
- **Catalyst Recycling** (98% recovery)

**Classical Resolution:** 50% waste
Not economically viable at >10,000 tonne/year scale

**Chiral Pool Approach**
No suitable, cheap starting material

**Asymmetric Catalysis**
No precedent at this scale
High risk, high reward

**Rh-phosphine catalysts**
60-70% ee (need >80% ee)
75% ee with Rh-DuPhos

**Switch to Ir catalysts** (Pfaltz)
Phosphinooxazoline ligands: 85% ee
TON ~1,000 (too low for commercial use)

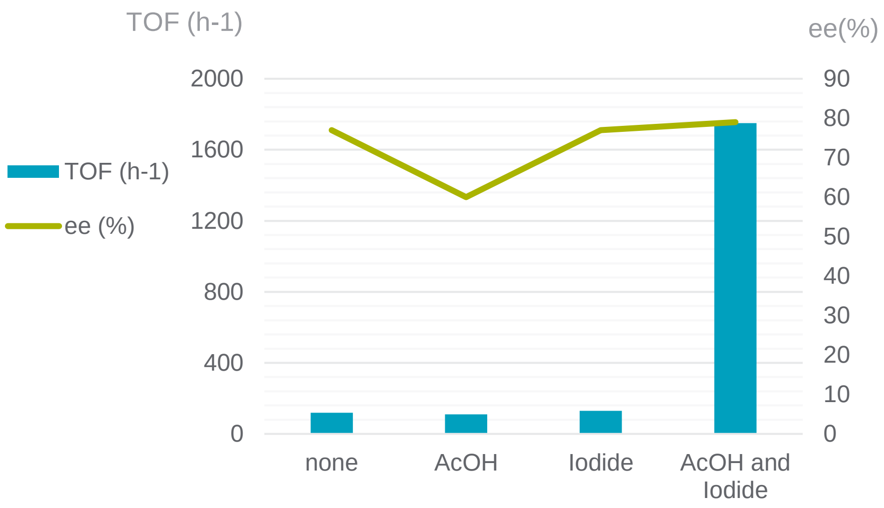
**AcOH/Iodide Additive Discovery**
**Massive TOF increase:** 10,000 → 2,000,000 $h^{-1}$ (200x faster!)
Catalyst so cheap, recycling no longer needed!

**Xyliphos Discovery (Blaser, Spindler)**
- Bulky, electron-rich substituents
- **50+ ligand** variants synthesized
- 85-90% ee
- **TON: >1,000,000**
- **TOF: ~10,000 $h^{-1}$**
- **1 ppm** Ir (0.0001 mol%)

Classification: PUBLIC

*Chimia* **1996**, *50*, 86; Asymmetric Catalysis on Industrial Scale, Eds. (Wiley-VCH, Weinheim, Germany, 2004), 55; *Adv. Synth. Catal.* **2002**, *334*, 17; Acc. *Chem. Res.* **2007**, *40*, 1240

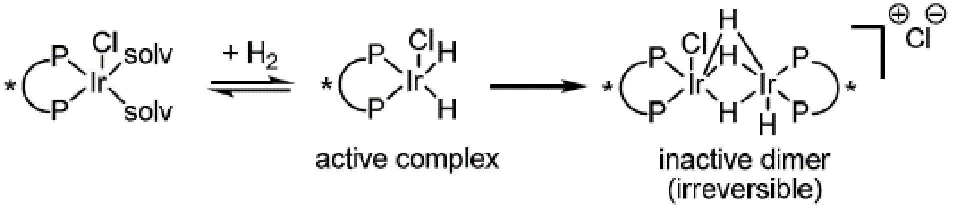
# Imine hydrogenation – Discovery of additive effects AcOH and I$^-$:



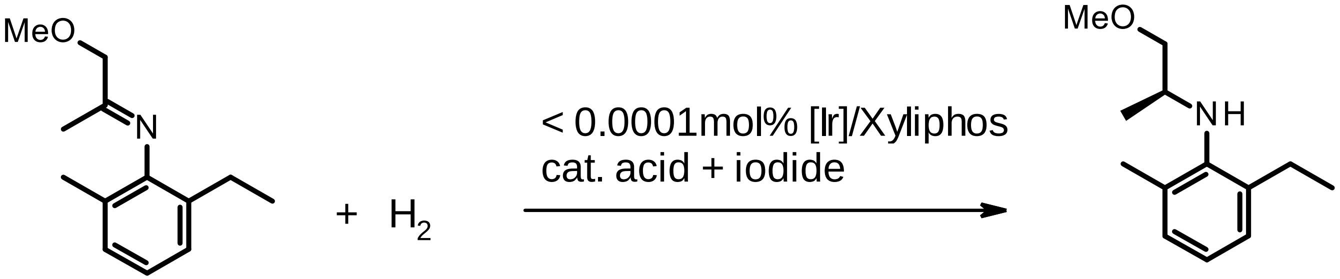
**AcOH** (substrate activation)
**Iodide** as ligand makes Ir more electron-rich, easier $H_2$ activation (oxidative addition), acts as "proton shuttle" between Ir and substrate

**AcOH alone: 10x faster I$^-$ alone: 20-50x faster**
**AcOH + I$^-$ together: 200-500x faster!**

**Irreversible catalyst deactivation** process is prevented by iodide
Rate acceleration by AcOH



One of the most productive homogeneous catalysts ever
Developed during initial years of asymmetric hydrogenation – a historical case study

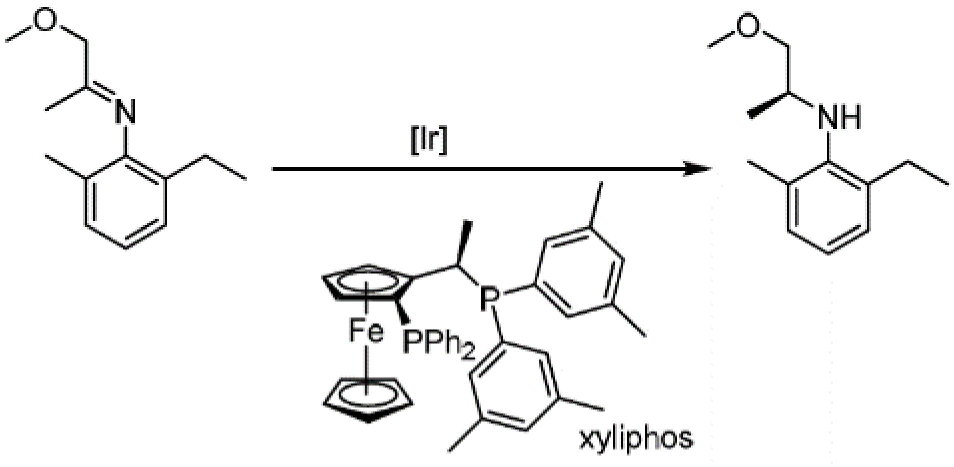

< 0.0001mol% [Ir]/Xyliphos
cat. acid + iodide

**79%ee**
>1’000’000 TON
>2’000’000 h$^{-1}$ TOF

*Chimia* **1996**, *50*, 86; Asymmetric Catalysis on Industrial Scale, Eds. (Wiley-VCH, Weinheim, Germany, 2004), 55; *Adv. Synth. Catal.* **2002**, *334*, 17; Acc. *Chem. Res.* **2007**, *40*, 1240

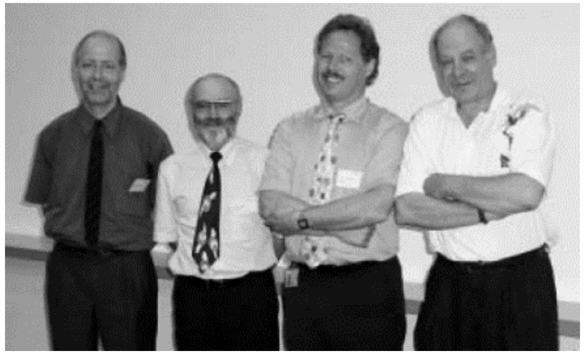
# Imine hydrogenation – The laboratory process

- >10 years of work
- 3 academic collaborations



55 °C, 1100 psi $H_2$, 48 h

35,000 TON and 70% ee

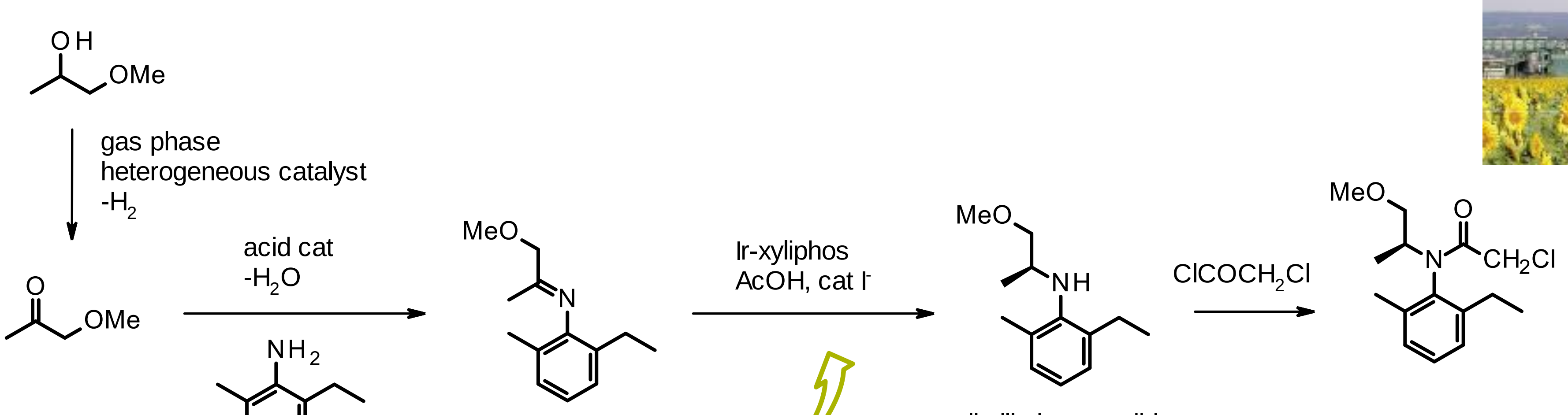


Benoit Pugin, Hans-Ulrich Blaser, Felix Spindler, and Hans-Peter Jalett

*Chimia* **1996**, *50*, 86; Asymmetric Catalysis on Industrial Scale, Eds. (Wiley-VCH, Weinheim, Germany, 2004), 55; *Adv. Synth. Catal.* **2002**, *334*, 17; Acc. *Chem. Res.* **2007**, *40*, 1240

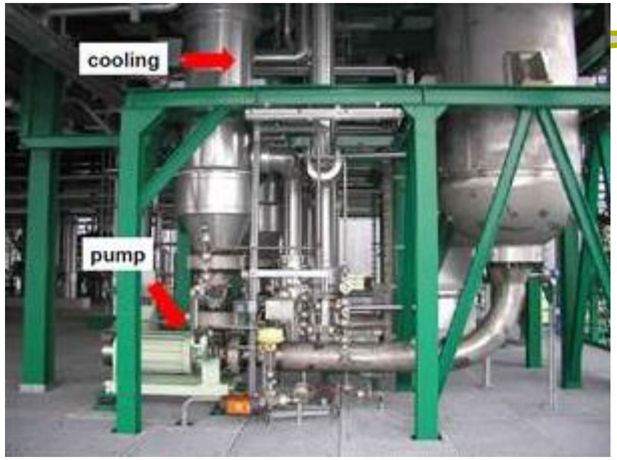
# Production process

Kaisten, Switzerland



distillation possible
-> high substrate quality

distillation possible
-> catalyst removal



Bottom part of loop hydrogenation reactor

Loop hydrogenation reactor = designed for optimal mass and heat transfer (highly exothermic reaction/high pressure)

All intermediate streams liquid

=> neat / continuous processing

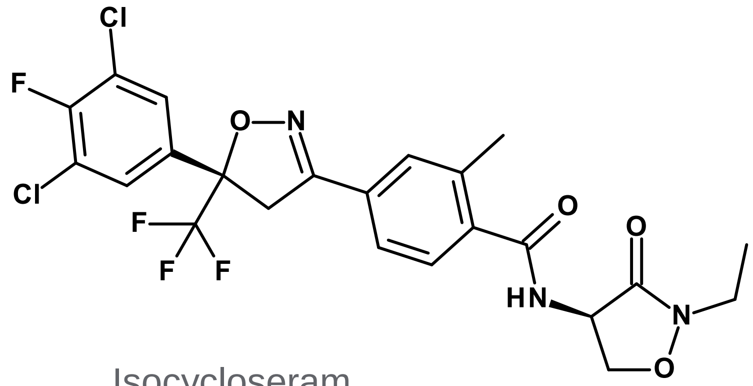
=> high productivity

*Chimia* **1996**, *50*, 86; Asymmetric Catalysis on Industrial Scale, Eds. (Wiley-VCH, Weinheim, Germany, 2004), 55; *Adv. Synth. Catal.* **2002**, *334*, 17; Acc. *Chem. Res.* **2007**, *40*, 1240

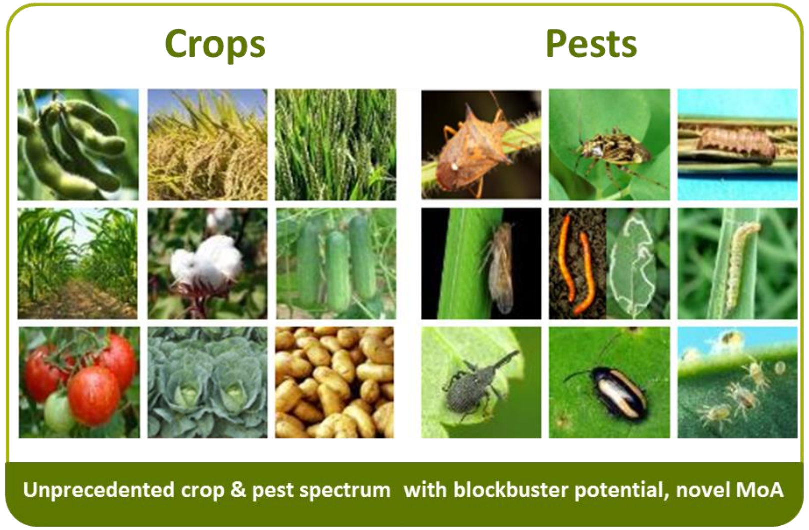
# Enantioselective Catalysis

## PLINAZOLIN® technology - new insect control technology for a wide variety of pests

- Broad spectrum insecticide with blockbuster potential across Crop Protection and Seed Care.
- New mode of action with no cross resistance anticipated.
- Key crops: Soybean, Rice, Vegetables, Specialty, Cereals&Corn
- Introduced to the market in 2022 (in Argentina).



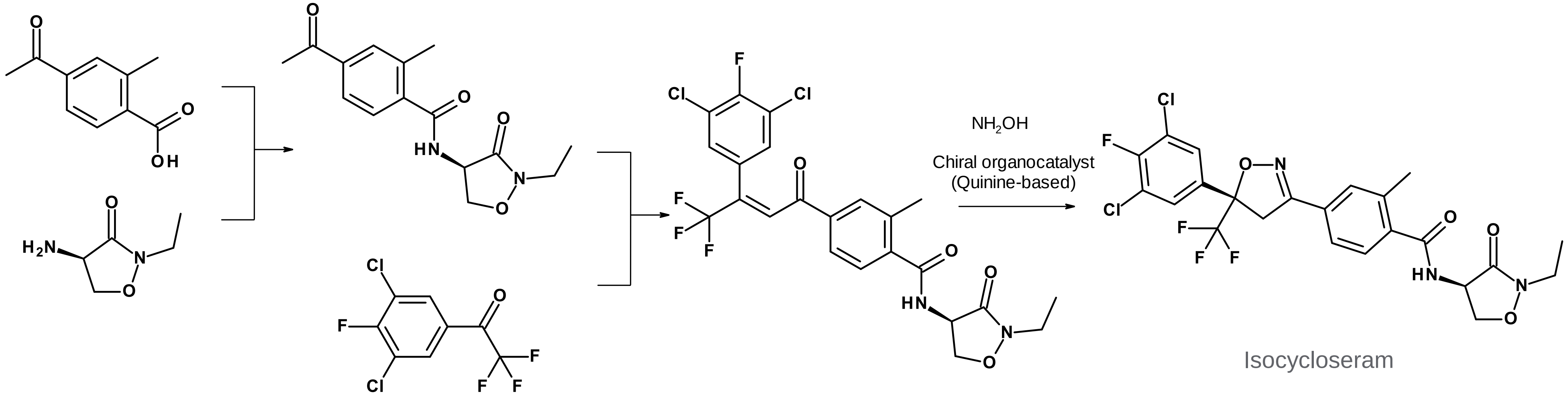
Isocycloseram



# Enantioselective Catalysis

**PLINAZOLIN® technology - new insect control technology for a wide variety of pests**

- More than 20 chemical steps in total
- 2 Chiral centers, one of which is formed by an enantioselective transformation
- One of the most complex AIs we have ever had to develop and manufacture
- Cost of goods and environmental impact are of particular importance



Isocycloseram

*Recent Highlights in the Discovery and Optimization of Crop Protection Products, Maienfisch, P. and Mangelinckx, S., Elsevier 2021*
Chapter 9 - The discovery of isocycloseram: A novel isoxazoline insecticide, pages 165-212

# 12 Principles of Green and Sustainable Chemistry

1.Prevent waste

2.Atom economy

3.Less Hazardous Synthesis

4.Design Benign Chemicals

5.Benign Solvent

6.Energy efficiency

7. Use of renewable feedstocks

8. Reduce derivatives

9. Catalysis

10. Design for degradation

11. Real-time analysis for pollution prevention

12. Safer chemistry for accident prevention

Classification: PUBLIC

# Exercise

Route A: Uses diazomethane ($CH_2N_2$) as a methylating agent

- Diazomethane is highly explosive and toxic
- Reaction is very clean and high-yielding (95%)
- Reaction runs at room temperature in 30 minutes

Route B: Uses dimethyl sulfate ($Me_2SO_4$) as a methylating agent

- Dimethyl sulfate is toxic and a suspected carcinogen
- Reaction gives 85% yield with some side products
- Requires heating to 80°C for 4 hours

**Which statement BEST reflects the industrial decision-making process?**

A) Route A is preferred because the reaction is faster and cleaner, and modern safety equipment can handle any reagent safely.

B) Route B is preferred because, although dimethyl sulfate is hazardous, it can be contained and handled with proper engineering controls, whereas diazomethane's explosive nature presents unmitigable risks.

C) Both routes are equally acceptable since both reagents are hazardous; the choice depends only on cost and yield.

D) Route A is preferred because the shorter reaction time reduces worker exposure to hazardous materials, making it inherently safer

# Safety

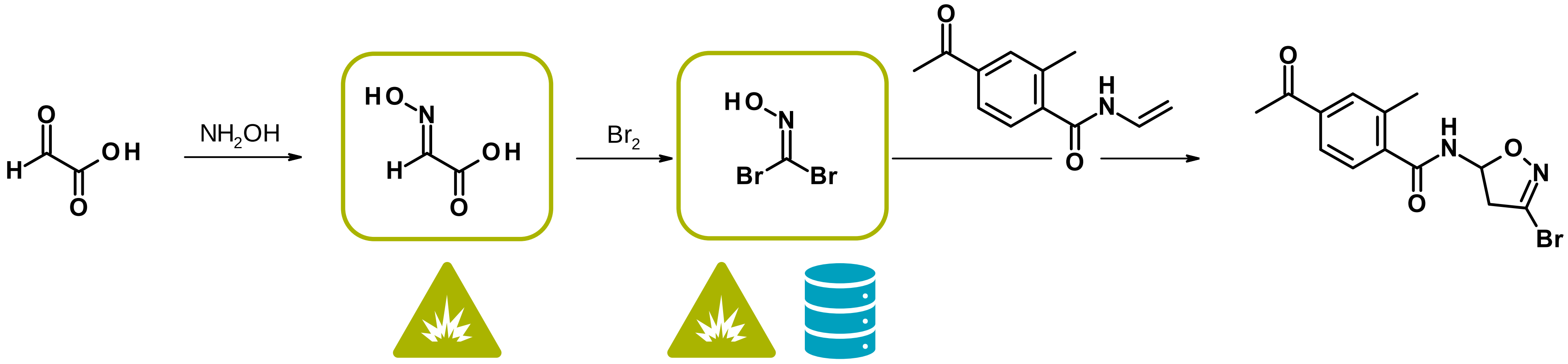
- Often confusion process safety and handling hazardous reagents
- Process safety: DSC, calorimetry data. Often handle using continuous chemistry (ex: diazomethane)
- Handling hazardous reagents can be done, containment (adds cost)
- Number 1 priority. Cannot afford to lose neither plant operator nor a plant
- Never do all-in reactions. Always dose reagents.
- You never add catalyst last
- Usually work at highest possible temperature (rate of reaction is highest)

# Less Hazardous Chemical Synthesis

## Use continuous technology to perform chemistry safely

We wished to prepare and use an intermediate named Dibromoformaldoxime

Issues: this intermediate and its raw material are highly thermally unstable



Safety issue

Storage issue

*Organic Process Research & Development* **2017,** *21*, 10, 1588

# Less Hazardous Chemical Synthesis

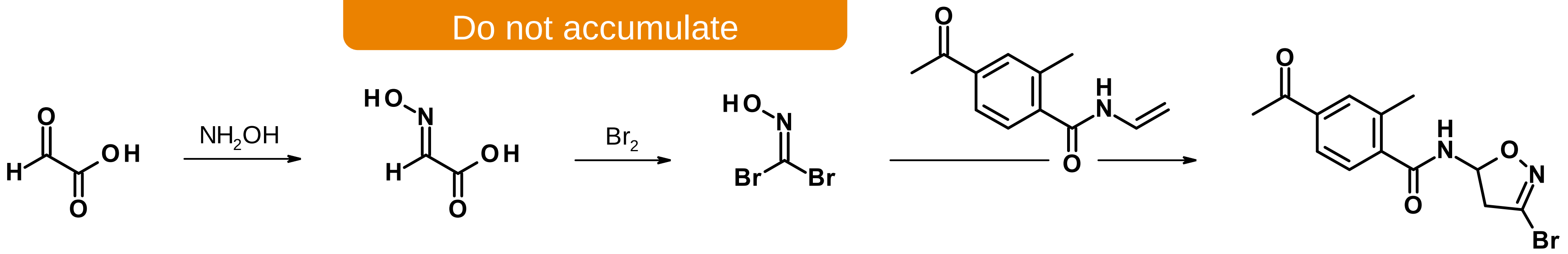
## Use continuous technology to perform chemistry safely

We wished to use an intermediate named Dibromoformaldoxime

Issues: this intermediate and its raw material are highly thermally unstable

On-demand conti synthesis

Do not store
Do not accumulate



### hydroxyiminoacetic acid

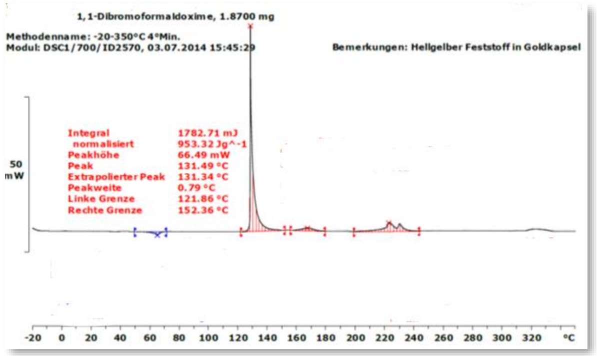
**High thermal unstability**

Onset Temp: 124°C Normalized decomposition energy ca. 2200J/g

### Dibromoformaldoxime

**High thermal unstability**

Onset Temp: 110°C Normalized decomposition energy ca. 1000J/g



1,1-Dibromoformaldoxime, 1.8700 mg

Methodenname: -20-350°C 4°Min.
Modul: DSC1/700/ID2570, 03.07.2014 15:45:29

Bemerkungen: Hellgelber Feststoff in Goldkapsel

| | |
|---|---|
| Integral | 1782.71 mJ |
| normalisiert | 953.32 Jg^-1 |
| Peakhöhe | 66.49 mW |
| Peak | 131.49 °C |
| Extrapolierter Peak | 131.34 °C |
| Peakweite | 0.79 °C |
| Linke Grenze | 121.86 °C |
| Rechte Grenze | 152.36 °C |

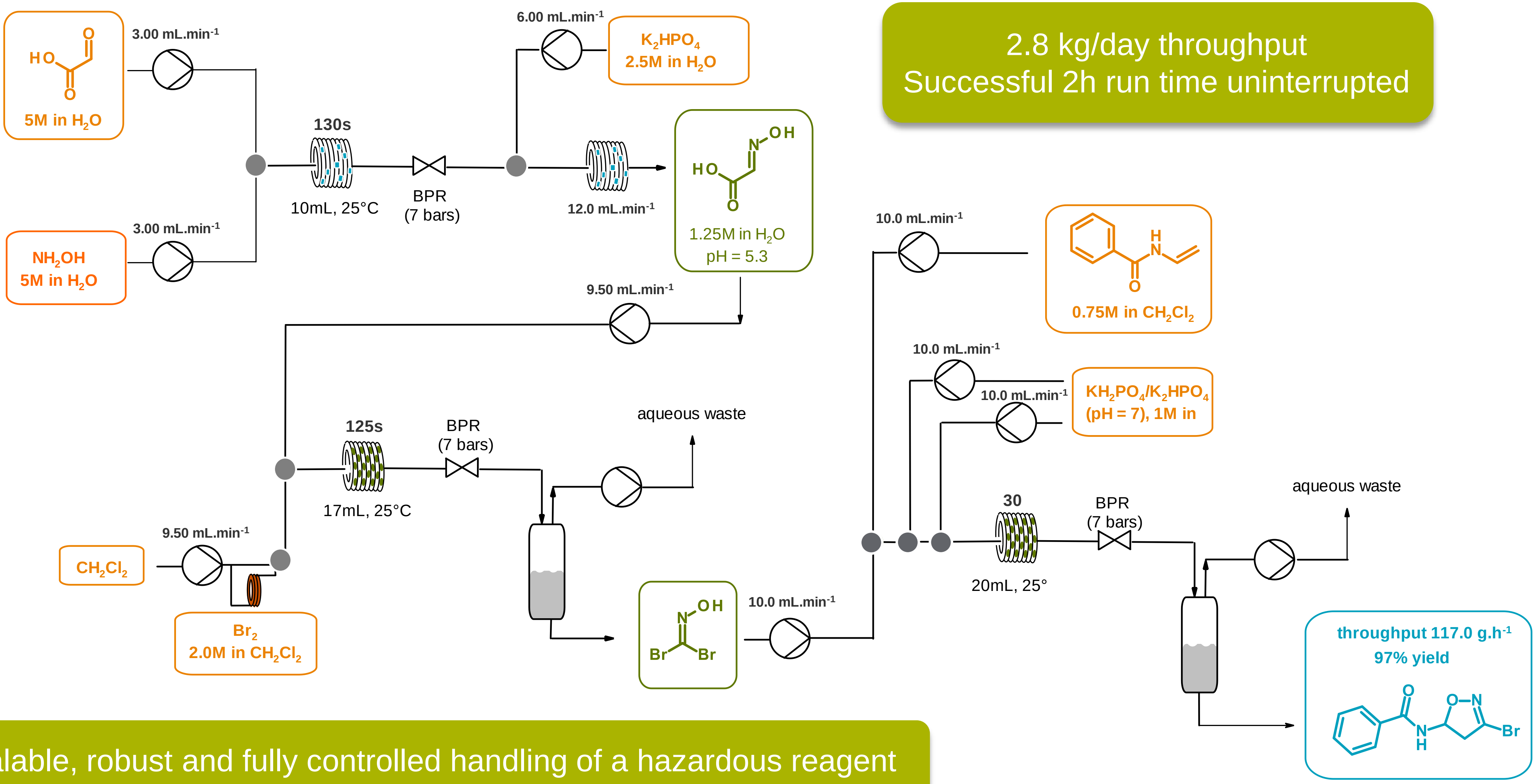
As reference: TNT 4800 J/g

*Organic Process Research & Development* **2017,** *21*, 10, 1588

syngenta

# Less Hazardous Chemical Synthesis

2.8 kg/day throughput
Successful 2h run time uninterrupted



scalable, robust and fully controlled handling of a hazardous reagent

*Org. Proc. Res. Dev.* **2017,** *21*, 1588

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5.Benign Solvent

6.Energy efficiency

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8. Reduce derivatives

9. Catalysis

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11. Real-time analysis for pollution prevention

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*Green Chemistry: Theory* and *Practice*,  Ox. Uni. Press, New York, *1998*

www.menti.com

71 95 70 73

link

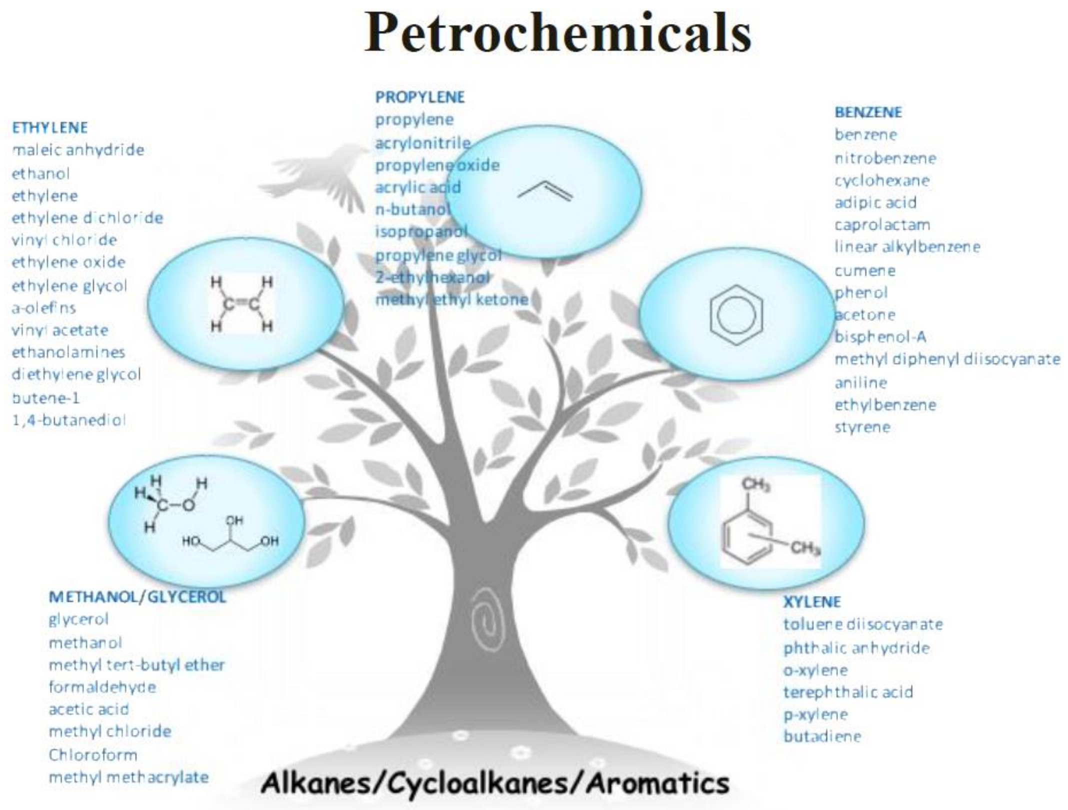
# Fossil fuels

- What is a biobased raw material? Oil also comes from Nature
- Oil, coal, natural gas  are the result of the anaerobic decomposition of fossils (zooplankton and phytoplancton) over millions of years
- Coal is primarily used as a fuel (to produce for example electricity)
- Natural gas, primarily as a fuel but also has chemical feedstock (plastic manufacturing etc…)
- Crude Oil (alkanes, naphtenes, aromatics, aphaltics) is further refined and separated into many products: kerosene, gasoline, propane, ethylene, xykenes)

Source: https://robbieandrew.github.io/GCB2022/

# Petrochemical dependant industry

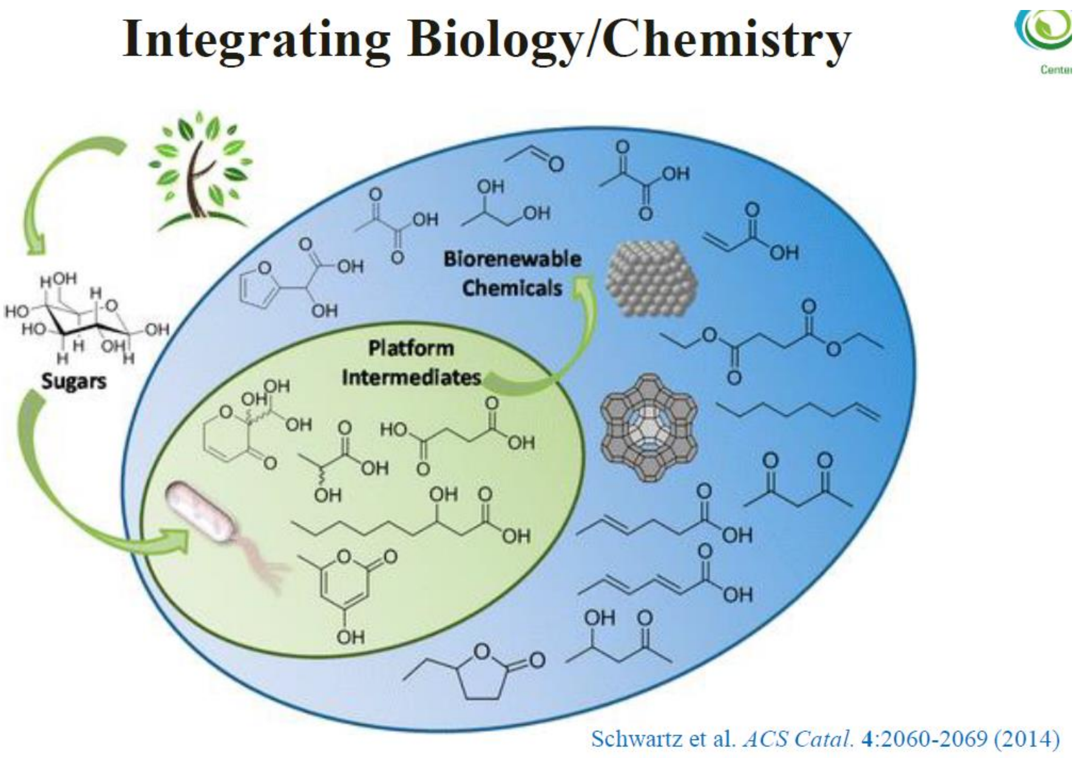
- Resource (was) abundant.
- Oil extraction extremely cheap.
- Overall amount of energy (value) in 1kg of oil is enormous (compared to any other resource)
- Five major «classes» of products come from oil.
  - further derived over time into many other chemicals (leaves at first)
  - leaves themselves progressively led to all the chemicals we are using
- Chemical market created demands for existing building blocks but also for new ones which over time themselves also became very large
- Over the years, original branches became enormous. New branches and all their leaves are themselves. Via economy of scale, all are cheap as well



Source: https://robbieandrew.github.io/GCB2022/

# Renewable resources: definition

- What is a ~~biobased raw~~ renewable and sustainable raw material?
- A  material which Nature gives us and which is regenerated (using energy resources, ex: $CO_2$ and sunlight which are unlimited (from human standpoint)
- It is renewable as long as you harvest the resources at a rate slower than its consumption



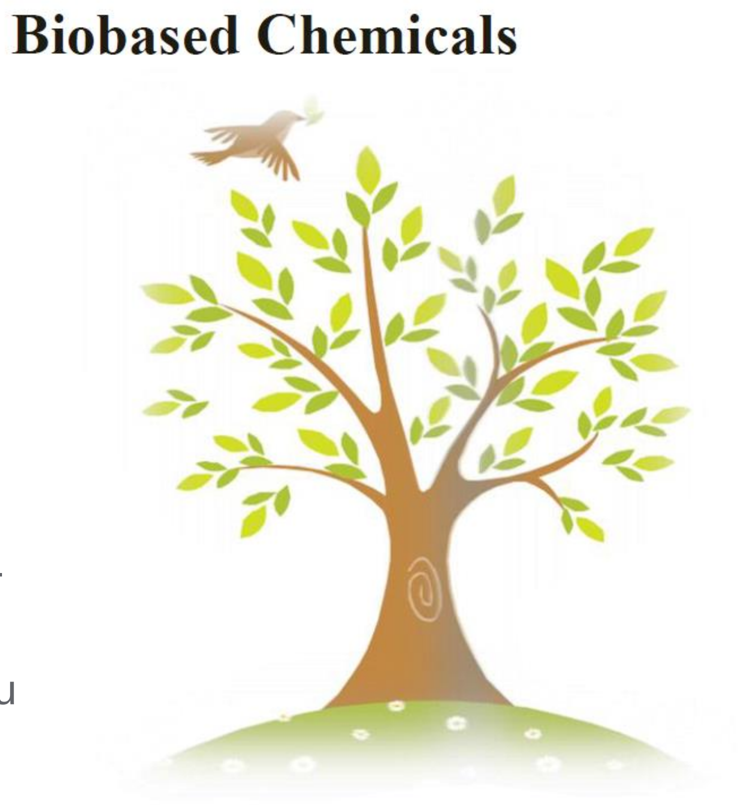
**Integrating Biology/Chemistry**

Schwartz et al. *ACS Catal.* **4**:2060-2069 (2014)

# Renewable resources: challenges

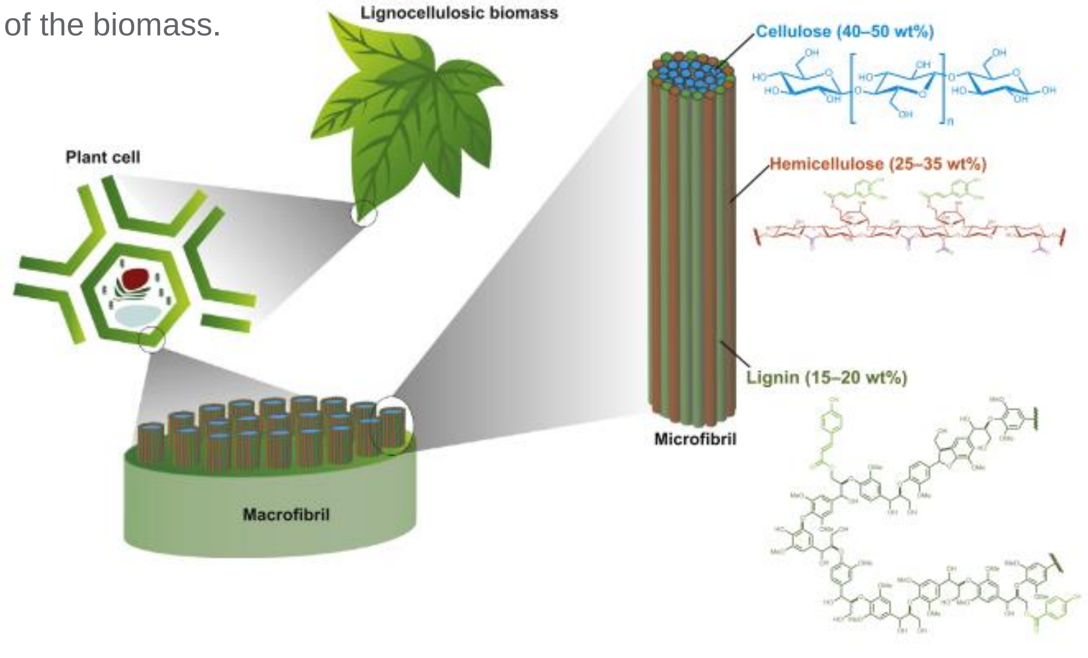
- Tree from renewable starting materials is much less developped
  - Must be further elaborated
  - Combined use of biology of chemistry

- Industrial chemists demands
  - Can we have the renewable material we need **on the scale we need**?
  - Can we have the renewable material we need **all through the year** (for chemicals coming from plants, harvested seasonally, this can be a challenge)
  - Can we get **reproducible quality** of raw materials (often Nature provides mixtures). Is it consistent over plants (if multiple species are the prime resource)
- Economy of scale **not yet** operating. Materials (still) more expensive than from oil-derived resources
- Does a renewable resource necessarily have a better carbon footprint? What if you need for example very large amount of solvents/water or energy to extract/refine the materials ?



# Renewable resources: Lignocellulose

- Lignocellulose is the major structural component of plants,3,4 and is by far the most abundant type of terrestrial biomass
- **Cellulose** (40–50%):
  - β-1,4-glycosidic bond polymer.
  - Polymerisation degree of up to 10 000 units.
  - Insoluble in most conventional solvents, including water
- **Hemicellulose** (25–35%):
  - branched carbohydrate polymers.
  - Containing pentoses (e.g. xylose, arabinose) and hexoses (e.g. galactose, glucose, mannose).
  - Composition of hemicellulose can strongly vary, depending on the botanical origin of the biomass.
  - Degree of polymerisation generally between 50–300 units.
  - More easily solubilised



Trends in Chemistry 2020, 2, 440-453

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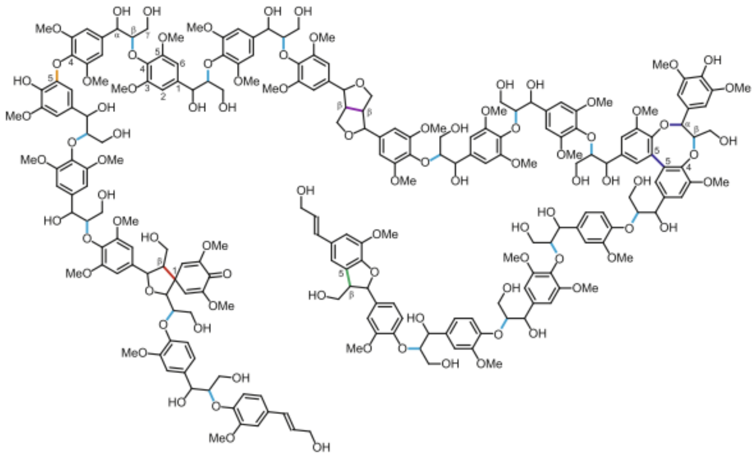
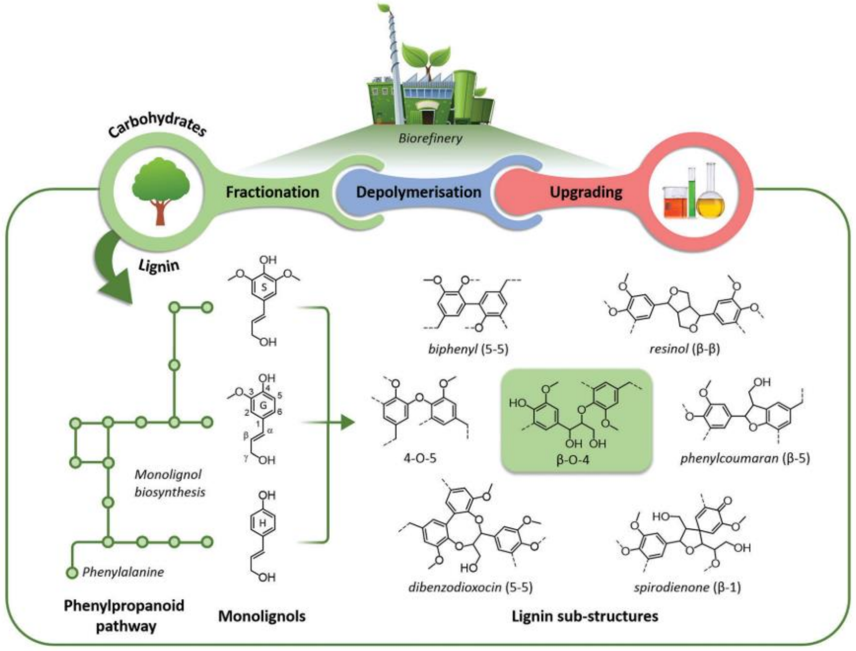
  - Composition of hemicellulose can strongly vary, depending on the botanical origin of the biomass.
  - Degree of polymerisation generally between 50–300 units.
  - More easily solubilised
- **Lignin** (15–20%).
  - Irregular, oxygenated p-propylphenol polymer, formed by free radical polymerisation of monolignols in the plant cell wall.
  - provides rigidity to the plant cell wall as well as resistance to microbial attack.
  - Monolignols: H ( p-hydroxyphenyl), G (guaiacyl), and S (syringyl)
  - Relative distribution strongly differs between plant species. Softwood lignin (e.g. pine, spruce) exclusively contains G units. Hardwood lignin (e.g. birch, poplar, eucalyptus): composed of both G and S units

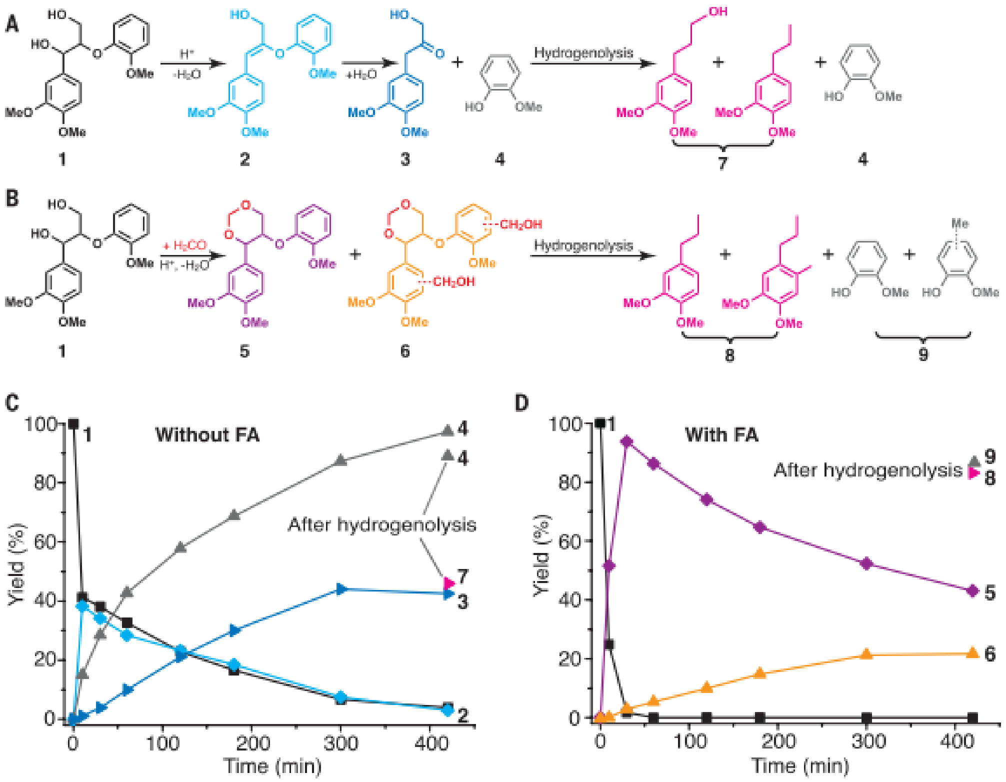


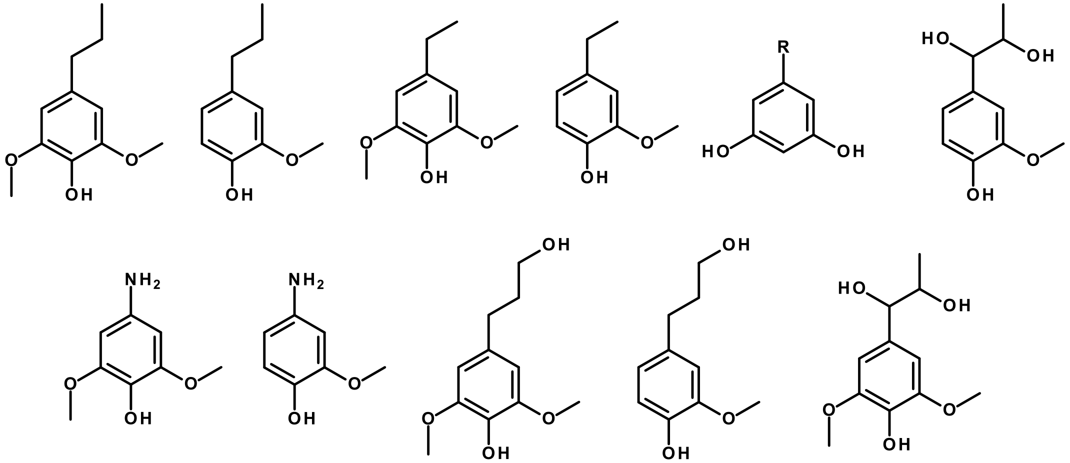


Chemical Society Reviews 2018, 47, 852-908, CHIMIA 2019, 73, 591-598

# Renewable resources: Lignin

- Example: Lignin depolymerization improved with formaldehyde
- Technology commercialized by Bloom Renewables

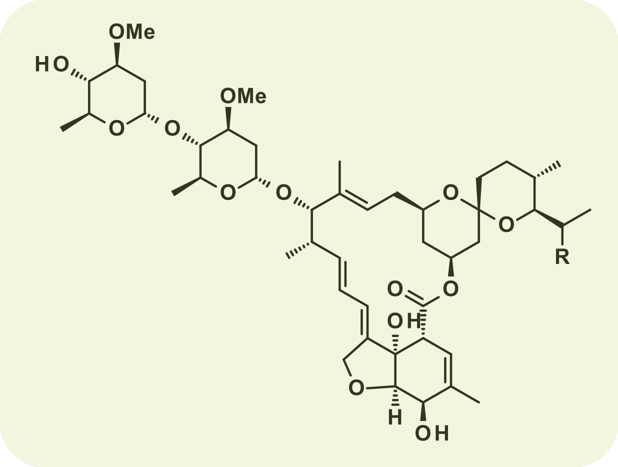




Science 2016, 354, 329

# Renewable resources: Abamectin

- Abamectin or Ivermectin: discovered in 1975 in Japan
- Used in veterinary, pharmaceutical fields also in crops
- William Campbell and Satoshi Ōmura: Nobel prize in Physiology and Medicine in 2015
- Acts via the γ-aminobutyric acid (GABA)/glutamate-gated chloride channels, which results in the disruption of nerve impulses and paralysis of the targeted insects
- Particularly effective against a large number of mite and lepidopteran pest insect species



**1**

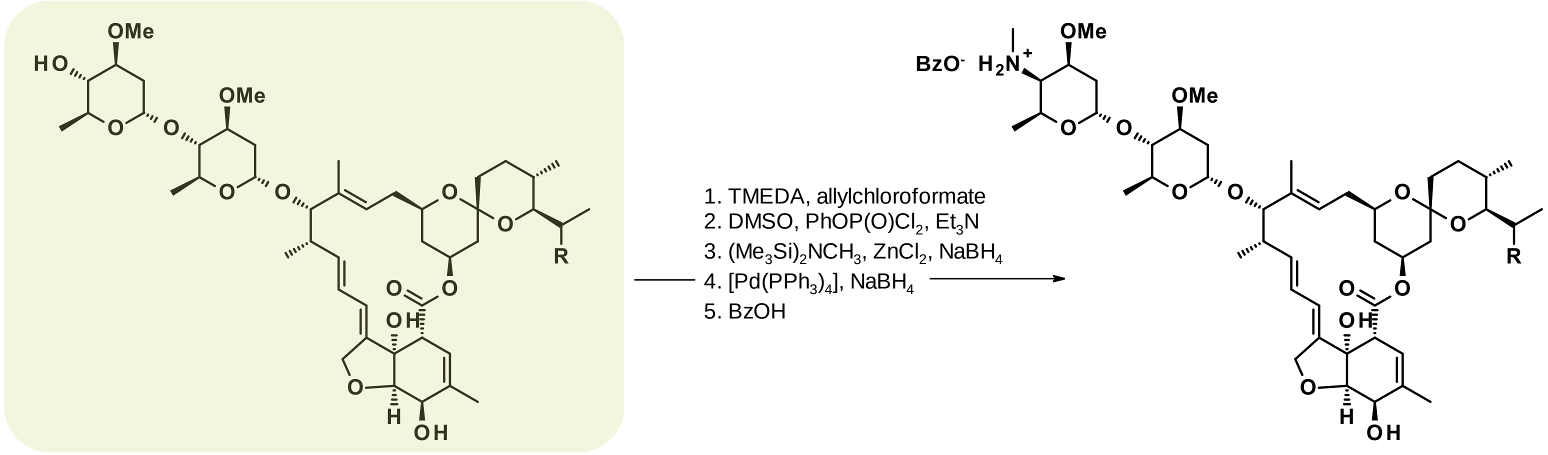
Abamectin

**R = $CH_3$ (<20%)**
**= $C_2H_5$ (>80%)**

T. Pitterna, In *Modern Crop Protection Compounds*; W. Krämer, U. Schirmer, Eds. Wiley: Weinheim, **2007**, *3*, 1069

# Renewable resources: Emamectin Benzoate

- Semi-synthetic analog of Abamectin which was introduced to the market by Novartis (now Syngenta Crop Protection) in 1997
- Prepared from Abamectin by a selective protection of the most reactive allylic hydroxyl group at C5 as an O-allyloxycarbonyl derivative, followed by the C4’’ hydroxyl group oxidation to the ketone
- **10-fold increase** in activity against a broad spectrum of lepidoptera
- Outstanding efficacy: application rates as low as 10–30 g/ha (one teaspoon of the active ingredient to protect the area of a soccer pitch)
- 85% of atoms in Emamectin benzoate come from renewable resources



1. TMEDA, allylchloroformate
2. DMSO, $PhOP(O)Cl_2$, $Et_3N$
3. $(Me_3Si)_2NCH_3$, $ZnCl_2$, $NaBH_4$
4. $[Pd(PPh_3)_4]$, $NaBH_4$
5. BzOH

**1**

Abamectin

R = $CH_3$ (<20%)
= $C_2H_5$ (>80%)

**2**

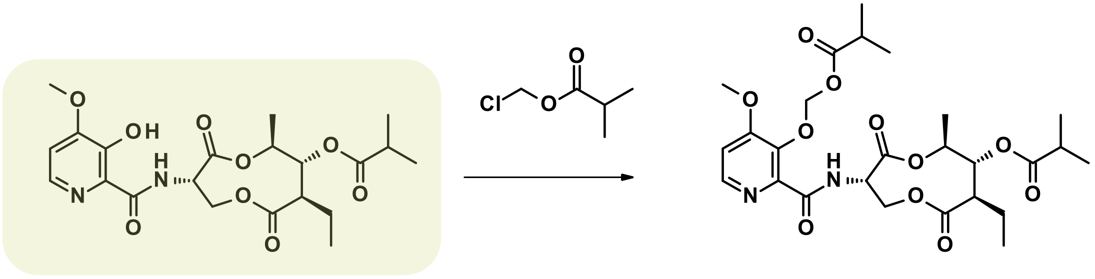
Emanectin benzoate

R = $CH_3$ (<20%)
= $C_2H_5$ (>80%)

J.Org.Chem. 1994, 59, 7704; Hortic. Entomol. 1995, 88, 708

# Renewable resources: Fenpicoxamid

- Example: semi-synthetic active ingredient Fenpicoxamid (Inatreq$^{TM}$ active)
- Corteva$^{TM}$ Agriscience
- highly effective for controlling pathogens in cereals and other crops
- molecular target is the Qi ubiquinone binding site of the mitochondrial complex III of the target fungi,
- no cross-resistance to other widely used fungicides (for ex: different to the Qo binding site of strobilurins)
- UK-2A has a strong antifungal activity but is too unstable photolitically and is readily degraded – before it has time to deliver its biological effect (when deposited as a thin film on a leaf, after 24h less than 10% of the compound is still present)
- Improved stability (photostability in particular) was achieved by capping of the free hydroxyl group present on the picolinamide ring
- increases the fungal activity by a factor of roughly 1000 in comparison to the parent natural product



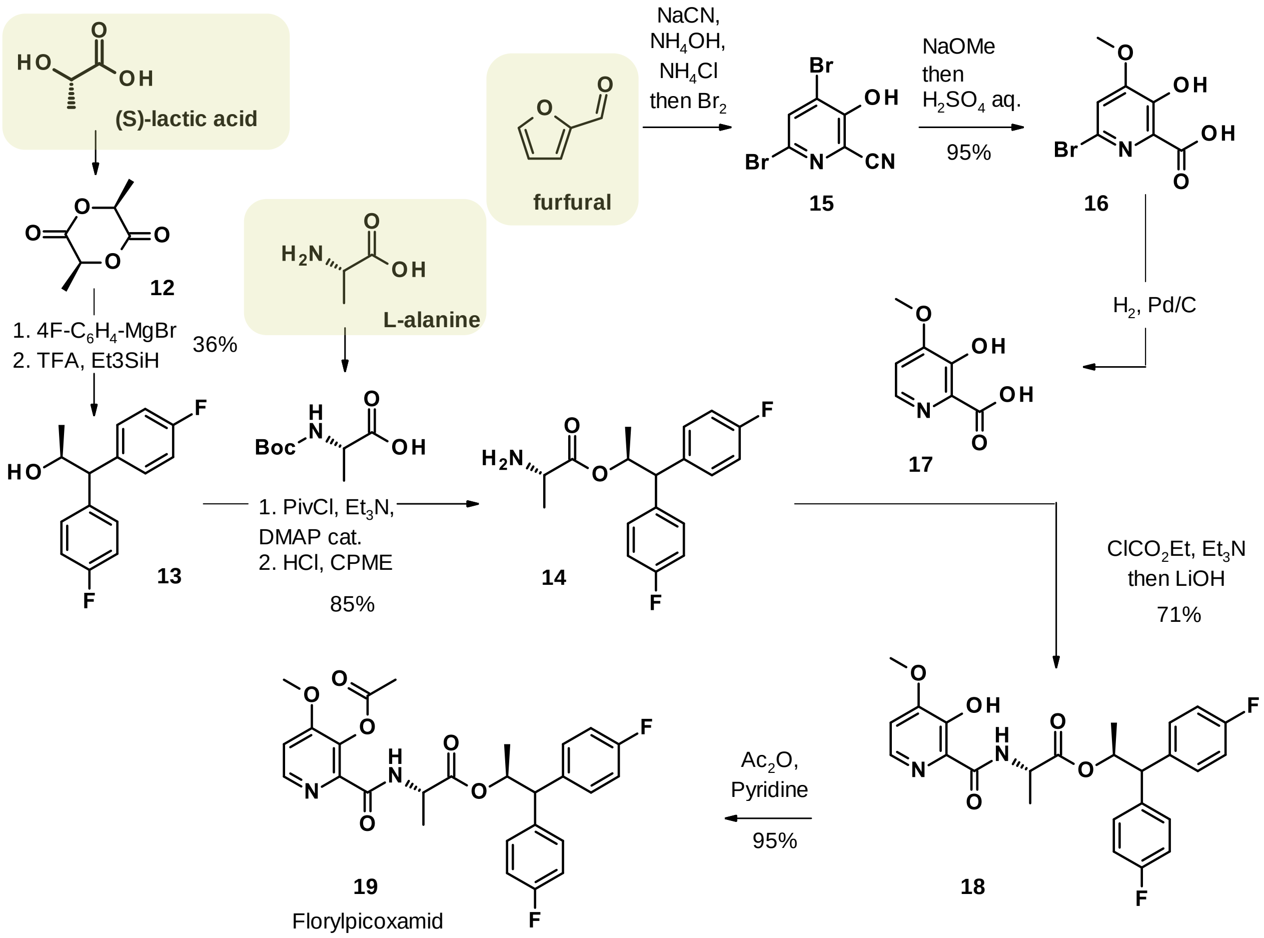
**UK-2A**

**11**
fenpicoxamid

*Pest Manag. Sci.* **2017**, *73*, 2005

# Renewable resources: Florylpicoxamide

- Example 2: deconstruction of UK-2A’s macrocycle gave birth to another crop protection product, florylpicoxamide (AdaveltTM active)
- Why a second fungicide?
  - **broader spectrum** of action *vs* fenpicoxamid and enables, for example, good control of powdery mildew pathogens
  - rapid plant uptake, systemicity (*i.e.* the ingredient translocates throughout the plant for its protection)
  - curative activity (*i.e.* it stops the dissemination of the pathogen once the plant has been infected).
- not prepared from a natural product starting material, but:
  - **Furfural** is derived from lignocellulosic biomass and is a raw material that mostly comes from agricultural waste
  - **(S)-lactic** acid which is readily available from renewable carbohydrates sources
  - **L-alanine** is industrially produced from the decarboxylation from L-aspartic acid using immobilized Pseudomonas dacunhae cells



Green Chem. 2020, 22, 6047; Chimia 2021, 75, 772-779

## www.menti.com

## 71 95 70 73

link

# Atom Economy

- Term first coined from B.Trost (Science 1991, 254, 1471)
- The closer to 100 the AE is the better. Reflects how many « atoms » are wasted in the overall process

$$AE = \frac{MW(Product) \times 100}{\sum MW(Raw\ Materials) + \sum MW(Reagents)}$$

Note: catalyst, solvents are not counted in the equation

**-> No lab data needed is needed for calculation. Great metric for prioritizing approaches**

- Can be calculated at reaction level
- At sequence level

**One can have a reaction with excellent AE and bad PMI. But one cannot have an excellent PMI and bad AE**

Green Chemistry 2002, 4, 521-527

# Atom Economy

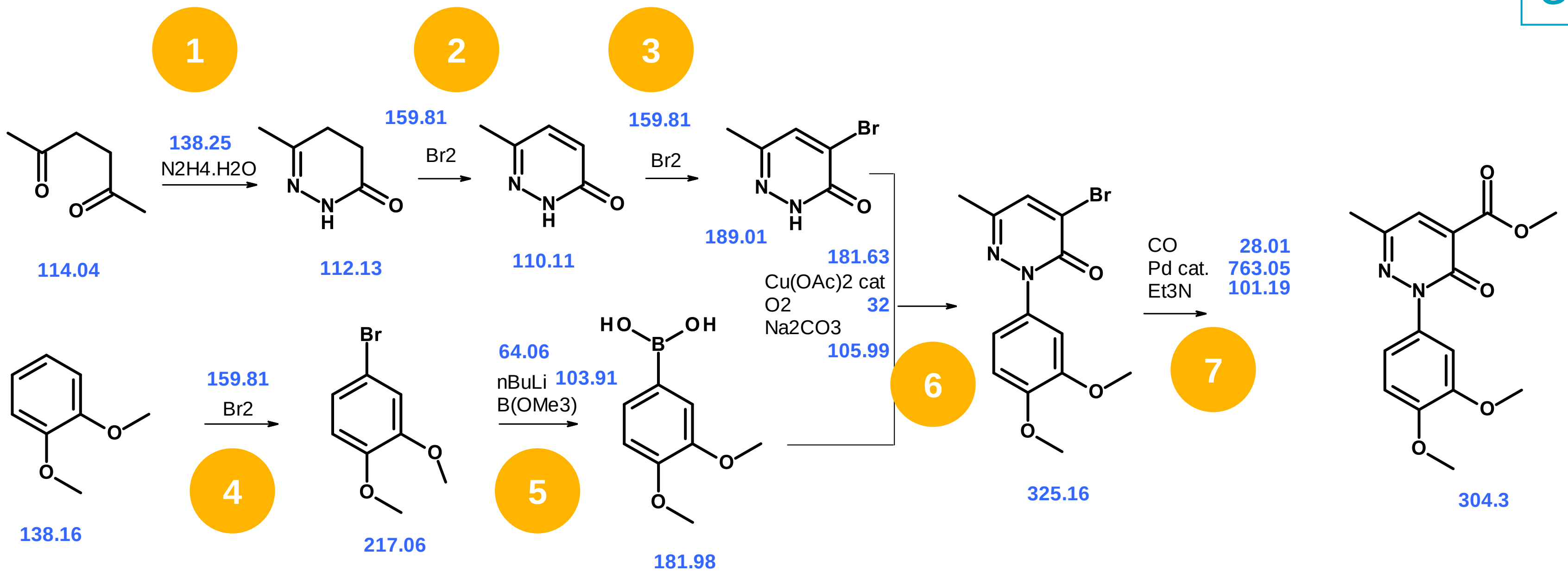
Consider the sequence below

- What is the Atom economy of each step?
- What is the Atom economy of the overall sequence?

**Activity**

Make 7 groups

Group 1 -> calculate AE for step 1
Group 2 -> calculate AE for step 2
Group 3 -> calculate AE for step 3
Group 4 -> calculate AE for step 4
Group 5 -> calculate AE for step 5
Group 6 -> calculate AE for step 6
Group 7 -> calculate AE for step 7



Classification: PUBLIC

*OPRD* 2021, 25, 10, 2205-2220

syngenta

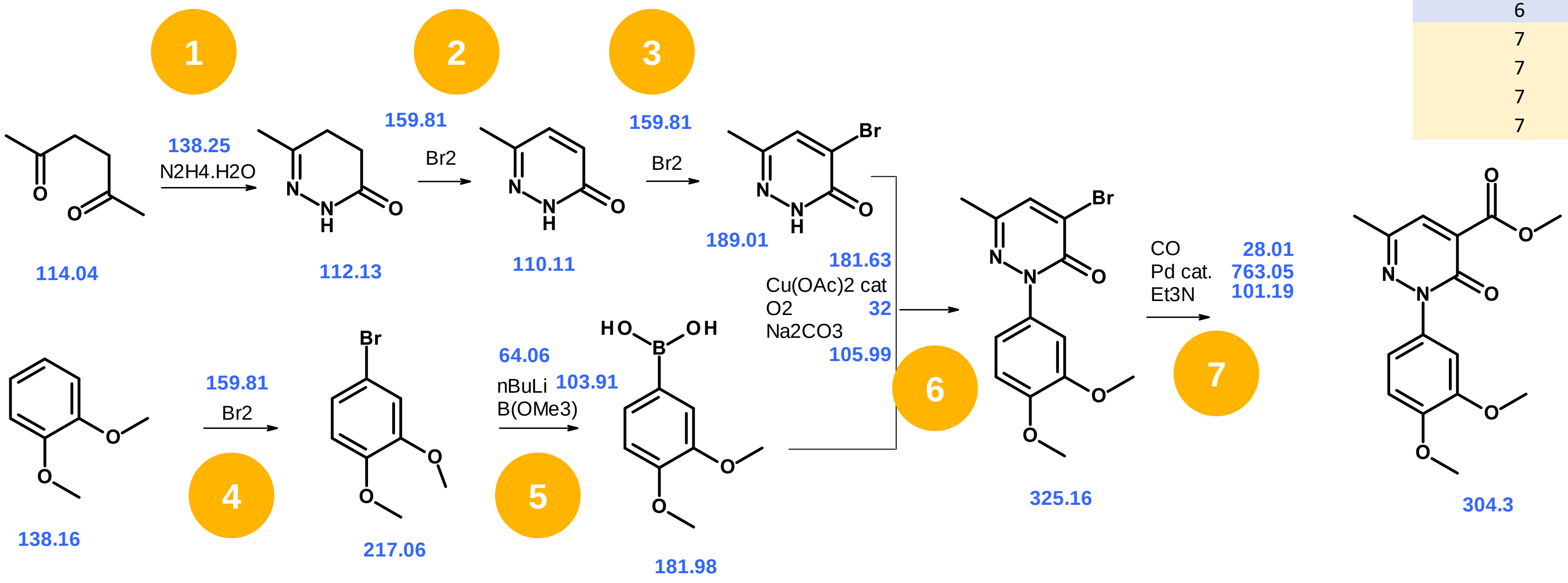
# Atom Economy

Consider the sequence below

- What is the Atom economy of each step?
- What is the Atom economy of the overall sequence?

| reaction | starting materials | product |
|---|---|---|
| 1 | 114.04 | 112.13 |
| 1 | 138.25 | |
| 2 | 112.13 | 110.11 |
| 2 | 159.81 | |
| 3 | 110.11 | 189.01 |
| 3 | 159.81 | |
| 4 | 138.16 | 217.06 |
| 4 | 159.81 | |
| 5 | 217.06 | 181.98 |
| 5 | 64.06 | |
| 5 | 103.91 | |
| 6 | 189.01 | 325.16 |
| 6 | 181.98 | |
| 6 | 32 | |
| 6 | 105.99 | |
| 7 | 325.16 | 304.3 |
| 7 | 28.01 | |
| 7 | 101.19 | |
| 7 | 32.04 | |

| Reaction | Reagents | Product | AE |
|---|---|---|---|
| 1 | 252.29 | 112.13 | **44%** |
| 2 | 271.94 | 110.11 | **40%** |
| 3 | 269.92 | 189.01 | **70%** |
| 4 | 297.97 | 217.06 | **73%** |
| 5 | 385.03 | 181.98 | **47%** |
| 6 | 508.98 | 325.16 | **64%** |
| 7 | 486.4 | 304.3 | **63%** |
| **Synthesis** | **Reagents** | **Product** | **AE** |
| | 1337.08 | 304.3 | **23%** |



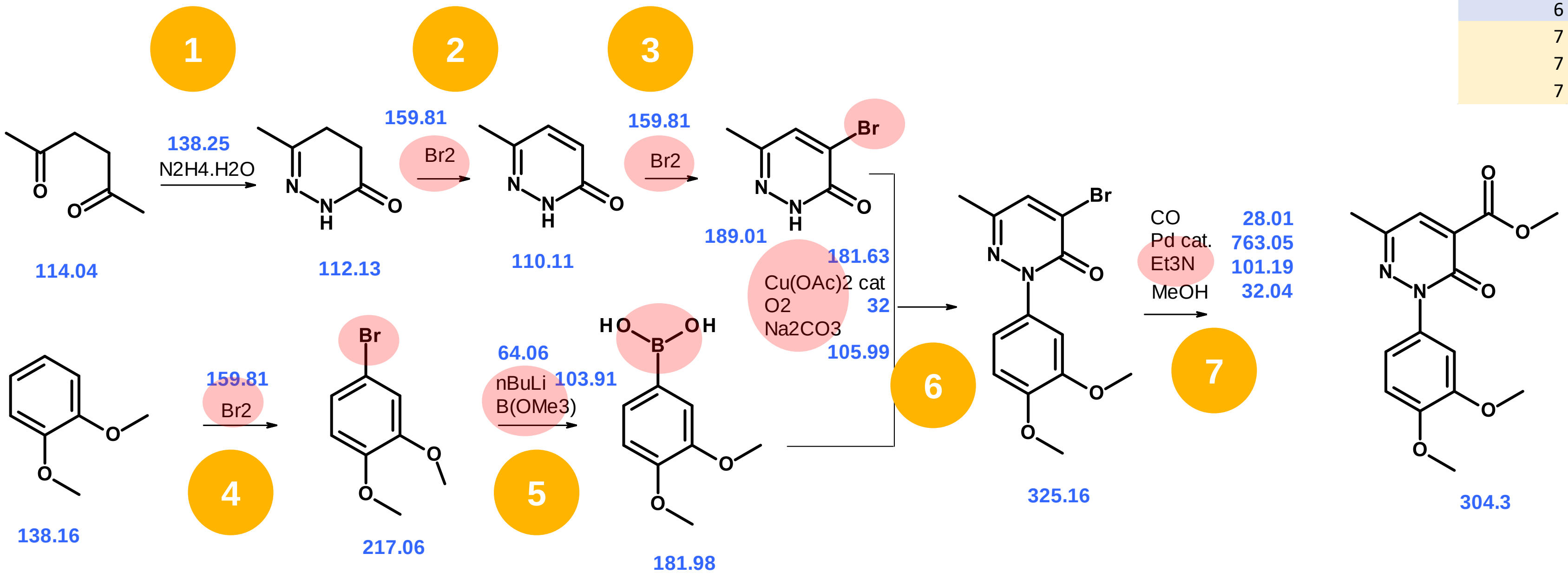
*OPRD* 2021, 25, 10, 2205-2220

# Atom Economy

- Some steps are poor: 1 ; 2 and 5 and waste many atoms
- Two are efficient: 4 and 5
- Overall in the synthesis more than **77% of atoms** used are not ending in the product

| reaction | starting materials | product |
|---|---|---|
| 1 | 114.04 | 112.13 |
| 1 | 138.25 | |
| 2 | 112.13 | 110.11 |
| 2 | 159.81 | |
| 3 | 110.11 | 189.01 |
| 3 | 159.81 | |
| 4 | 138.16 | 217.06 |
| 4 | 159.81 | |
| 5 | 217.06 | 181.98 |
| 5 | 64.06 | |
| 5 | 103.91 | |
| 6 | 189.01 | 325.16 |
| 6 | 181.98 | |
| 6 | 32 | |
| 6 | 105.99 | |
| 7 | 325.16 | 304.3 |
| 7 | 28.01 | |
| 7 | 101.19 | |

| Reaction | Reagents | Product | AE |
|---|---|---|---|
| 1 | 252.29 | 112.13 | **44%** |
| 2 | 271.94 | 110.11 | **40%** |
| 3 | 269.92 | 189.01 | **70%** |
| 4 | 297.97 | 217.06 | **73%** |
| 5 | 385.03 | 181.98 | **47%** |
| 6 | 508.98 | 325.16 | **64%** |
| 7 | 454.36 | 304.3 | **67%** |
| **Synthesis** | **Reagents** | **Product** | **AE** |
| | 1305.04 | 304.3 | **23%** |



*OPRD* 2021, 25, 10, 2205-2220

# Atom Economy

Second generation synthesis

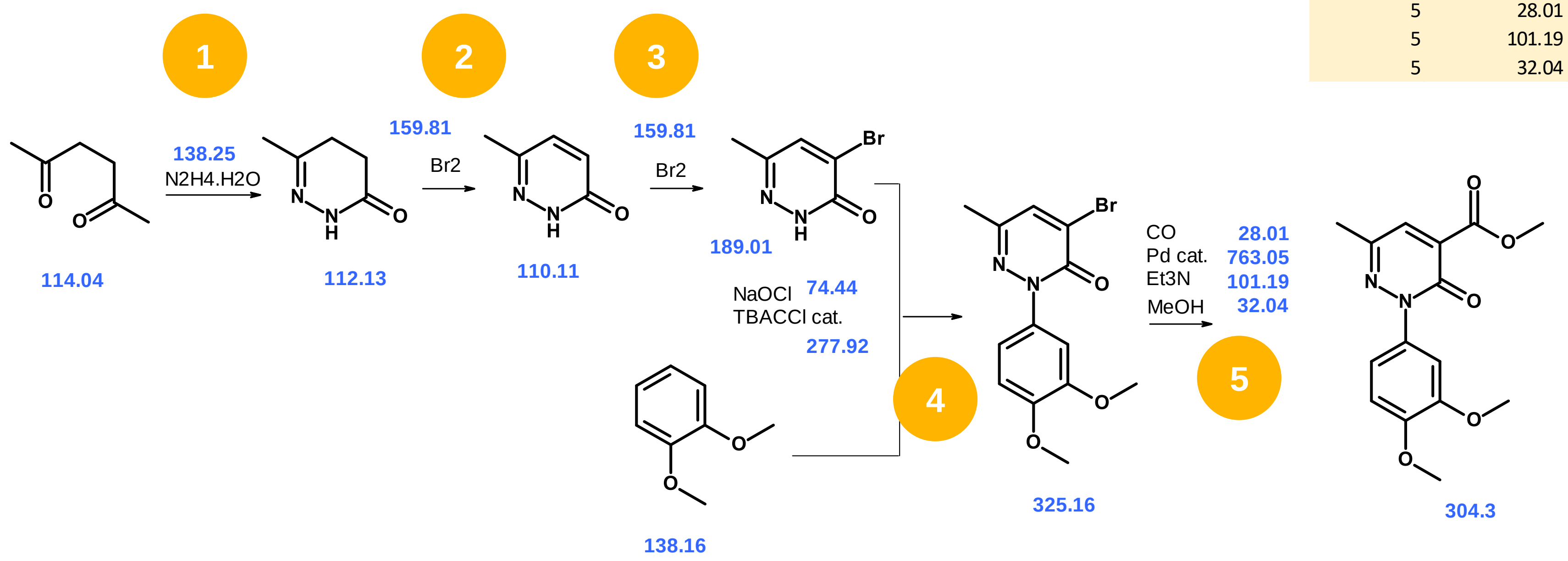
- Shorter sequence, steps 1 and 2 are still poor performing
- Step 4 becomes high performing. Ideal connection between two building blocks. **Very few atoms wasted**

**WASTE = EXPENSE**

- Overal substantial improvement for the entire sequence

| reaction | starting materials | product |
|---|---|---|
| 1 | 114.04 | 112.13 |
| 1 | 138.25 | |
| 2 | 112.13 | 110.11 |
| 2 | 159.81 | |
| 3 | 110.11 | 189.01 |
| 3 | 159.81 | |
| 4 | 189.01 | 325.16 |
| 4 | 138.16 | |
| 4 | 74.44 | |
| 5 | 325.16 | 304.3 |
| 5 | 28.01 | |
| 5 | 101.19 | |
| 5 | 32.04 | |

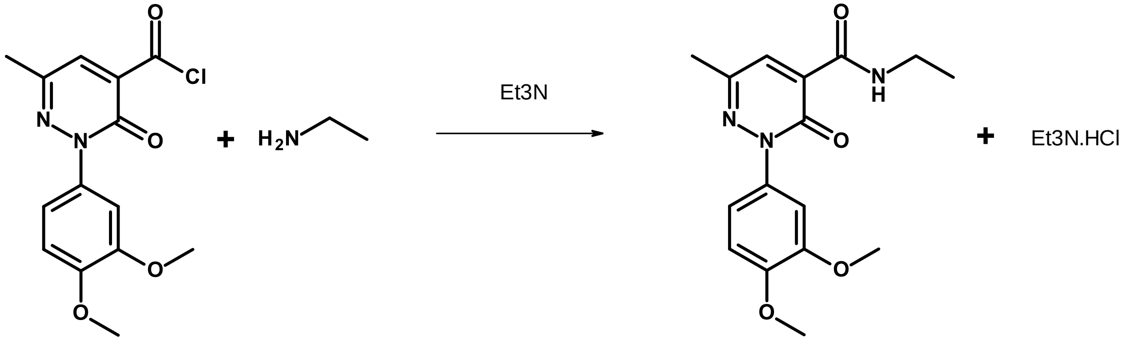
| Reaction | Reagents | Product | AE |
|---|---|---|---|
| 1 | 252.29 | 112.13 | **44%** |
| 2 | 271.94 | 110.11 | **40%** |
| 3 | 269.92 | 189.01 | **70%** |
| 4 | 401.61 | 325.16 | **81%** |
| 5 | 486.4 | 304.3 | **63%** |
| **Synthesis** | **Reagents** | **Product** | **AE** |
| | 945.75 | 304.3 | **32%** |



Green Chemistry 2002, 4, 521-527

# Atom Economy: Some techniques to mitigate loss of atoms

Consider this classical acylation reaction



**Recyling $Et_3N$ is possible**

- Waste is collected as $Et_3NHCl$ salt:
  - free-base with NaOH
  - drying (optional)
  - distillation (collect only fraction with a lower than x% water content)
- Net atom losses
  - Et3N.HCl: 101 + 1 + 35 = 137
  - NaCl, H2O: MW = 23 + 35 + 2 + 16 = 76

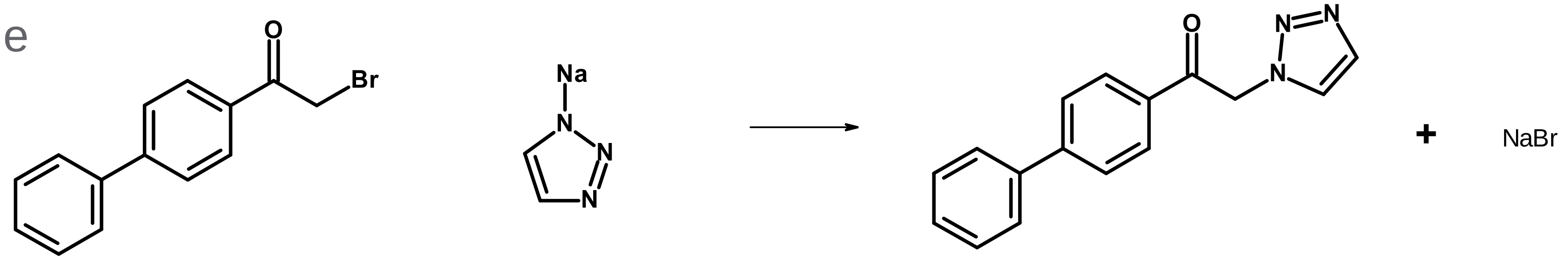
- On large plant facilitities, it is not uncommon to **collect waste streams from different processes** and purify them all together (mutualize/shared cost for multiple processes)
- The recycling is done only if:

**Price of fresh $Et_3N$ > price of fresh NaOH + recycling operational cost**

Green Chemistry 2002, 4, 521-527

# Atom Economy: Some techniques to mitigate loss of atoms

Another example



- Performing  the reaction with the corresponding chloride inefficient (kinetics, reaction profile for example)
- Recyling Br- (much less common)
- Br- waste are collected under the form of NaBr, KBr, HBr.... After some processing (concentration, separation of major other contaminants), **Br- can be re-oxidized into $Br_2$ using $Cl_2$** (Kubierski process)

$NaBr + 1/2Cl_2$ - > $1/2Br_2 + NaCl$

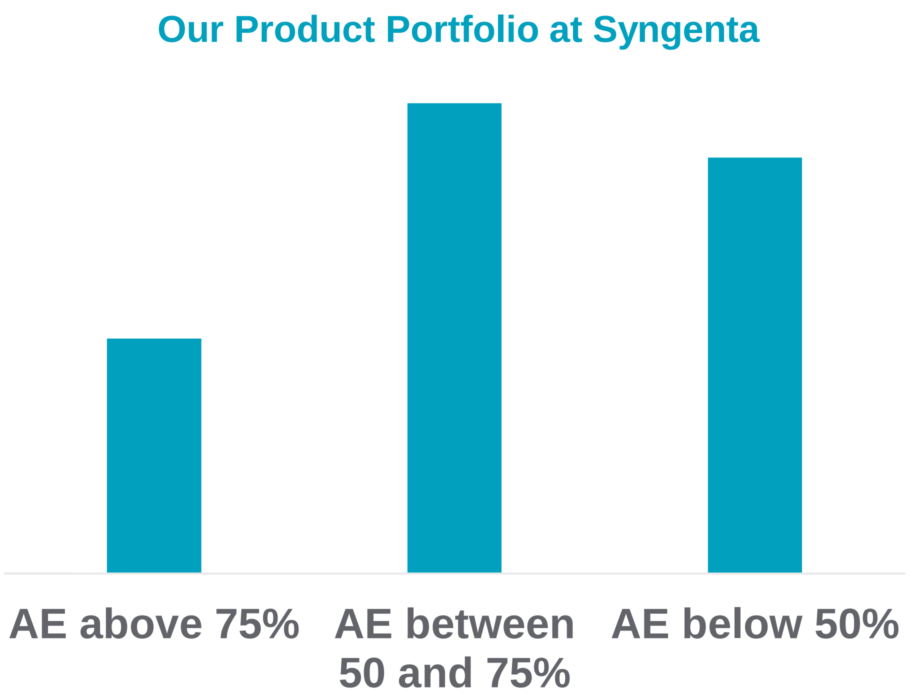
- Net atom losses
  - NaBr: 23 + 79 = 102
  - NaCl:  MW = 23 + 35 = 58
- The recycling justified if:

Price of fresh $Br_2$ > price of fresh $Cl_2$ + recycling infrastructure and operational cost

Green Chemistry 2002, 4, 521-527

# Atom Economy

- Typically, atom economy in Ag



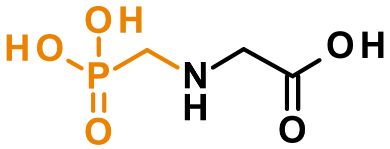
# Prevent Waste

Classification: PUBLIC

*Green Chemistry: Theory* and *Practice*, Ox. Uni. Press, New York, *1998*

# Glyphosate

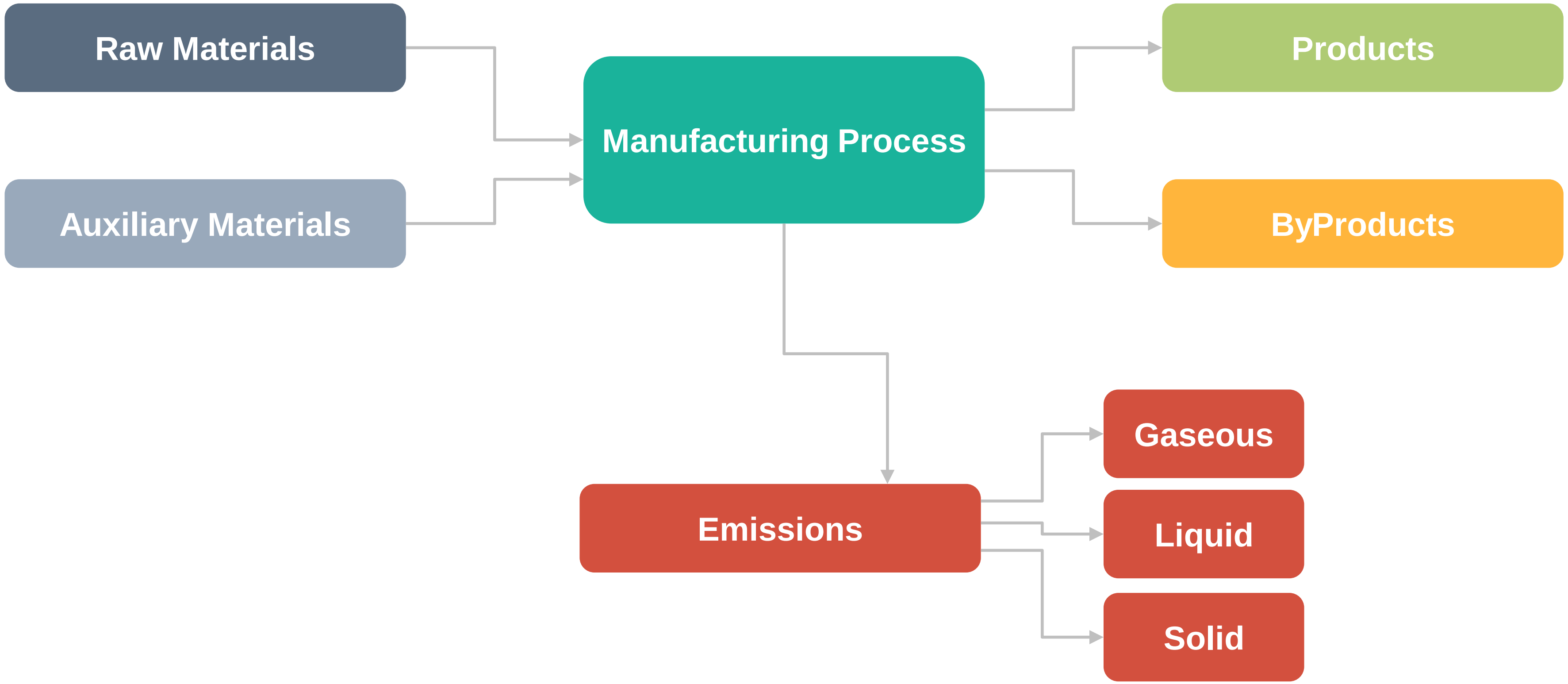
- Main active  component: N-phosphonomethyl-glycine
- NSH: Non-Selective Herbicide
- binds to and inhibits the activity of regulatory enzyme in the shikimate pathway, enolpyruvlshikimate-3-phosphate synthase (EPSPS) that plants need to make amino acids and proteins



**Glyphosate**

- Unusual large scale agrochemical: annual production: > 1 000 000 tons – Very mature process (>20 years)

# Industrial Process Flow



Raw Materials

Auxiliary Materials

Manufacturing Process

Products

ByProducts

Emissions

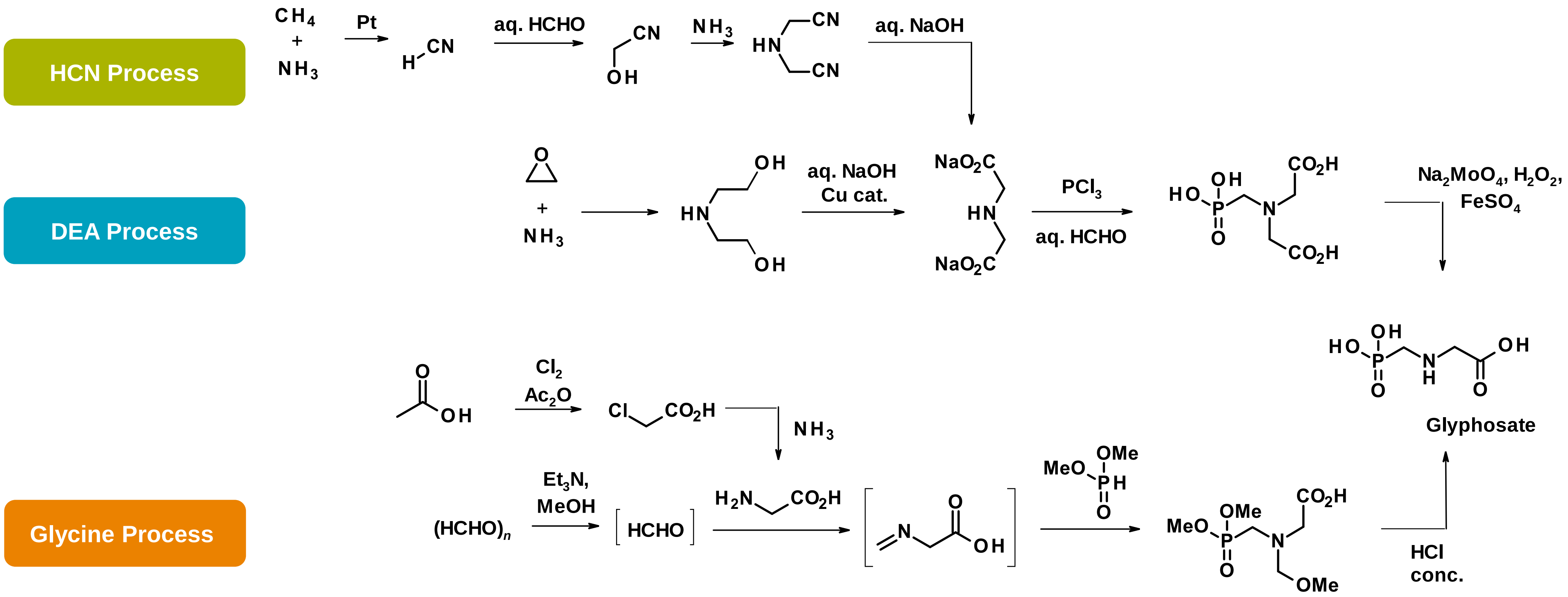
Gaseous

Liquid

Solid

# Three Main Processes how ot make glyphosate

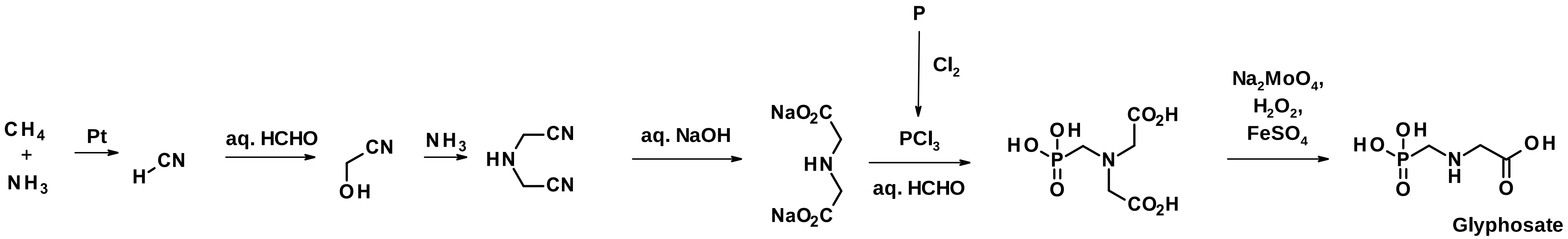
## Unusual large scale agrochemical



*Green Chem*. **2012**, *14*, 1990

# Glyphosate synthesis: HCN process

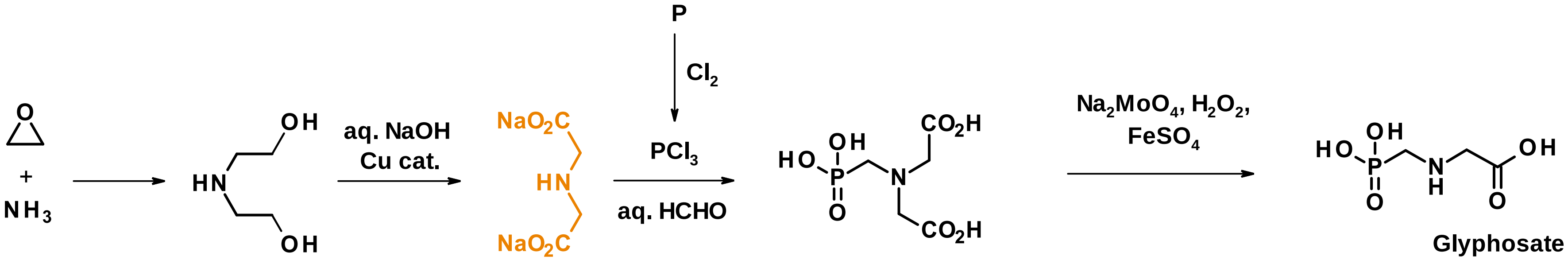
- Key raw materials: $CH_4$, $NH_3$, paraformaldehyde, NaOH, P, $Cl_2$
- Mostly used in China



*Green Chem*. **2012**, *14*, 1990

# Glyphosate synthesis: DiEthanolAmine Process (DEA)

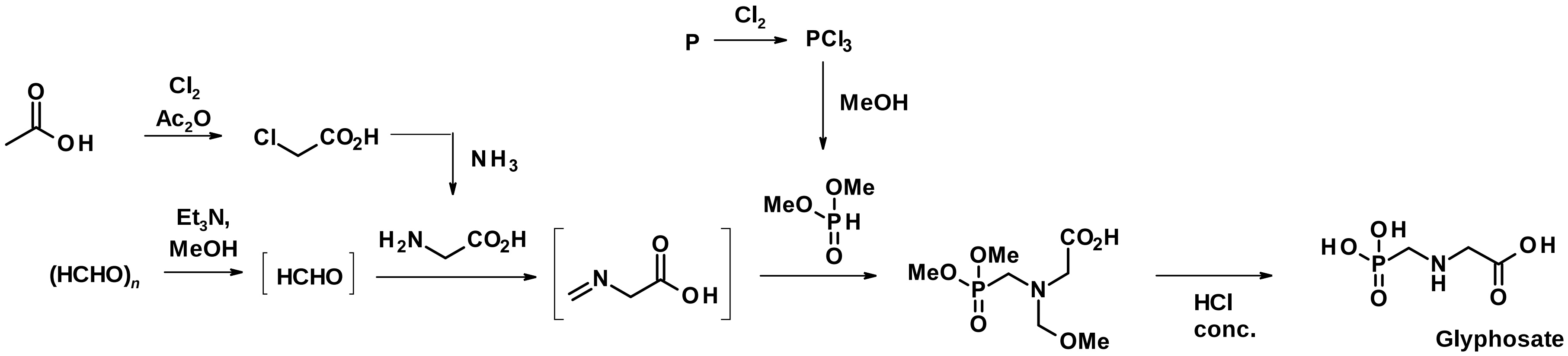
- Key raw materials: Ethylene oxide, Chlorine, NH3, paraformaldehyde, NaOH, P, Methanol
- Key dehydrogenation Method invented by Monsanto
- Cheapest process



*Green Chem*. **2012**, *14*, 1990

# Glyphosate synthesis: Glycine Process

- Key raw materials: Acetic acid, Chlorine, $NH_3$, paraformaldehyde, NaOH, P, Methanol
- Method cheap, clean and efficient: better yield and minimal to no environmental pollution



*Green Chem*. **2012**, *14*, 1990

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link

# How Are Industry Sectors Performing vs Green Chemistry?

**The larger the scale, the greener the process**

Yet, in an absolute sense, larger scale process are generating more waste

**Key Performance indicator**

Process Mass Intensity (PMI)

$$\text{PMI} = \frac{\text{[Mass (in kg) of all inputs]}}{\text{Mass (in kg) of product}}$$

| Industry Segment | Tonnes produced per year | PMI | Tons of waste generated* |
|---|---|---|---|
| Oil refining | 1’000’000 to 100’000’000 | <1.1 kg/kg | 100’000 to 10’000’000 |
| Bulk chemicals | 10’000 to 1’000’000 | <1-5 kg/kg | 30’000 to 3’000’000 |
| **Fine Chemicals** | **1’000 to 10’000** | **5-50 kg/kg** | **25’000 to 250’000** |
| Pharmaceuticals | 10 to 1’000 | >25-100 kg/kg | 600 to 60’000 |

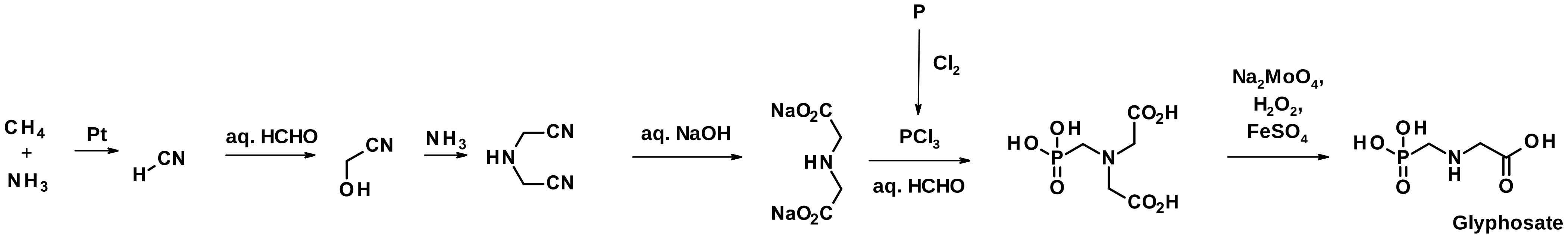
*Green Chemistry*, **2017**, *19*, 18

# Glyphosate synthesis: which process is best?

**If we have data, let's look at data. If all we have are opinions, let's go with mine**

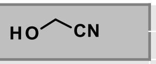
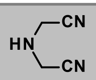
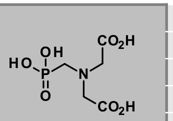
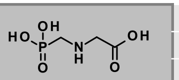
*[James L. Barksdale - former president and CEO of Netscape Communications]*

# HCN process

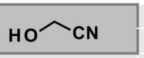
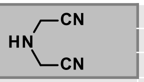
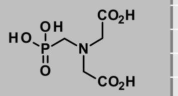
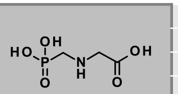


*Green Chem*. **2012**, *14*, 1990

# Mass Flow Sheet

| in | | | | step | | | | out | | |
|---|---|---|---|---|---|---|---|---|---|---|
| name | role | kg | | | | | | name | role | kg |
| **CH4** | raw material | **562** | → | **HCN Synthesis** | | | → | **(NH4)2SO4** | by-product | **436** |
| **NH3** | raw material | **487** | → | | | | → | **Offgas** | gaseous emission | **365** |
| **H2SO4** | raw material | **314** | → | | | | | | | |
| **Pt** | auxiliary material | **0.0001** | → | | | | | | | |
| | | | | HCN | product | 523 | | | | |
| | | | | ↓ | | | | | | |
| **HCN** | Intermediate | **523** | → | **HOCH2CN**  | | | | | | |
| **HCHO** | raw material | **1489** | → | | | | | | | |
| | | | | HOCH2CN | product | 2053 | | | | |
| | | | | ↓ | | | | | | |
| **HOCH2CN** | Intermediate | **2053** | → | **IDAN**  | | | → | **NH3 waste** | liquid effluent | **24** |
| **NH3** | raw material | **153** | → | | | | → | **cyanohydrin side pdt** | liquid effluent | **171** |
| | | | | | | | → | **H2O** | liquid effluent | **1268** |
| | | | | IDAN | product | 742 | | | | |
| | | | | ↓ | | | | | | |
| **IDAN** | Intermediate | **742** | → | **PMIDA**  | | | → | **Glycine side waste** | liquid effluent | **101** |
| **NaOH** | raw material | **2010** | → | | | | → | **HCHO waste** | liquid effluent | **65** |
| **PCl3** | Intermediate | **1270** | → | | | | → | **H3PO3 waste** | liquid effluent | **230** |
| **HCHO** | raw material | **700** | → | | | | → | **NaCl** | liquid effluent | **882** |
| | | | | | | | → | **HCl** | liquid effluent | **416** |
| | | | | | | | → | **NH4Cl** | liquid effluent | **65** |
| | | | | | | | → | **H2O** | liquid effluent | **1239** |
| | | | | PMIDA | product | 1490 | | | | |
| | | | | ↓ | | | | | | |
| **PMIDA** | Intermediate | **1490** | → | **PMG (glyphosate)**  | | | → | **HCo2H** | liquid effluent | **129** |
| **H2O2 30%** | raw material | **810** | → | | | | → | **HCHO** | liquid effluent | **84** |
| **Na2MoO4** | auxiliary material | **5** | → | | | | → | **CO2** | gaseous emission | **247** |
| **FeSO4** | auxiliary material | **30** | → | | | | → | **Fe(SO4)3** | liquid effluent | **35** |
| | | | | | | | → | **side products** | liquid effluent | **184** |
| | | | | | | | → | **H2O** | liquid effluent | **655** |
| | | | | Gylphosate | Active Ingredient | 1000 | | | | |
| **P** | raw material | **292** | → | **PCl3** | | | → | **Cl2 waste** | gaseous emission | **79** |
| **Cl2** | raw material | **1080** | → | | | | → | **other waste** | liquid effluent | **23** |
| | | | | PCl3 | product | 1270 | | | | |

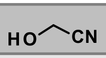
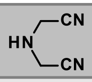
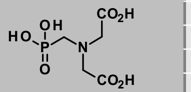
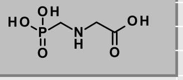
# Mass Flow Sheet - what’s in = what’s out

| in | | | | step | | | | out | | |
|---|---|---|---|---|---|---|---|---|---|---|
| name | role | kg | | | | | | name | role | kg |
| CH4 | raw material | 562 | → | **HCN Synthesis** | | | → | (NH4)2SO4 | by-product | 436 |
| NH3 | raw material | 487 | → | | | | → | Offgas | gaseous emission | 365 |
| H2SO4 | raw material | 314 | → | | | | | | | |
| Pt | auxiliary material | 0.0001 | → | | | | | | | |
| | | | | HCN | product | 523 | | | | |
| | | | | ↓ | | | | | | |
| HCN | Intermediate | 523 | → | **HOCH2CN** | |  | | | | |
| HCHO | raw material | 1489 | → | | | | | | | |
| | | | | HOCH2CN | product | 2053 | | | | |
| | | | | ↓ | | | | | | |
| HOCH2CN | Intermediate | 2053 | → | **IDAN** | |  | → | NH3 waste | liquid effluent | 24 |
| NH3 | raw material | 153 | → | | | | → | cyanohydrin side pdt | liquid effluent | 171 |
| | | | | | | | → | H2O | liquid effluent | 1268 |
| | | | | IDAN | product | 742 | | | | |
| | | | | ↓ | | | | | | |
| IDAN | Intermediate | 742 | → | **PMIDA** | |  | → | Glycine side waste | liquid effluent | 101 |
| NaOH | raw material | 2010 | → | | | | → | HCHO waste | liquid effluent | 65 |
| PCl3 | Intermediate | 1270 | → | | | | → | H3PO3 waste | liquid effluent | 230 |
| HCHO | raw material | 700 | → | | | | → | NaCl | liquid effluent | 882 |
| | | | | | | | → | HCl | liquid effluent | 416 |
| | | | | | | | → | NH4Cl | liquid effluent | 65 |
| | | | | | | | → | NH3 | liquid effluent | 234 |
| | | | | | | | → | H2O | liquid effluent | 1239 |
| | | | | PMIDA | product | 1490 | | | | |
| | | | | ↓ | | | | | | |
| PMIDA | Intermediate | 1490 | → | **PMG (glyphosate)** | |  | → | HCo2H | liquid effluent | 129 |
| H2O2 30% | raw material | 810 | → | | | | → | HCHO | liquid effluent | 84 |
| Na2MoO4 | auxiliary material | 5 | → | | | | → | CO2 | gaseous emission | 247 |
| FeSO4 | auxiliary material | 30 | → | | | | → | Fe(SO4)3 | liquid effluent | 35 |
| | | | | | | | → | side products | liquid effluent | 184 |
| | | | | | | | → | H2O | liquid effluent | 655 |
| | | | | Gylphosate | Active Ingredient | 1000 | | | | |
| P | raw material | 292 | → | **PCl3** | | | → | Cl2 waste | gaseous emission | 79 |
| Cl2 | raw material | 1080 | → | | | | → | other waste | liquid effluent | 23 |
| | | | | PCl3 | product | 1270 | | | | |
| | | 7932 | | | | | | | | 6932 |

= 7932 kg

= 7932 kg

# Mass Flow Sheet: Usage factor

| in | | | | step | | | | out | | | usage factors | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| name | role | kg | | | | | | name | role | kg | in (kg/kg) | out (kg/kg) |
| CH4 | raw material | 562 | → | **HCN Synthesis** | | | → | (NH4)2SO4 | by-product | 436 | 0.562 | 0.436 |
| NH3 | raw material | 487 | → | | | | → | Offgas | gaseous emission | 365 | 0.487 | 0.365 |
| H2SO4 | raw material | 314 | → | | | | | | | | 0.314 | |
| Pt | auxiliary material | 0.0001 | → | | | | | | | | 0.000 | |
| | | | | HCN | product | 523 | | | | | | |
| | | | | ↓ | | | | | | | | |
| HCN | Intermediate | 523 | → | **HOCH2CN**  | | | | | | | 0.523 | |
| HCHO | raw material | 1489 | → | | | | | | | | 1.489 | |
| | | | | HOCH2CN | product | 2053 | | | | | | 2.053 |
| | | | | ↓ | | | | | | | | |
| HOCH2CN | Intermediate | 2053 | → | **IDAN**  | | | → | NH3 waste | liquid effluent | 24 | 2.053 | 0.024 |
| NH3 | raw material | 153 | → | | | | → | cyanohydrin side pdt | liquid effluent | 171 | 0.153 | 0.171 |
| | | | | | | | → | H2O | liquid effluent | 1268 | | 1.268 |
| | | | | IDAN | product | 742 | | | | | | 0.742 |
| | | | | ↓ | | | | | | | | |
| IDAN | Intermediate | 742 | → | **PMIDA**  | | | → | Glycine side waste | liquid effluent | 101 | 0.742 | 0.101 |
| NaOH | raw material | 2010 | → | | | | → | HCHO waste | liquid effluent | 65 | 2.010 | 0.065 |
| PCl3 | Intermediate | 1270 | → | | | | → | H3PO3 waste | liquid effluent | 230 | 1.270 | 0.230 |
| HCHO | raw material | 700 | → | | | | → | NaCl | liquid effluent | 882 | 0.700 | 0.882 |
| | | | | | | | → | HCl | liquid effluent | 416 | | 0.416 |
| | | | | | | | → | NH4Cl | liquid effluent | 65 | | 0.065 |
| | | | | | | | → | NH3 | liquid effluent | 234 | | 0.234 |
| | | | | | | | → | H2O | liquid effluent | 1239 | | 1.239 |
| | | | | PMIDA | product | 1490 | | | | | | 1.490 |
| | | | | ↓ | | | | | | | | |
| PMIDA | Intermediate | 1490 | → | **PMG (glyphosate)**  | | | → | HCo2H | liquid effluent | 129 | 1.490 | 0.129 |
| H2O2 30% | raw material | 810 | → | | | | → | HCHO | liquid effluent | 84 | 0.810 | 0.084 |
| Na2MoO4 | auxiliary material | 5 | → | | | | → | CO2 | gaseous emission | 247 | 0.005 | 0.247 |
| FeSO4 | auxiliary material | 30 | → | | | | → | Fe(SO4)3 | liquid effluent | 35 | 0.030 | 0.035 |
| | | | | | | | → | side products | liquid effluent | 184 | | 0.184 |
| | | | | | | | → | H2O | liquid effluent | 655 | | 0.655 |
| | | | | Gylphosate | Active Ingredient | 1000 | | | | | | |
| P | raw material | 292 | → | **PCl3** | | | → | Cl2 waste | gaseous emission | 79 | 0.292 | 0.079 |
| Cl2 | raw material | 1080 | → | | | | → | other waste | liquid effluent | 23 | 1.080 | 0.023 |
| | | | | PCl3 | product | 1270 | | | | | | |
| | | 7932 | | | | | | | | 6932 | | |

# Glyphosate synthesis: HCN process Mass Flow Sheet

- Process Mass Intensity

$$\mathbf{PMI} = \frac{\textbf{kg input needed}}{\textbf{kg Product formed}}$$

- E factor

$$\mathbf{E_{factor}} = \frac{\textbf{kg waste}}{\textbf{kg product}}$$

Waste: defined as everything but the desired product (takes the chemical yield into account, reagents, solvents losses, all process aids…)

So waste = [kg inputs – kg product], so **$E_{factor}$ = PMI +1**

**Best $E_{factor}$ is 0. Best PMI is 1**

# Glyphosate synthesis: HCN process Mass Flow Sheet

| in | | | | step | | | out | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| name | role | kg | | | | | | name | role | kg |
| CH4 | raw material | 562 | → | **HCN Synthesis** | | | → | (NH4)2SO4 | by-product | 436 |
| NH3 | raw material | 487 | → | | | | → | Offgas | gaseous emission | 365 |
| H2SO4 | raw material | 314 | → | | | | | | | |
| Pt | auxiliary material | 0.0001 | → | | | | | | | |
| | | | | HCN | product | 523 | | | | |
| | | | | ↓ | | | | | | |
| HCN | Intermediate | 523 | → | **HOCH2CN** | | | | | | |
| HCHO | raw material | 1489 | → | | | | | | | |
| | | | | HOCH2CN | product | 2053 | | | | |
| | | | | ↓ | | | | | | |
| HOCH2CN | Intermediate | 2053 | → | **IDAN** | | | → | NH3 waste | liquid effluent | 24 |
| NH3 | raw material | 388 | → | | | | → | cyanohydrin side pdt | liquid effluent | 171 |
| | | | | | | | → | H2O | liquid effluent | 1268 |
| | | | | IDAN | product | 742 | | | | |
| | | | | ↓ | | | | | | |
| IDAN | Intermediate | 742 | → | **PMIDA** | | | → | Glycine side waste | liquid effluent | 101 |
| NaOH | raw material | 2010 | → | | | | → | HCHO waste | liquid effluent | 65 |
| PCl3 | Intermediate | 1270 | → | | | | → | H3PO3 waste | liquid effluent | 230 |
| HCHO | raw material | 700 | → | | | | → | NaCl | liquid effluent | 882 |
| | | | | | | | → | HCl | liquid effluent | 416 |
| | | | | | | | → | NH4Cl | liquid effluent | 65 |
| | | | | | | | → | NH3 | liquid effluent | 234 |
| | | | | | | | → | H2O | liquid effluent | 1239 |
| | | | | PMIDA | product | 1490 | | | | |
| | | | | ↓ | | | | | | |
| PMIDA | Intermediate | 1490 | → | **PMG (glyphosate)** | | | → | HCo2H | liquid effluent | 129 |
| H2O2 30% | raw material | 810 | → | | | | → | HCHO | liquid effluent | 84 |
| Na2MoO4 | auxiliary material | 5 | → | | | | → | CO2 | gaseous emission | 247 |
| FeSO4 | auxiliary material | 30 | → | | | | → | Fe(SO4)3 | liquid effluent | 35 |
| | | | | | | | → | side products | liquid effluent | 184 |
| | | | | | | | → | H2O | liquid effluent | 655 |
| | | | | Gylphosate | Active Ingredient | 1000 | | | | |
| P | raw material | 292 | → | **PCl3** | | | → | Cl2 waste | gaseous emission | 79 |
| Cl2 | raw material | 1080 | → | | | | → | other waste | liquid effluent | 23 |
| | | | | PCl3 | product | 1270 | | | | |
| | | 8167 | | | | | | | | 6932 |

$$\mathbf{PMI} = \frac{\text{kg input needed}}{\text{kg Product formed}}$$

$$\text{PMI} = \frac{8167}{1000} = 8.17\ \text{kg/kg}$$

# Make 6 groups and calculate the PMI of each steps

| in | | | | step | | | | out | | |
|---|---|---|---|---|---|---|---|---|---|---|
| name | role | kg | | | | | | name | role | kg |
| CH4 | raw material | 562 | → | **HCN Synthesis** | | | → | (NH4)2SO4 | by-product | 436 |
| NH3 | raw material | 487 | → | | | | → | Offgas | gaseous emission | 365 |
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| Pt | auxiliary material | 0.0001 | → | | | | | | | |
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| HCN | Intermediate | 523 | → | **HOCH2CN** | | | | | | |
| HCHO | raw material | 1489 | → | | | | | | | |
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| HOCH2CN | Intermediate | 2053 | → | **IDAN** | | | → | NH3 waste | liquid effluent | 24 |
| NH3 | raw material | 388 | → | | | | → | cyanohydrin side pdt | liquid effluent | 171 |
| | | | | | | | → | H2O | liquid effluent | 1268 |
| | | | | IDAN | product | 742 | | | | |
| | | | | ↓ | | | | | | |
| IDAN | Intermediate | 742 | → | **PMIDA** | | | → | Glycine side waste | liquid effluent | 101 |
| NaOH | raw material | 2010 | → | | | | → | HCHO waste | liquid effluent | 65 |
| PCl3 | Intermediate | 1270 | → | | | | → | H3PO3 waste | liquid effluent | 230 |
| HCHO | raw material | 700 | → | | | | → | NaCl | liquid effluent | 882 |
| | | | | | | | → | HCl | liquid effluent | 416 |
| | | | | | | | → | NH4Cl | liquid effluent | 65 |
| | | | | | | | → | NH3 | liquid effluent | 234 |
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| PMIDA | Intermediate | 1490 | → | **PMG (glyphosate)** | | | → | HCo2H | liquid effluent | 129 |
| H2O2 30% | raw material | 810 | → | | | | → | HCHO | liquid effluent | 84 |
| Na2MoO4 | auxiliary material | 5 | → | | | | → | CO2 | gaseous emission | 247 |
| FeSO4 | auxiliary material | 30 | → | | | | → | Fe(SO4)3 | liquid effluent | 35 |
| | | | | | | | → | side products | liquid effluent | 184 |
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| Cl2 | raw material | 1080 | → | | | | → | other waste | liquid effluent | 23 |
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| | | 8167 | | | | | | | | 6932 |

$$\mathbf{PMI} = \frac{\text{kg input needed}}{\text{kg Product formed}}$$

## Activity

**Make 6 groups**

**Group 1 -> calculate PMI for step 1**
**Group 2 -> calculate PMI for step 2**
**Group 3 -> calculate PMI for step 3**
**Group 4 -> calculate PMI for step 4**
**Group 5 -> calculate PMI for step 5**
**Group 6 -> calculate PMI for step 6**

# Make 6 groups and calculate the PMI of each steps

$$\textbf{PMI} = \frac{\text{kg input needed}}{\text{kg Product formed}}$$

| in | | | | step | | | | out | | |
|---|---|---|---|---|---|---|---|---|---|---|
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| Pt | auxiliary material | 0.0001 | → | | | | | | | |
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| HCHO | raw material | 1489 | → | | | | | | | |
| | | | | HOCH2CN | product | 2053 | | | | |
| | | | | ↓ | | | | | | |
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| IDAN | Intermediate | 742 | → | **PMIDA** | | | → | Glycine side waste | liquid effluent | 101 |
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| PCl3 | Intermediate | 1270 | → | | | | → | H3PO3 waste | liquid effluent | 230 |
| HCHO | raw material | 700 | → | | | | → | NaCl | liquid effluent | 882 |
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| H2O2 30% | raw material | 810 | → | | | | → | HCHO | liquid effluent | 84 |
| Na2MoO4 | auxiliary material | 5 | → | | | | → | CO2 | gaseous emission | 247 |
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| Cl2 | raw material | 1080 | → | | | | → | other waste | liquid effluent | 23 |
| | | | | PCl3 | product | 1270 | | | | |
| | | 8167 | | | | | | | | 6932 |

PMI_Step1 = 1363/523 = 2.60 kg/kg

PMI_Step2 = 2012/2053 = 0.98 kg/kg ?

PMI_Step3 = 2441/742 = **3.29 kg/kg**

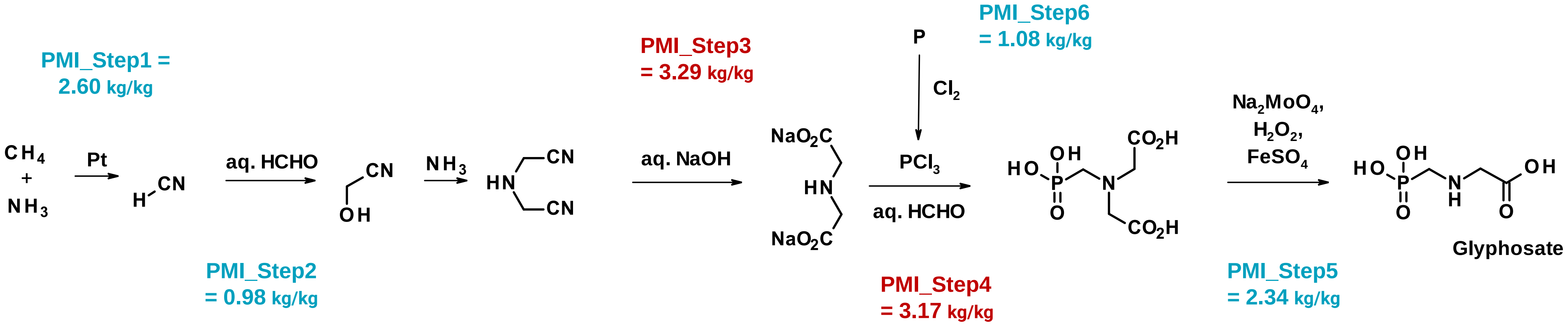
PMI_Step4 = 4722/1490 = **3.17 kg/kg**

PMI_Step5 = 2335/1000 = 2.34 kg/kg

PMI_Step6 = 1372/1270 = 1.08 kg/kg

# Glyphosate synthesis: HCN process Mass Flow Sheet

- PMI is NOT additive. Overall PMI = 7.93 kg/kg



PMI_Step1 = 2.60 kg/kg

PMI_Step2 = 0.98 kg/kg

PMI_Step3 = 3.29 kg/kg

PMI_Step4 = 3.17 kg/kg

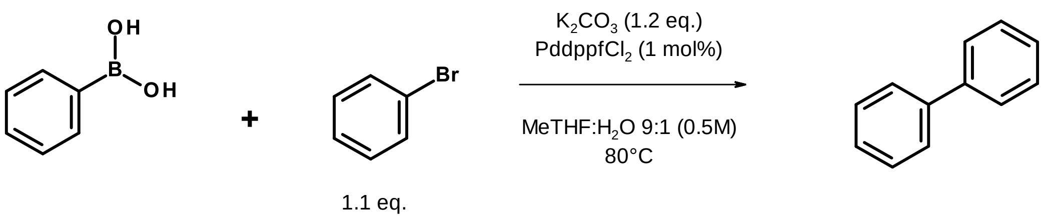
PMI_Step5 = 2.34 kg/kg

PMI_Step6 = 1.08 kg/kg

**Where efforts might get focused on to improve the sustainability of the overall process**

# How to improve PMI

- Trick one: don’t count everything…



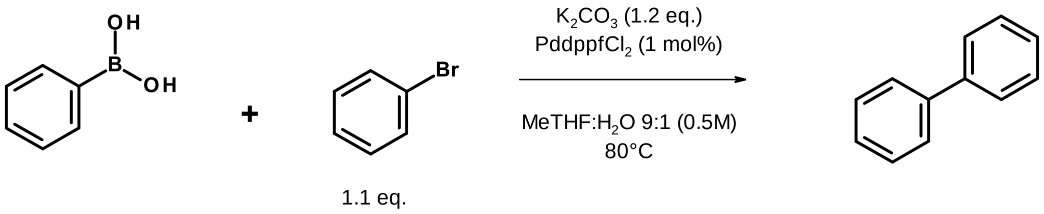
| name | MW | equiv. | mmol | Mass (g) | yield |
|---|---|---|---|---|---|
| boronic acid | 121.9 | 1 | 10 | 1219.0 | |
| aryl bromide | 157 | 1.1 | 11 | 1727.0 | |
| potassium carbonate | 138 | 1.2 | 12 | 1656.0 | |
| Pd catalyst | 731.7 | 0.001 | 0.01 | 7.3 | |
| MeTHF | 83.5 | | 184 | 15364.0 | |
| H2O | 18 | | 111 | 1998.0 | |
| product | 154.21 | | | 1310.8 | 0.85 |

| | |
|---|---|
| inputs (g) | 21971.3 |
| output (g) | 1310.7 |

PMI = 16.8 kg/kg

# How to improve PMI

- Trick one: don't count everything…



| name | MW | equiv. | mmol | Mass (mg) | yield |
|---|---|---|---|---|---|
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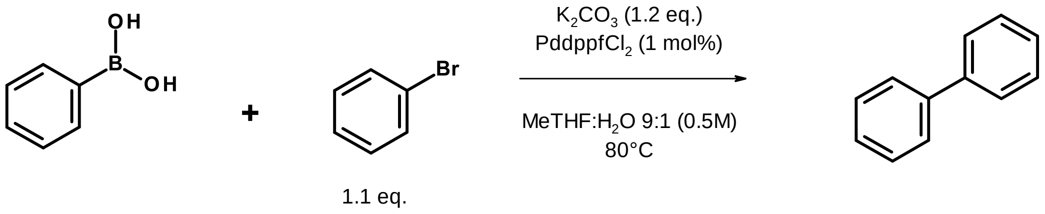
| aryl bromide | 157 | 1.1 | 11 | 1727.0 | |
| potassium carbonate | 138 | 1.2 | 12 | 1656.0 | |
| Pd catalyst | 731.7 | 0.001 | 0.01 | 7.3 | |
| MeTHF | 83.5 | | 184 | 15364.0 | |
| H2O | 18 | | 111 | 1998.0 | |
| | | | | | |
| aqueous NH4Cl | | | | 10000.0 | |
| MeTHF(extract#1) | | | | 2500.0 | |
| MeTHF(extract#2) | | | | 2500.0 | |
| Brine | | | | 10000.0 | |
| MeTHF | | | | 2500.0 | |
| | | | | | |
| product | 154.21 | | | 1310.8 | 0.85 |

| inputs (g) | 49471.3 |
|---|---|
| output (g) | 1310.7 |

**PMI = 37.7 kg/kg**

# Breaking down PMI into different reaction parts



| Reactants | Amount (in g) |
|---|---|
| boronic acid | 1.22 g |
| aryl bromide | 1.73 g |
| | |
| | |
| | |

| Reagents | Amount (in g) |
|---|---|
| potassium carbonate | 1.66 g |
| Pd catalyst | 0.07 g |
| | |
| | |
| | |
| | |
| | |
| | |
| | |

| Solvents | Amount (in g) |
|---|---|
| MeTHF | 22.86 g |
| | |
| | |
| | |
| | |
| | |

| Aqueous | Amount (in g) |
|---|---|
| aqueous NH4Cl | 10.00 g |
| **Brine** | 10.00 g |
| H2O | 2.00 g |
| | |
| | |
| | |

| Product | |
|---|---|
| Product isolated (in g) | 1.31 g |
| Product Purity (in %) | 100% |
| Product isolated corrected for purity | 1.31 g |

| PROCESS STEP METRICS | |
|---|---|
| Mass Reactants (kg) | 2.9 g |
| Mass Reagents (kg) | 1.7 g |
| Mass Solvents (kg) | 22.9 g |
| Mass Aqueous (kg) | 22.0 g |

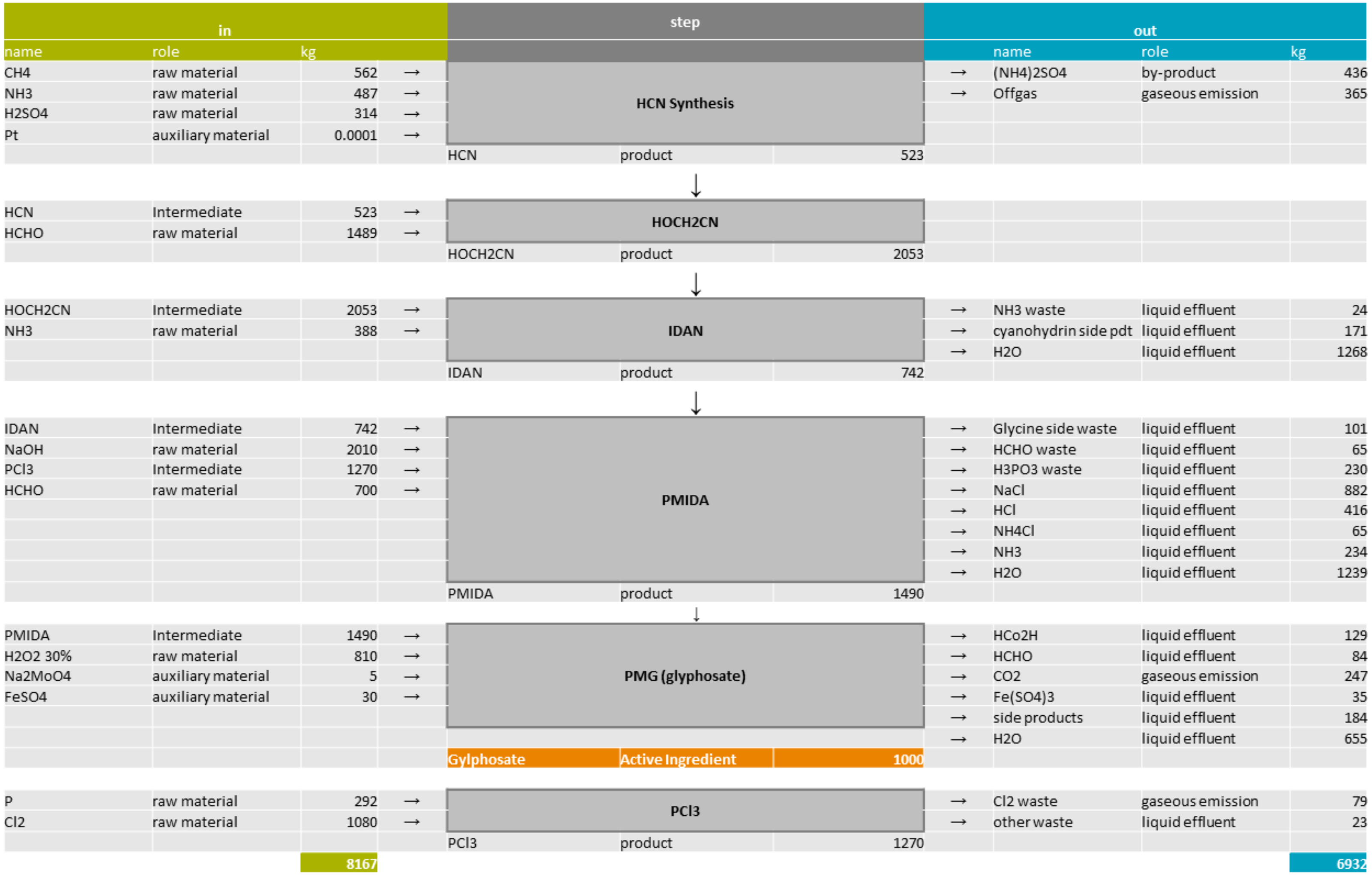
| **Step PMI** | **37.8 kg/kg** |
|---|---|
| Step PMI Reactants, Reagents, Solvents | 21.0 kg/kg |
| Step PMI Reactants and Reagents | 3.6 kg/kg |
| Step PMI Solvents | 17.5 kg/kg |
| Step PMI Water | 16.8 kg/kg |

**More granularity where improvements can be made**

# Glyphosate synthesis: How to improve

**Overall PMI = 7.93 kg/kg**

- Do you see a way?



| in | | | | step | | | | out | | |
|---|---|---|---|---|---|---|---|---|---|---|
| name | role | kg | | | | | | name | role | kg |
| $CH_4$ | raw material | 562 | → | HCN Synthesis | | | → | $(NH_4)_2SO_4$ | by-product | 436 |
| $NH_3$ | raw material | 487 | → | | | | → | Offgas | gaseous emission | 365 |
| $H_2SO_4$ | raw material | 314 | → | | | | | | | |
| Pt | auxiliary material | 0.0001 | → | | | | | | | |
| | | | | HCN | product | 523 | | | | |
| | | | | ↓ | | | | | | |
| HCN | Intermediate | 523 | → | $HOCH_2CN$ | | | | | | |
| HCHO | raw material | 1489 | → | | | | | | | |
| | | | | $HOCH_2CN$ | product | 2053 | | | | |
| | | | | ↓ | | | | | | |
| $HOCH_2CN$ | Intermediate | 2053 | → | IDAN | | | → | $NH_3$ waste | liquid effluent | 24 |
| $NH_3$ | raw material | 388 | → | | | | → | cyanohydrin side pdt | liquid effluent | 171 |
| | | | | | | | → | $H_2O$ | liquid effluent | 1268 |
| | | | | IDAN | product | 742 | | | | |
| | | | | ↓ | | | | | | |
| IDAN | Intermediate | 742 | → | PMIDA | | | → | Glycine side waste | liquid effluent | 101 |
| NaOH | raw material | 2010 | → | | | | → | HCHO waste | liquid effluent | 65 |
| $PCl_3$ | Intermediate | 1270 | → | | | | → | $H_3PO_3$ waste | liquid effluent | 230 |
| HCHO | raw material | 700 | → | | | | → | NaCl | liquid effluent | 882 |
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| PMIDA | Intermediate | 1490 | → | PMG (glyphosate) | | | → | $HCo_2H$ | liquid effluent | 129 |
| $H_2O_2$ 30% | raw material | 810 | → | | | | → | HCHO | liquid effluent | 84 |
| $Na_2MoO_4$ | auxiliary material | 5 | → | | | | → | $CO_2$ | gaseous emission | 247 |
| $FeSO_4$ | auxiliary material | 30 | → | | | | → | $Fe(SO_4)_3$ | liquid effluent | 35 |
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| P | raw material | 292 | → | $PCl_3$ | | | → | $Cl_2$ waste | gaseous emission | 79 |
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| | | 8167 | | | | | | | | 6932 |

**PMI = 3.28 kg/kg**

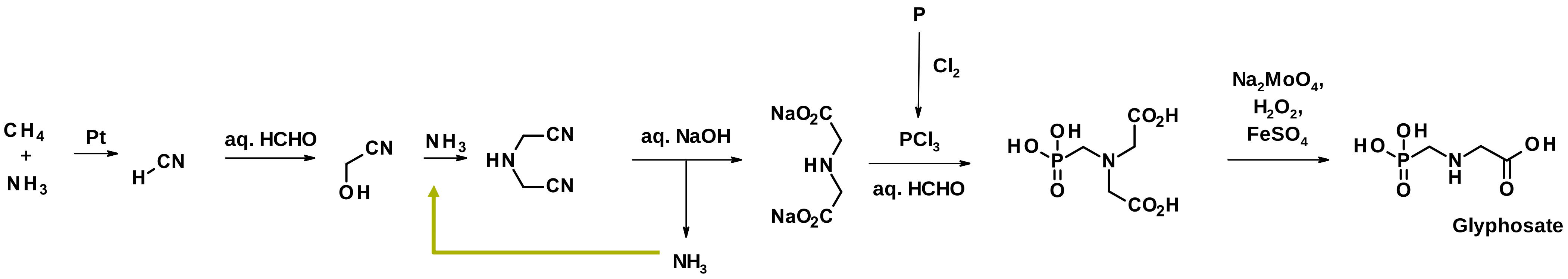
**PMI = 3.16 kg/kg**

Classification: PUBLIC

*Green Chem*. **2012**, *14*, 1990

# How to improve PMI

- **Recycle** when possible



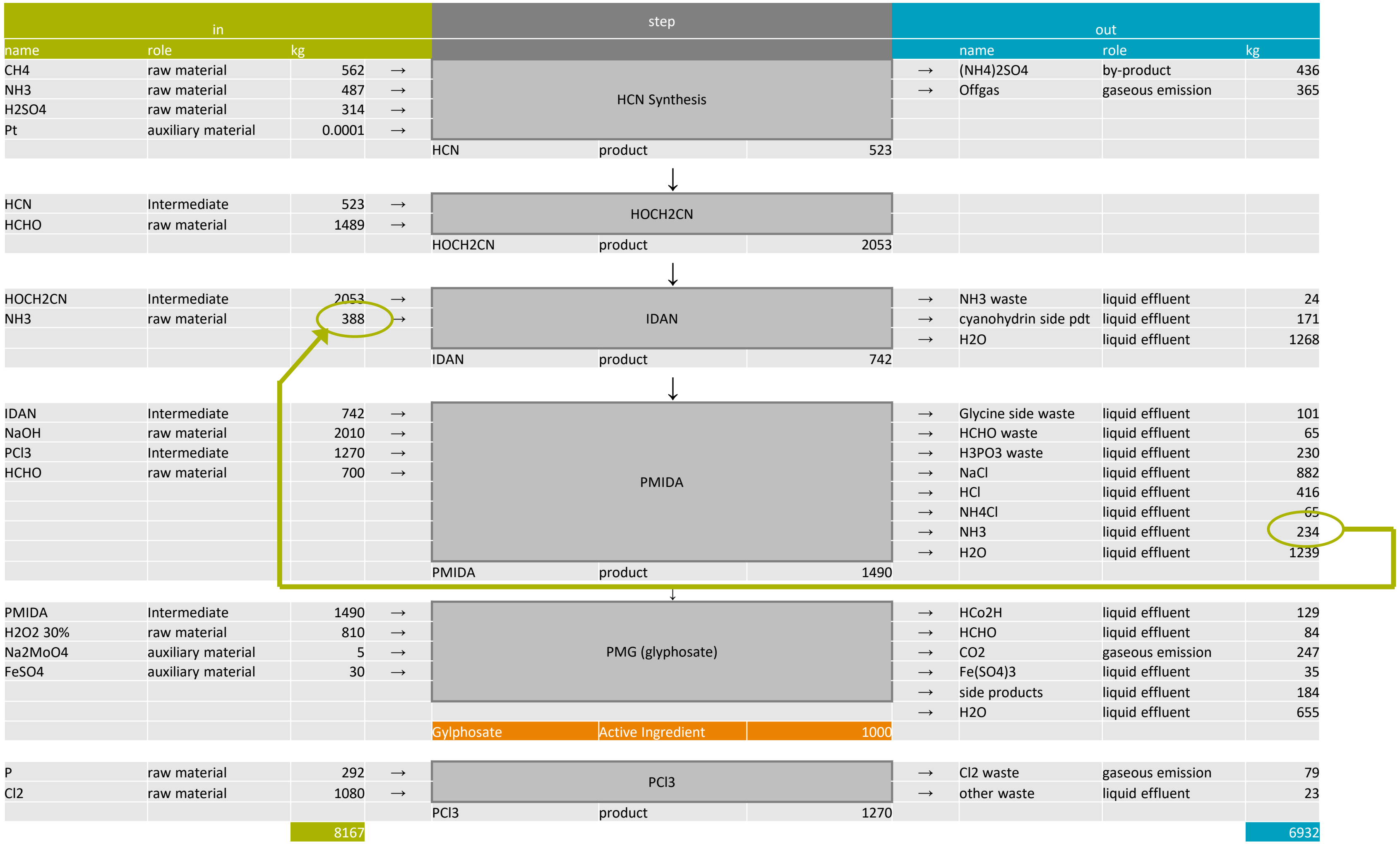
Classification: PUBLIC

*Green Chem*. **2012**, *14*, 1990

# Glyphosate synthesis: How to improve

Overall PMI = 8.16 kg/kg

- Recycle when possible



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| HCHO | raw material | 1489 | → | | | | | | | |
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| | | 8167 | | | | | | | | 6932 |

PMI = 2.97 kg/kg

PMI = 3.16 kg/kg

*Green Chem*. **2012**, *14*, 1990

# Glyphosate: Which Process Is Best

| Process | PMI*<br>(kg/kg) | | | |
|---|---|---|---|---|
| HCN | **5.3** | | | |
| DEA | 5.9 | | | |
| Glycine | 6.8 | | | |

**HCN process is best**

*PMI from the literature. If you try to reproduce, you will see $H_2O$ is not included. Should it be included?

*Green Chem*. **2012**, *14*, 1990

# Glyphosate: Which Process Is Best

| Process | PMI* (kg/kg) | | | Share of global production |
|---|---|---|---|---|
| HCN | 5.3 | | | 20% |
| DEA | 5.9 | | | 20% |
| Glycine | 6.8 | | | 60% |

**Glycine process is most used**

*PMI from the literature. If you try to reproduce, you will see $H_2O$ is not included. Should it be included?

*Green Chem*. **2012**, *14*, 1990

# Glyphosate manufacturing– An overview of complexity on scale

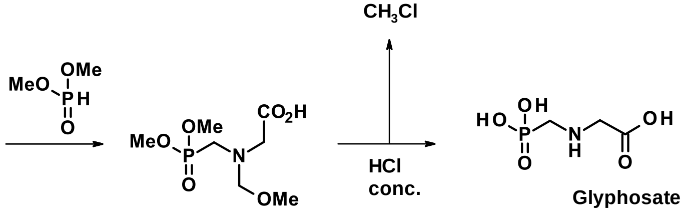
| Process | PMI (kg/kg) | Energy required (MJ) | Cost of raw materials ($/ton) | Share of global production |
|---|---|---|---|---|
| HCN | **5.3** | 24338 | 1705 | 20% |
| DEA | 5.9 | 62774 | 2830 | 20% |
| Glycine | 6.8 | 44759 | 2022 | 60% |

**HCN is toxic**

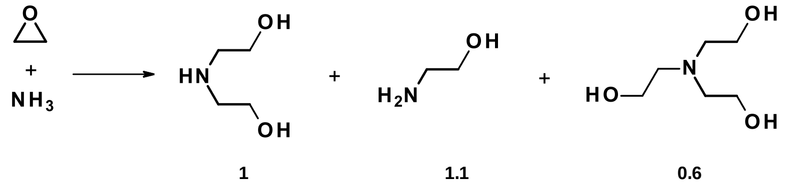
**Toxic waste**

**Specific equipment needed**

**$CH_3Cl$ is valorized**



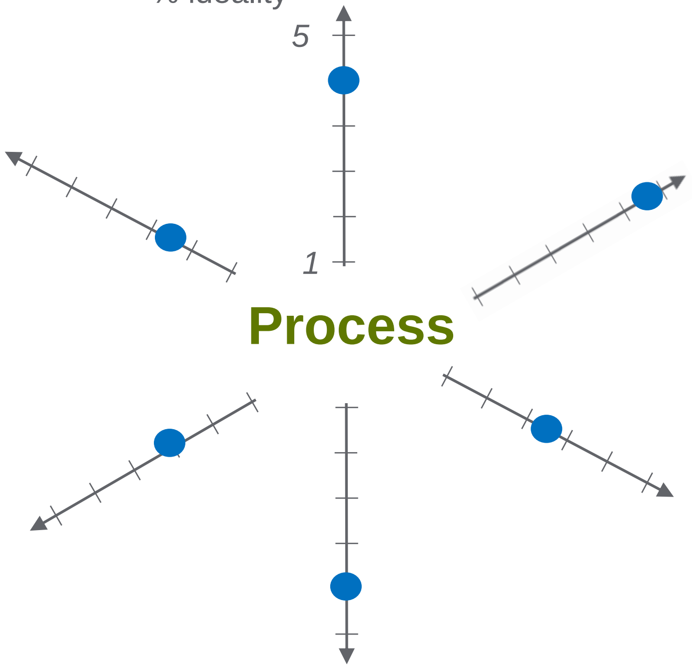
**One Unselective process -> Leads to higher PMI**



**But TEA and MEA are also valorized as commercial compounds…**

*Green Chem*. **2012**, *14*, 1990

# Choosing the right process is always multifactorial



## Performance

- Yield
- Purity
- Time yield (reaction, workup, purification)
- Volume yield
- % ideality

## Robustness

- Yield std. Dev.
- Purity std. Dev.
- Yield/purity std.dev. vs variability of key parameters (ex. quality of reagents…)

## Safety

- Reagents, reactants, solvents
- Process safety
- (in)tolerance vs maloperation

## Technology

- Are special equipment needed?
- Continuous process
- PAT

## Sourcing

- Raw materials easy to source? Price vs quantity? Price vs quality?
- Quality of raw materials

## Sustainability/Waste

- Atom economy, PMI
- Waste quantity
- Waste composition
- Disposal method (incinerate, recycle…)
- Energy
- % of biodegradable intermediate
- % of renewable resources

*Green Chem*. **2012**, *14*, 1990

# Key Takeaways

1. Choosing the right process is always multifactorial

2. You can do everything. Some approaches are better than others

3. Corporations ignoring long-term sustainability have an unlikely bright future

4. Industry needs needs a new generation of chemist with multidisplinary skillset and deep sustainability mindset

## Thank You

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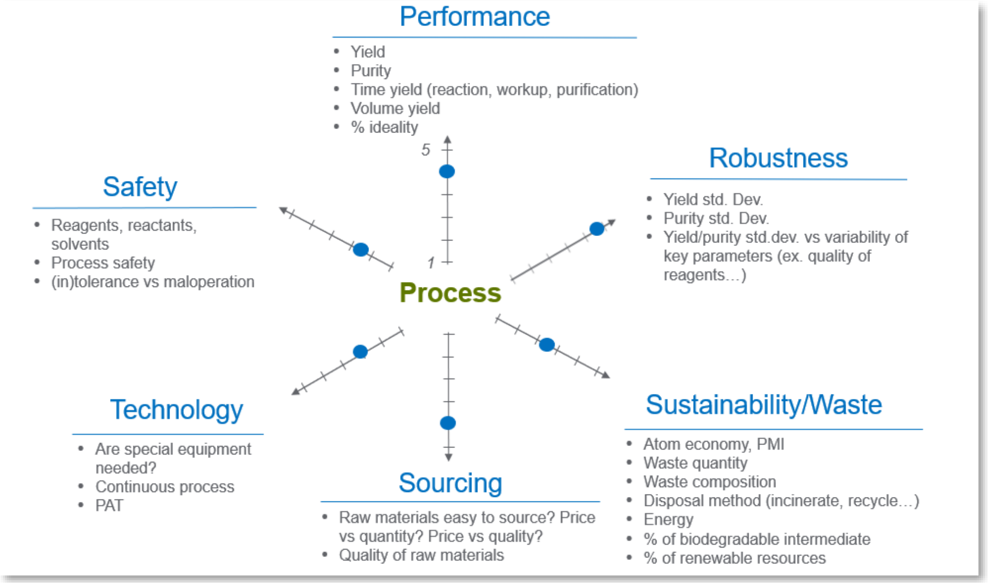

**Performance**
- Yield
- Purity
- Time yield (reaction, workup, purification)
- Volume yield
- % ideality

**Robustness**
- Yield std. Dev.
- Purity std. Dev.
- Yield/purity std.dev. vs variability of key parameters (ex. quality of reagents…)

**Safety**
- Reagents, reactants, solvents
- Process safety
- (in)tolerance vs maloperation

**Process**

**Technology**
- Are special equipment needed?
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