

**School of Industrial and Information Engineering**  
**Course 096125 (095857)**  
**Introduction to Green and Sustainable Chemistry**

 POLITECNICO DI MILANO



# Sustainable Solvents.

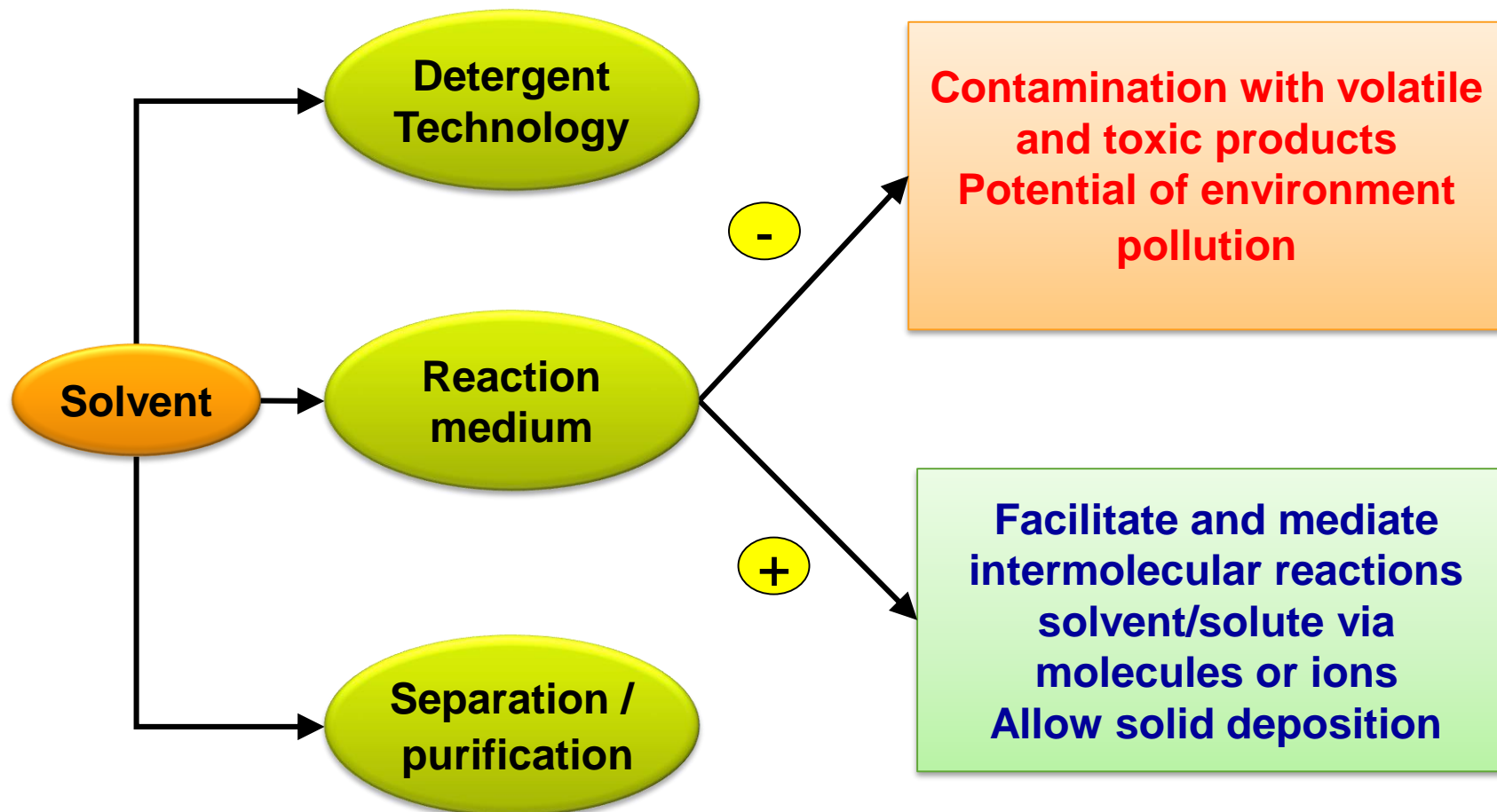
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<https://iscamapweb.chem.polimi.it/citterio/it/education/course-topics/>





# Organic Solvents in Manufacturing Processes.



**NB. When a solvent is substituted, SEVERAL parameters are changed!!**



# Why a Solvent has to be Used?

Widely used throughout the chemical industry:

## ■ Synthetic Chemistry

- Reaction medium on laboratory/industrial scale
- Dissolves and bring together reactants at suitable concentration, allowing mass transport
- Stabilizes transition states (i.e. selective catalyst)
- Energy control: moderates exothermic processes
- Efficient mixing and stirring
- Extended used in work-up (extraction, purification)

## ■ Analytical Chemistry

- Sample extraction/preparation (Spectroscopy).
- Chromatographic mobile phase (HPLC, TLC).

## ■ Crystallisation

- Recrystallisation to purify compounds and prepare crystals (also polymorph).





## Other Applications of Solvents.

Used much more widely than just synthetic chemistry.

### Coatings:

- Paints, adhesives
  - Solvent usually removed by evaporation after application leaving coating behind
  - Coating removal.



### Cleaning

- E.g. Dry cleaning – extensive use of  $C_2Cl_4$ , a known cancer suspect agent, which also contaminates groundwater supplies.

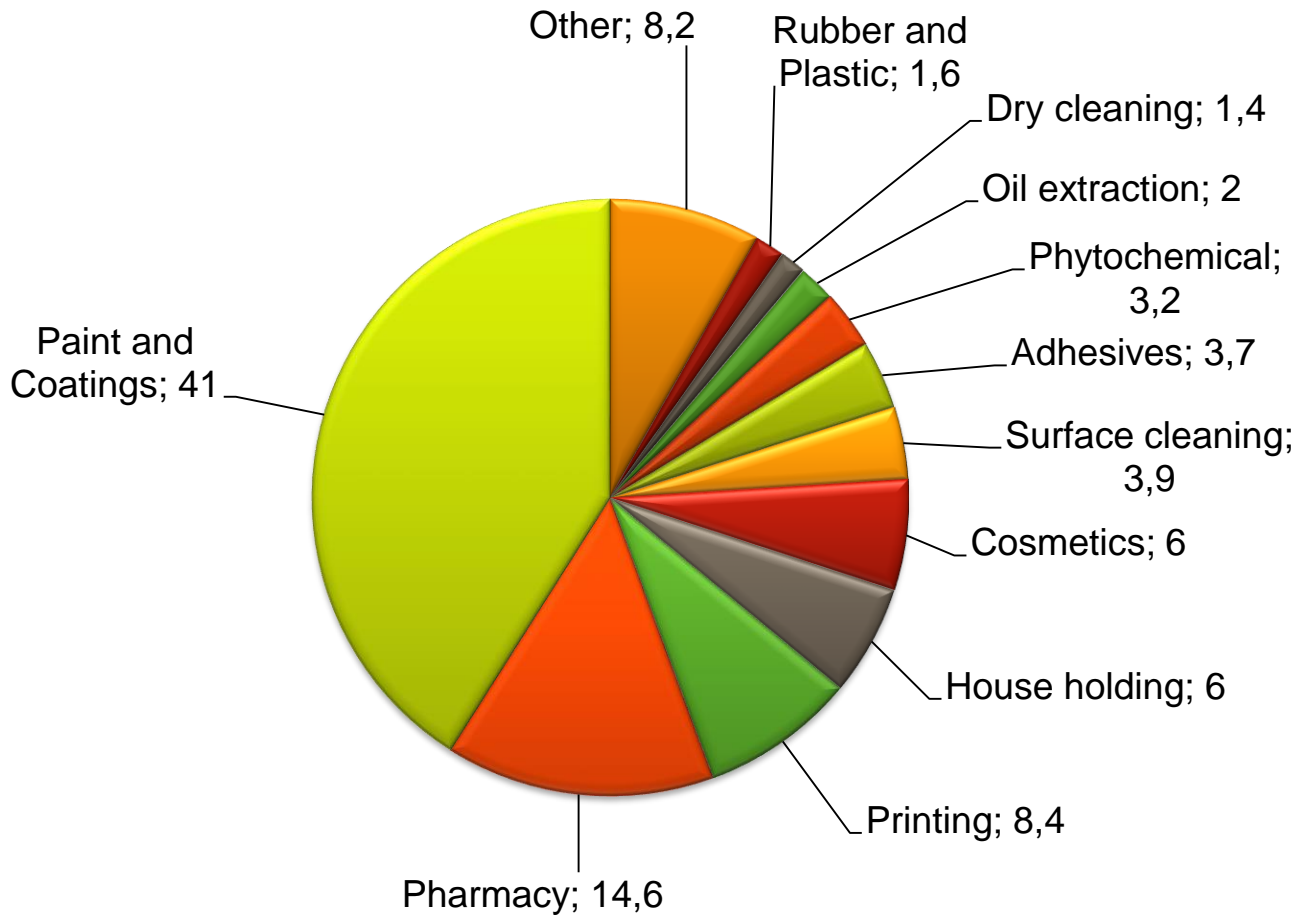
### Extraction

- E.g. Coffee decaffeination [EtOH,  $CH_3CH(OH)COOR$ ].
- E.g. Flavour and fragrances.





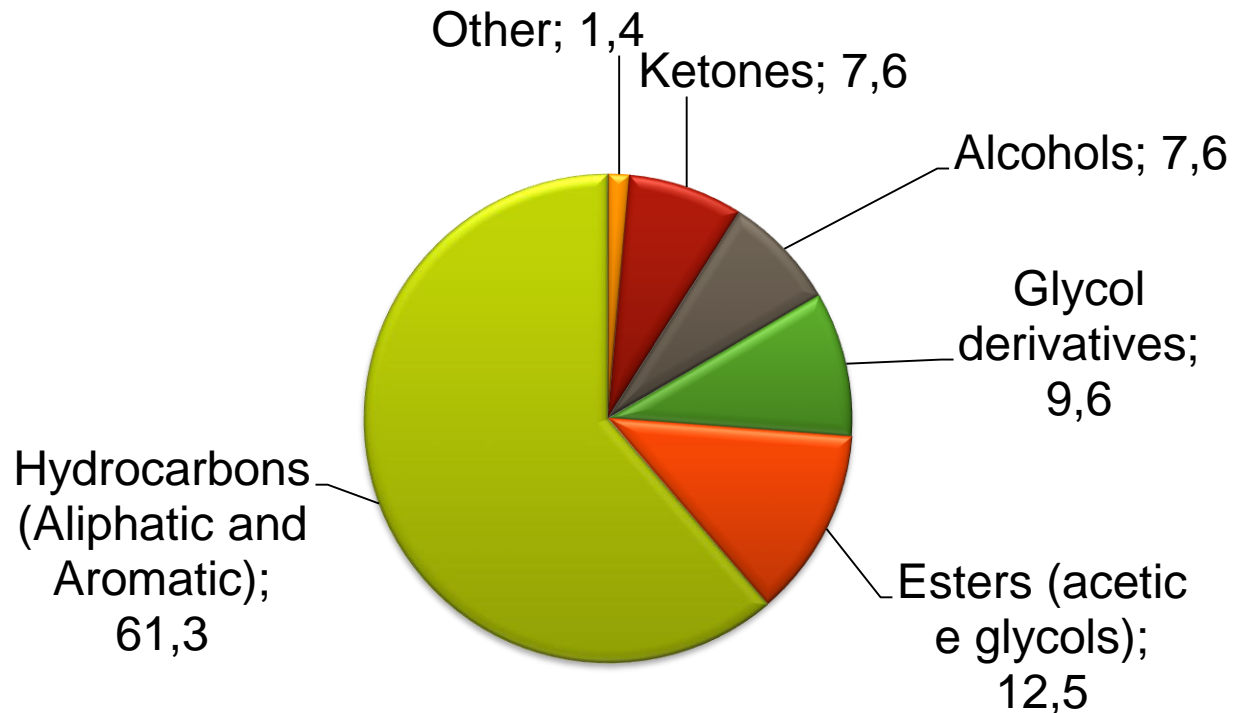
# Segmentation of Solvent Market.



Total 2010 : 4.1 millions tonnes  
EU-27 (2013) : 3.0 millions tonnes



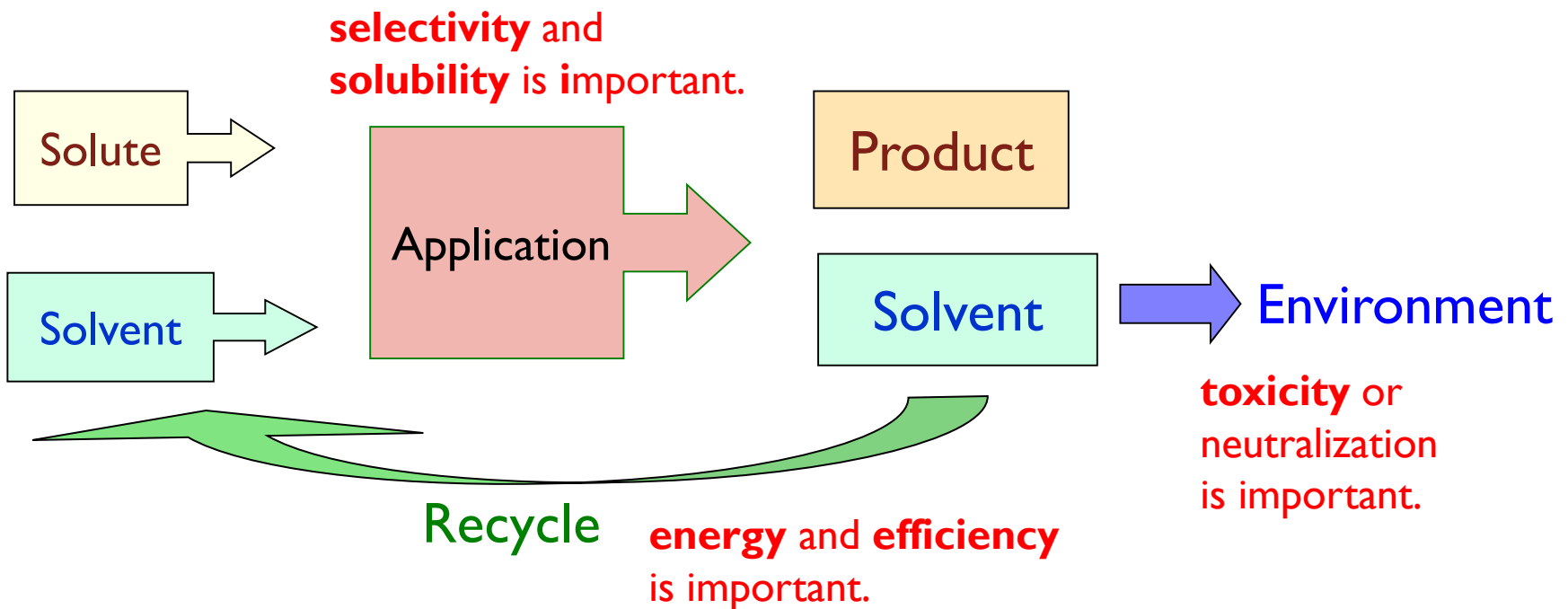
## Solvents used in Paints and Varnishes.



Total 2010 : 1.82 millions tons of solvents.

## Specific Solvent Issues in Chemical Process.

- Solubility of solutes and Reaction control
- Separation (and recycle?) from reaction mixture
- Health and Safety of human and environment
- One of the main issues is removing solvent from solutes.





## Solvent Properties.

- Solubility (i. e.  $K_{ps}$ )
- Polarity (several parameters: ET, etc.)
- Viscosity
- Volatility (b.p.)
- **Hazard**
  - Intrinsic Toxicity
  - Flammability
  - Explosivity
  - Stratospheric ozone depletion
  - Atmospheric ozone production
  - Global warming potential (greenhouse gases).





# Toxic hazard properties of various solvents.

All figures in ppm.

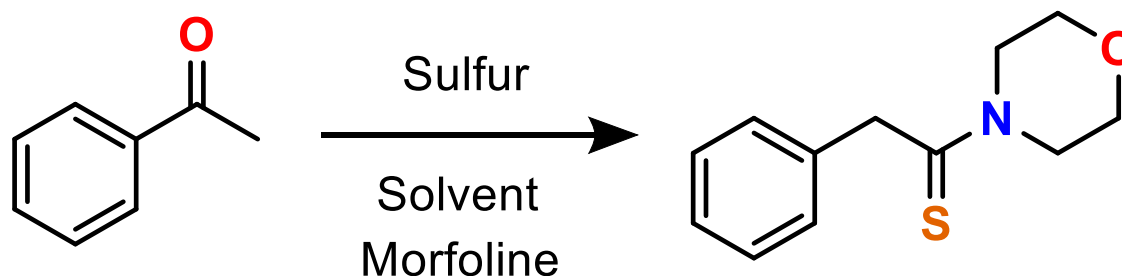
Solvent	Odour threshold	TLV	IDLH	Solvent saturated vapour at 21°C
Acetic acid	1	10	1 000	16 000
Acetone	100	750	20 000	250 000
Acetonitrile	40	40	4 000	94 000
Aniline	0.5	2	100	340
Benzene	5	10	2 000	105 000
n-Butyl acetate	10	150	10 000	14 000
n-Butanol	2.5	50	8 000	6 300
Chloroform	250	10	1000	220 000
Dichloromethane	250	100	5 000	500 000
Diethyl ether	1	400	10 000	100 000
DMF	100	10	3 500	3 700
Ethyl acetate	1	400	10 000	100 000



# Toxic hazard properties of various solvents.

All figures in ppm.

Solvent	Odour threshold	TLV	IDLH	Solvent saturated vapour at 21°C
Ethanol	10	1000	20 000	60 000
Heptane	220	400	19 000	610 000
Isopropanol	90	400	20 000	46 000
Methanol	100	200	25 000	130 000
Nitrobenzene	6	1	200	270
n-Pentane	10	600	5 000	580 000
n-Propanol	30	200	4 000	18 000
Pyridine	0.02	5	3 600	22 000
Perchloroethylene	5	50	500	22 000
Toluene	0.2	100	2000	31 000
Trichloroethylene	50	50	1 000	80 000
Xylenes	0.05	100	10 000	9 200



- Useful reaction when it works
- Unpredictable
- Mechanism not understood

Using statistical methods, reaction conditions for 13 different solvents were optimized varying 4 parameters.

R. Carlson, *Acta Chem. Scand.*, **40**. 694 (1986)

## Willgerodt Reaction - Optimal Conditions.

SOLVENT	S moles	Morpholine moles	Opt. Temp.	Time Hours	Yield % (Isolated)
Triethyleneglycol	17	9.5	145	2	91
N-Methyiacetamide	2	6	120	2	80
Ethanol	3.7	13.4	80	22	84
3-Methyibutanol	9.5	13.2	130	5	82
Quinoline	7.5	10.3	123	2	90
Benzene	11.6	12	80	22	85
Diisopropyi ether	6.5	13.7	70	22	45

- Notes:
1. In MeCN, PhCOCS-morpholine was the major product
  2. In PhCN no product was obtained
  3. Major side reactions in diisopropyl ether and dioxan

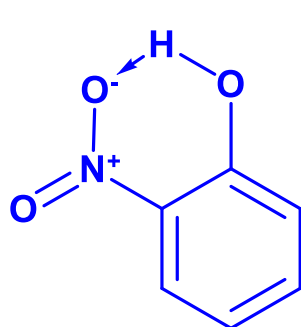
Results show that each solvent has its own optimum conditions.

## Solubility of Reagents and Products.

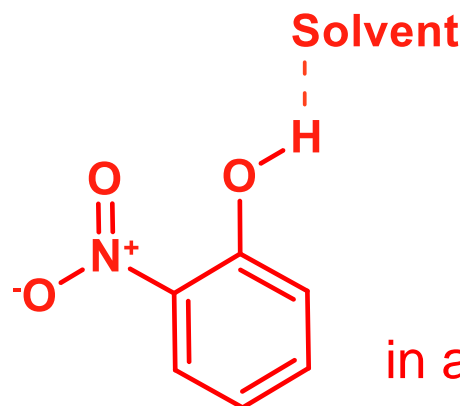
- Like dissolves like.
- To dissolve A in B: Intermolecular bonds of A and B molecules stronger than the bonds between A/A and B/B

$$K_{AB} > K_{AA} + K_{BB}$$

- Hydrogen bonding is very important.



in hydrocarbons, CCl<sub>4</sub>



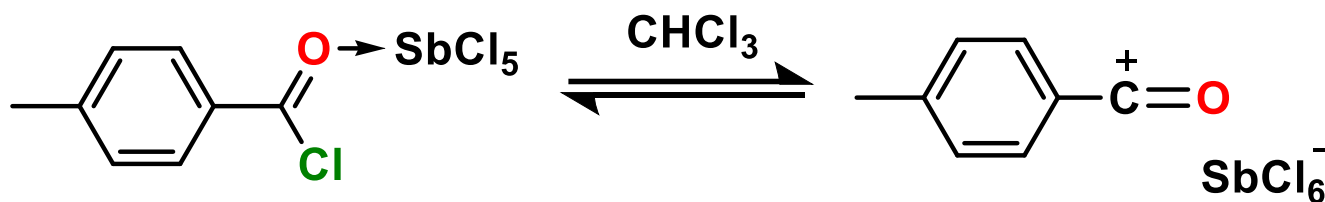
in anisole, DMF, HMPA



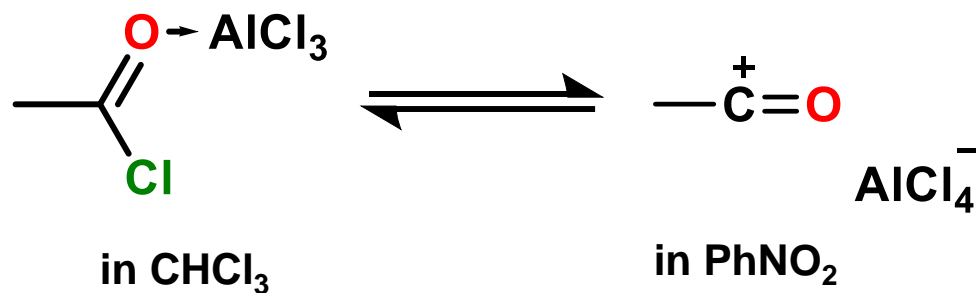
## Substrate-Solvent Interaction: EPD / EPA Ability.

- $\pi$  – donors                      aromatics, olefins
- $n$  – donors                        alcohols, amines  
ethers, nitriles, ketones, sulphoxides
- $\sigma$  - EPA                            halogen derivatives
- $\pi$  - EPA                                 $\text{SO}_2$
  
- **H-donors**                            alcohols, acids, water,  
(use H-bonding).

## Solvent Affects Dissociation.

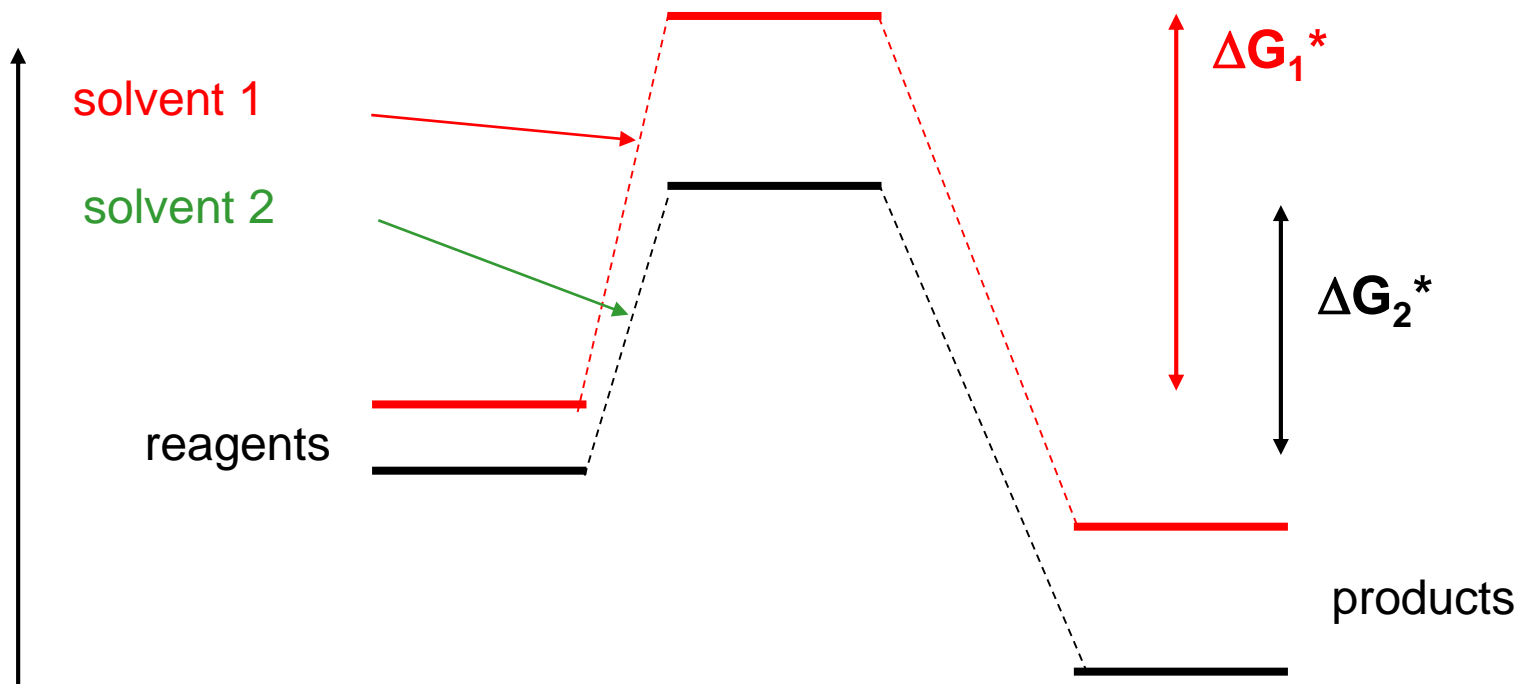


But



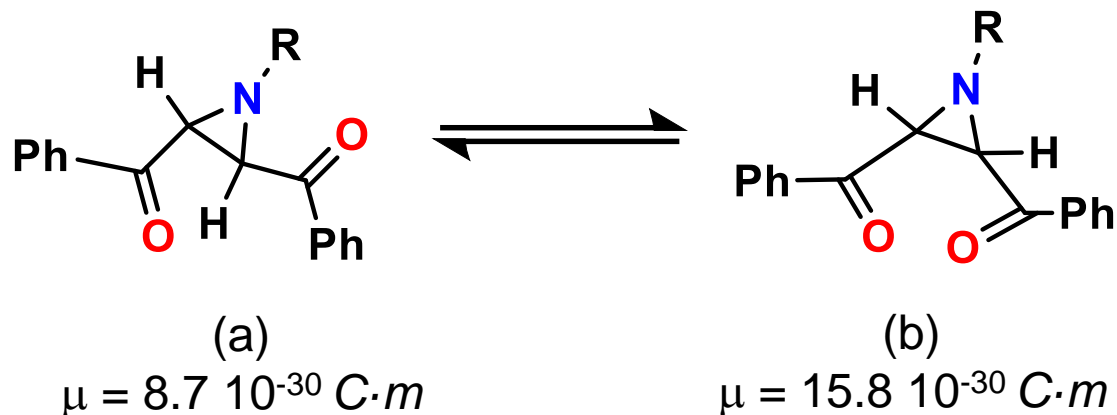
- Some compounds are more soluble in a mixture of solvents than in individual components.  
e.g. amine salts in alcohol/water.

## Solvent Effects on Activation Energy.



- Typical solvent effects:  $5\text{-}20 \text{ kJ}\cdot\text{mol}^{-1}$
- Sometimes as high as  $40 \text{ kJ}\cdot\text{mol}^{-1}$





Equilibrium constants and mole fractions at 33 °C:

Solvent	$\chi(b)$ (cmol/mol)	$K = [cis][trans]$
<i>tert</i> -Butanol	24	0.32
Ethanol	45	0.82
Methanol	62	1.63
Dimethylsulfoxide	84	5.25



## Aprotic Solvents.

	Solvent	Structure	Dielectric Constant (D)
Polar	DMSO	$(\text{CH}_3)_2\text{S}=\text{O}$	48.9
	acetonitrile	$\text{CH}_3\text{C}\equiv\text{N}$	37.5
	DMF	$(\text{CH}_3)_2\text{NHCHO}$	36.7
	acetone	$(\text{CH}_3)_2\text{C}=\text{O}$	20.7
Nonpolar	dichloromethane	$\text{CH}_2\text{Cl}_2$	9.1
	diethyl ether	$(\text{CH}_3\text{CH}_2)_2\text{O}$	4.3
	toluene	$\text{C}_6\text{H}_5\text{CH}_3$	2.3
	hexane	$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$	1.9



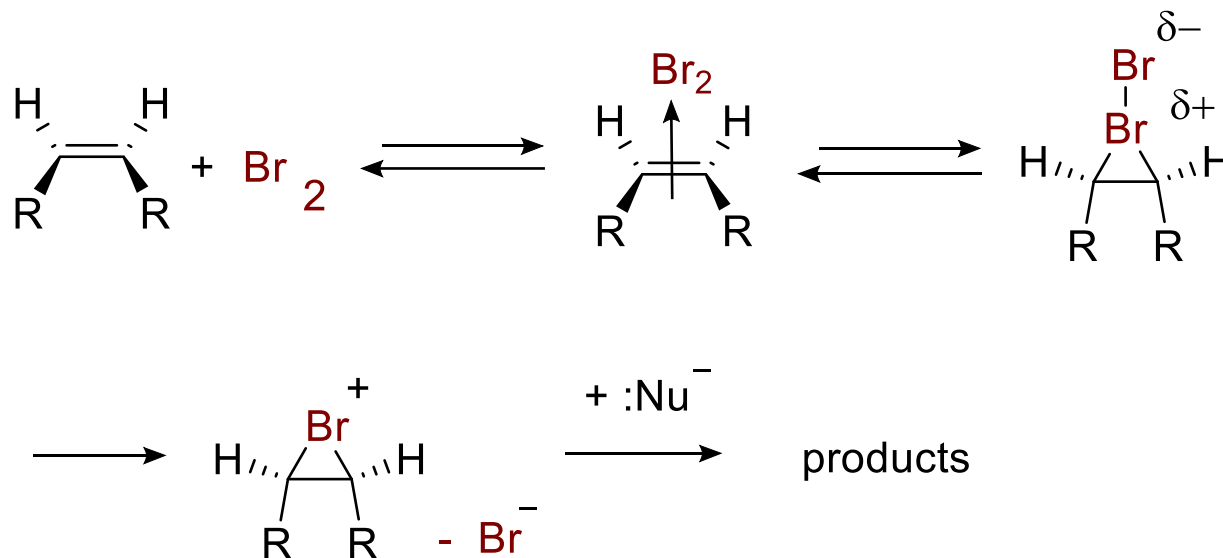
# Predicted Solvent Effects on Rates of Nucleophilic Substitution Reactions.

<u>Reaction type</u>	<u>Initial reactants</u>	<u>Activated complex</u>	<u>Change alteration during activation</u>	<u>Effect of increased solvent polarity on rate</u>
(a) S <sub>N</sub> 1	R-X	R <sup>δ+</sup> .....X <sup>δ-</sup>	Separation of unlike charges	Large increase
(b) S <sub>N</sub> 1	R-X <sup>≠</sup>	R <sup>δ+</sup> .....X <sup>δ-</sup>	Dispersal of charges	Small decrease
(c) S <sub>N</sub> 2	Y + R-X	Y <sup>δ+</sup> ...R...X <sup>δ-</sup>	Separation of unlike charges	Large increase
(d) S <sub>N</sub> 2	Y <sup>-</sup> + R-X <sup>≠</sup>	Y <sup>δ-</sup> ...R <sup>δ+</sup> ...X <sup>δ-</sup>	Dispersal of charges	Small decrease
(e) S <sub>N</sub> 2	Y <sup>-</sup> + R-X <sup>≠</sup>	Y <sup>δ-</sup> ...R...X <sup>δ+</sup>	Dispersal of charges	Small decrease
(f) S <sub>N</sub> 2	Y <sup>-</sup> + R-X <sup>≠</sup>	Y <sup>δ-</sup> ...R <sup>δ+</sup> ...X <sup>δ-</sup>	Destruction of charges	Large decrease

The terms “large” and “small” arise from the theory that the effect of the dispersal of charge should be notably smaller than the effect of its creation or destruction and have therefore only relative implication.

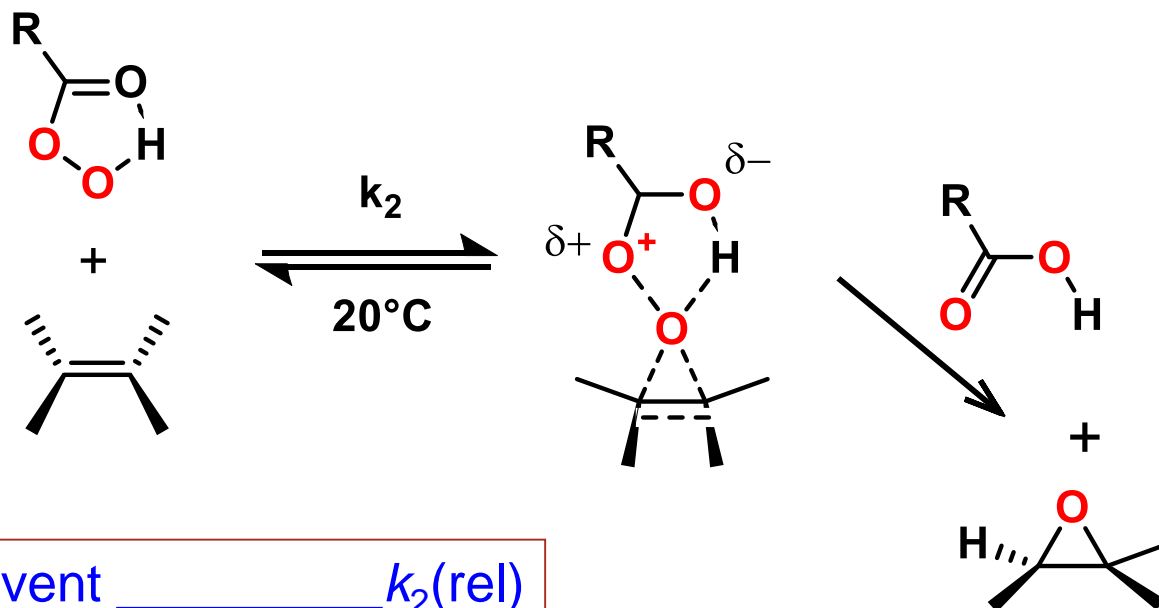


## Charge Separation



Solvent	$\text{CCl}_4$	Dioxan	$\text{CH}_3\text{CO}_2\text{H}$	$\text{CH}_3\text{OH}$	$\text{H}_2\text{O}$
$k_2(\text{rel})$	1	5.1	4860	$1.6 \cdot 10^5$	$1.1 \cdot 10^{10}$

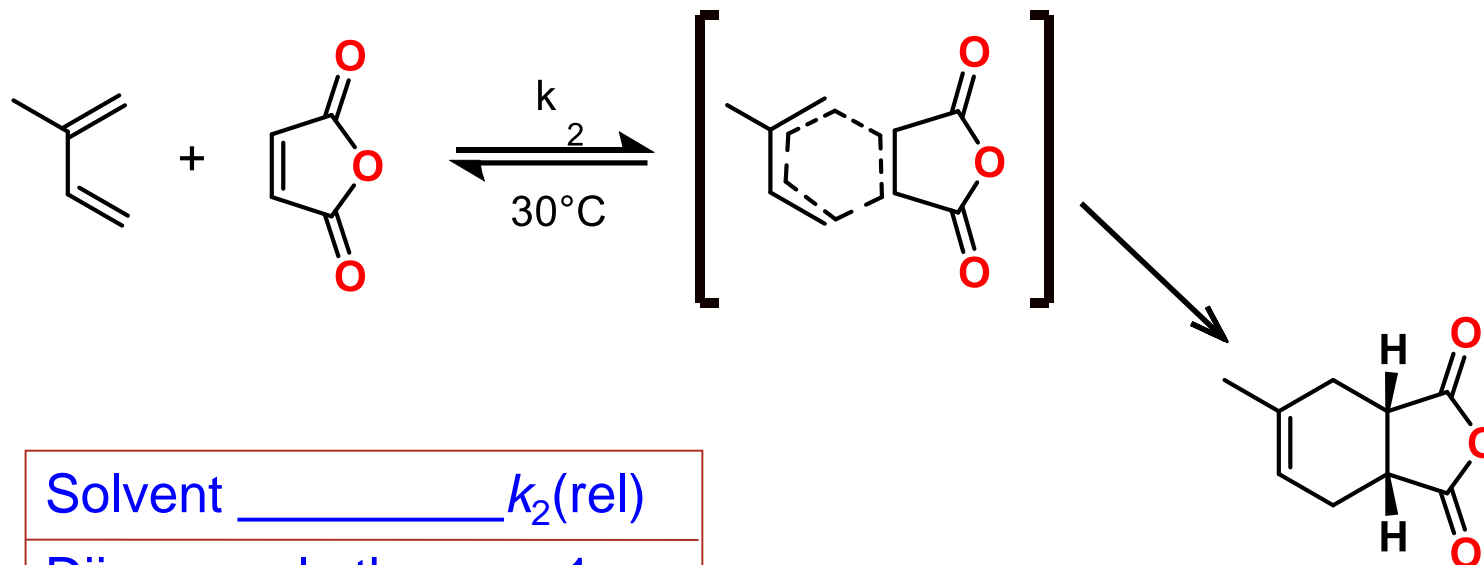
# Effect on Reaction Rate (epoxidation).



Solvent _____	$k_2$ (rel)
Diethyl ether	1
1,4-Dioxan	2.5
n-Hexane	6.2
Benzene	40
Dichloromethane	58
Chloroform	122

R = Phenyl  
olefin is cyclohexene

# Effect on Reaction Rate (Diels-Alder).

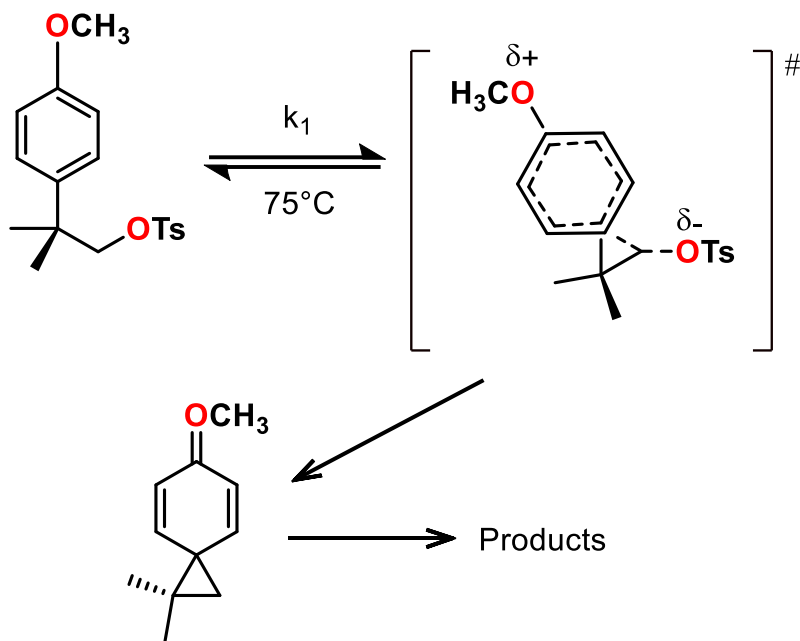


Solvent _____	$k_2(\text{rel})$
Diisopropyl ether	1
Benzene	3.5
Chlorobenzene	5.0
Nitromethane	6.6
Nitrobenzene	11
o-Dichlorobenzene	13



# Effect on Reaction Rate

(Rearrangements - 1° order reactions).



Solvent	$k_1(\text{rel})$
Diethyl ether	1
Tetrahydrofuran	17
Acetone	169
Dimethylformamide	980
Dimethylsulfoxide	3600
Ethanol	$1.2 \cdot 10^4$
Methanol	$3.2 \cdot 10^4$
Acetic acid	$3.3 \cdot 10^4$
Water	$1.3 \cdot 10^6$
Formic acid	$5.1 \cdot 10^6$

## Specific Ion Solvation and Living Groups.

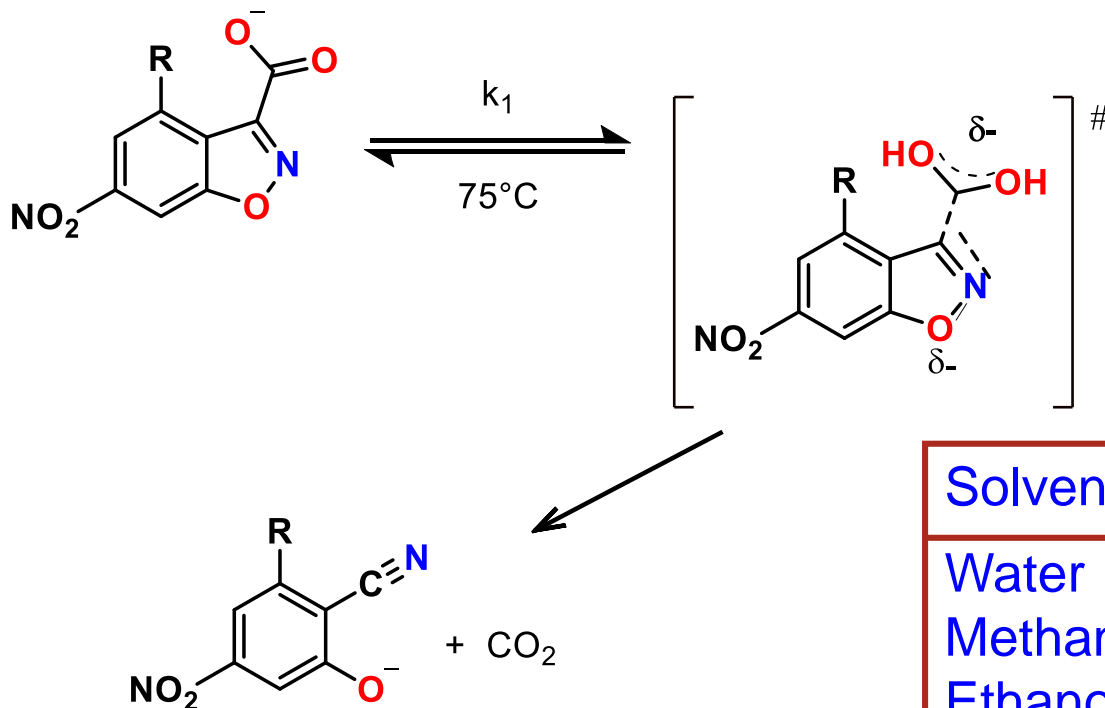
- H-bonding to anions can dramatically affect rate of SN reactions.
- H-bonding to departing anion preferred:
  - enhanced rate
- H-bonding to incoming anion preferred:
  - reduced rate
- Particularly important in decarboxylation reactions.
  - $I > Br > Cl$       **Methanol**
  - $Cl > Br > I$       **DMF**
  - In MeCN, acetate is excellent nucleophile**





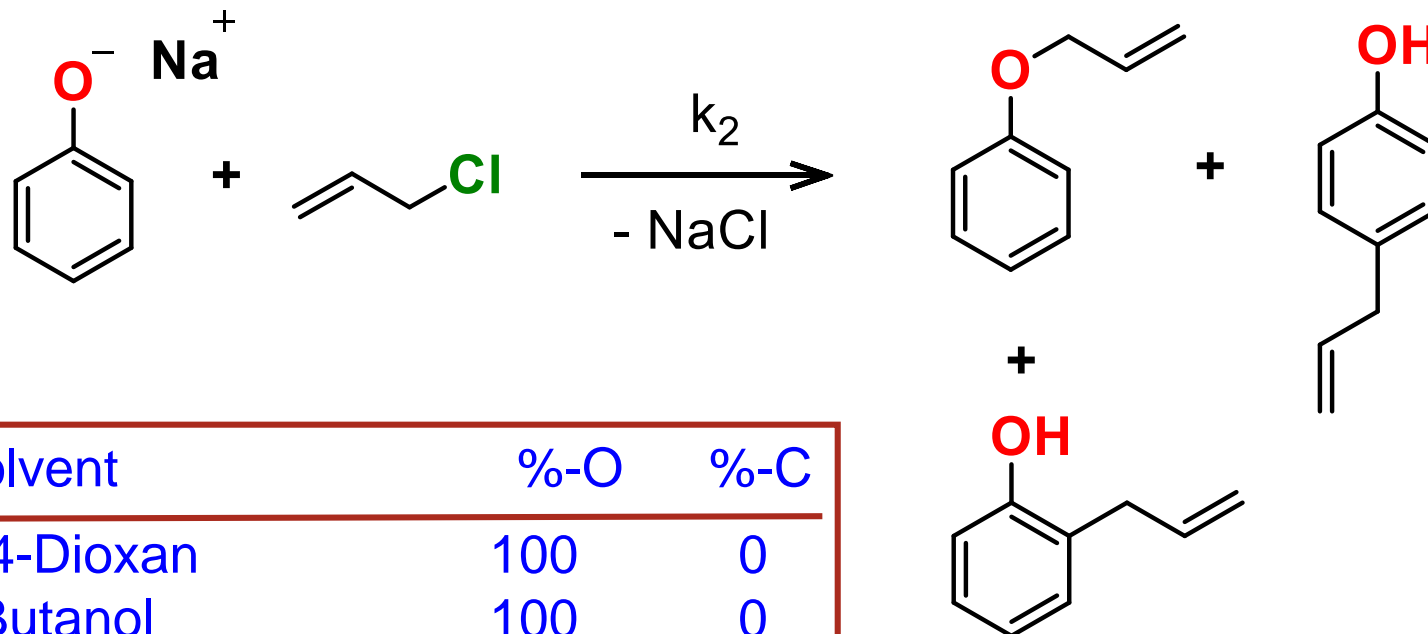
# Effect on Reaction Rate (Rearrangements with charge dispersal - 1° order Reactions).

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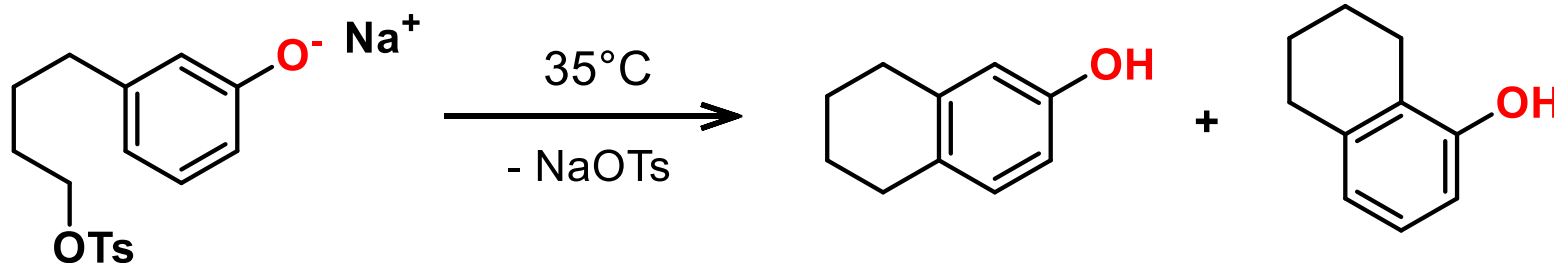
Solvent	$k_1(\text{rel})$
Water	1
Methanol	34
Ethanol	135
Methylene chloride	$6.4 \cdot 10^3$
Diethyl ether	$1.2 \cdot 10^4$
Acetonitrile	$3.9 \cdot 10^5$
Dimethylsulfoxide	$1.4 \cdot 10^4$
HMPT	$9.5 \cdot 10^7$

# O- vs. C-Alkylation.



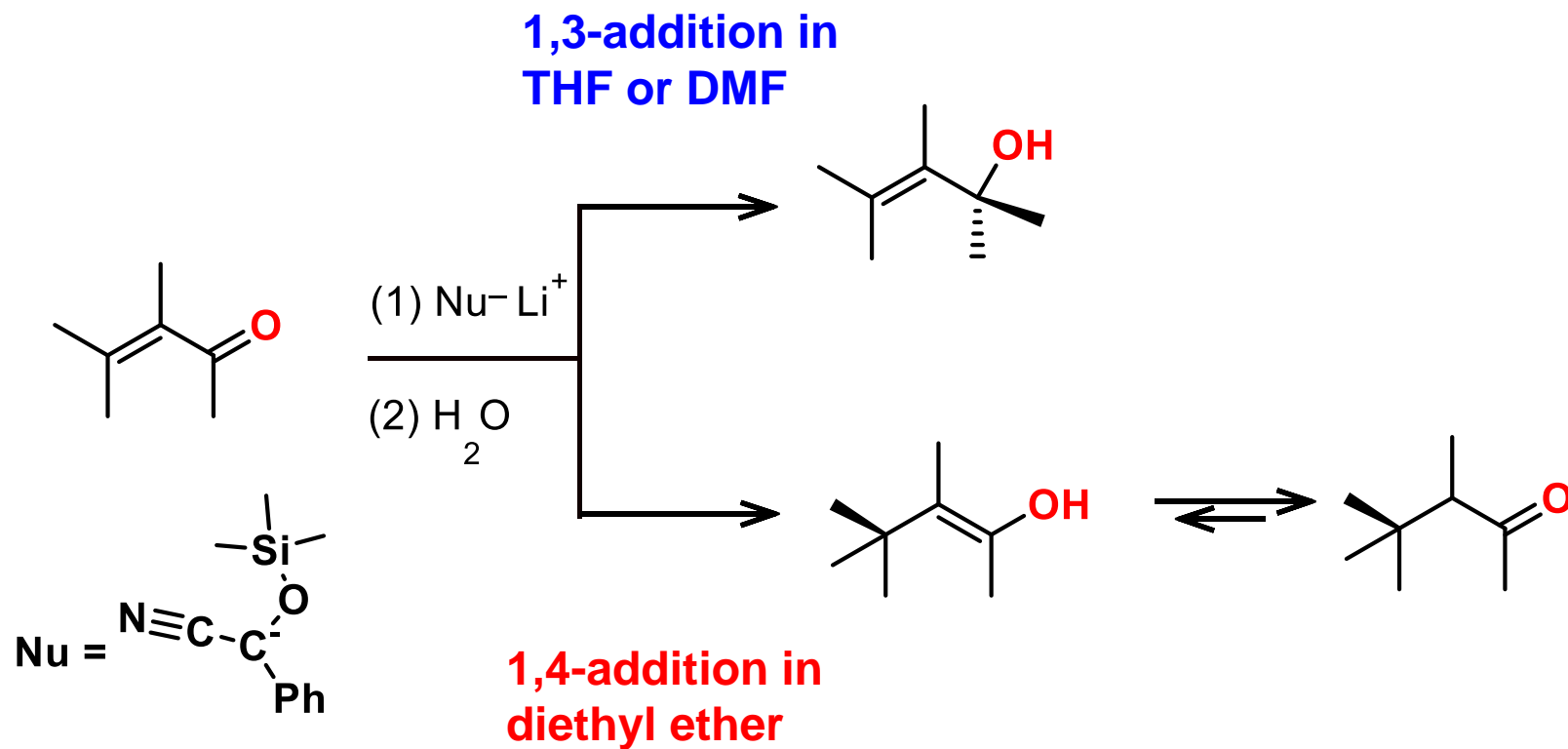
Solvent	%-O	%-C
1,4-Dioxan	100	0
<i>t</i> -Butanol	100	0
Ethanol	100	0
Dimethylformamide	100	0
Tetrahydrofuran	96	4
Water	49	41
Trifluoroethanol	37	42
Phenol	22	78

# Ortho vs. Para Cyclization.



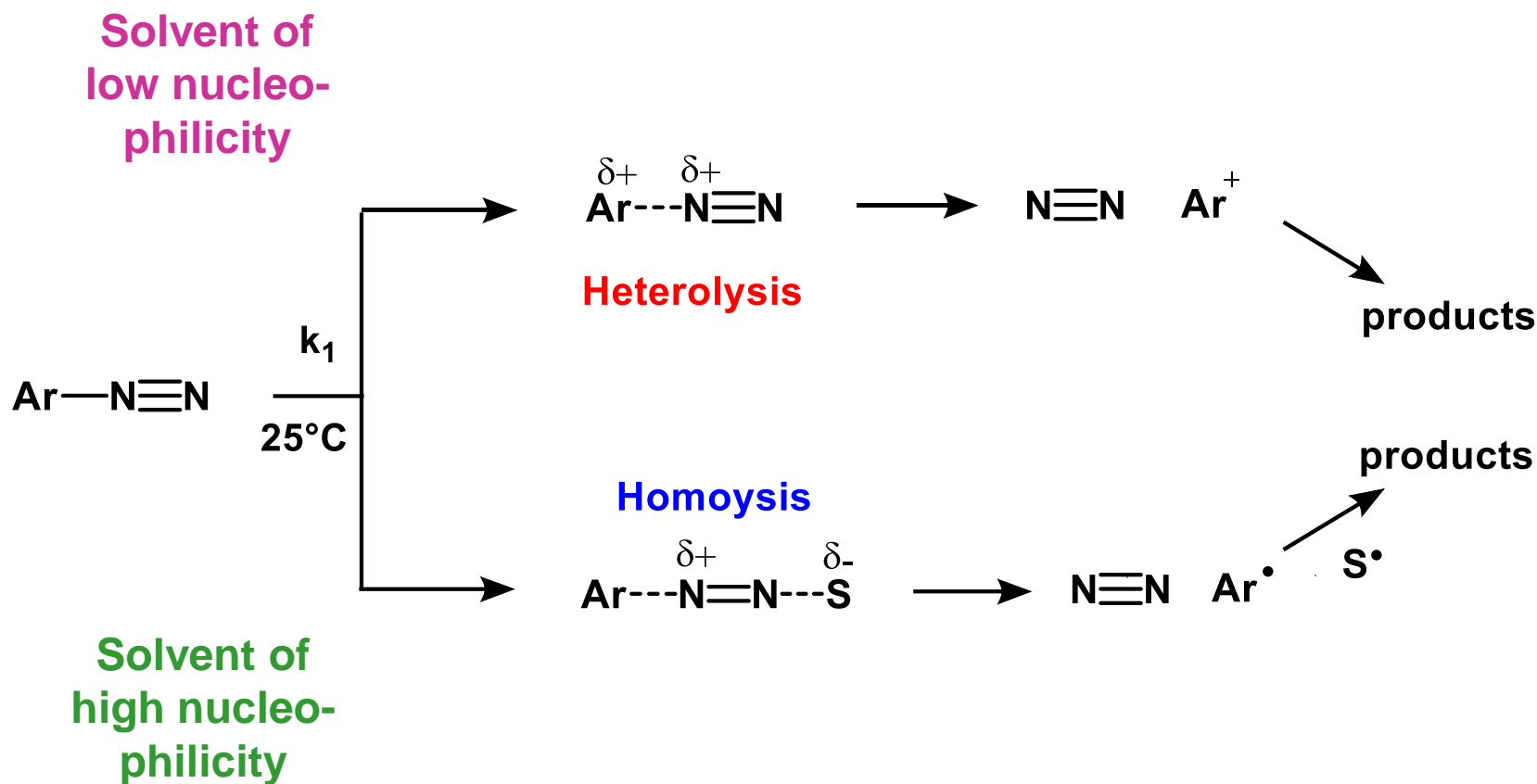
Solvent	<i>para</i> -product	<i>ortho</i> -product
Tetrahydrofuran	13	87
Methanol	49	51

# 1,2- vs. 1,4-Addition.





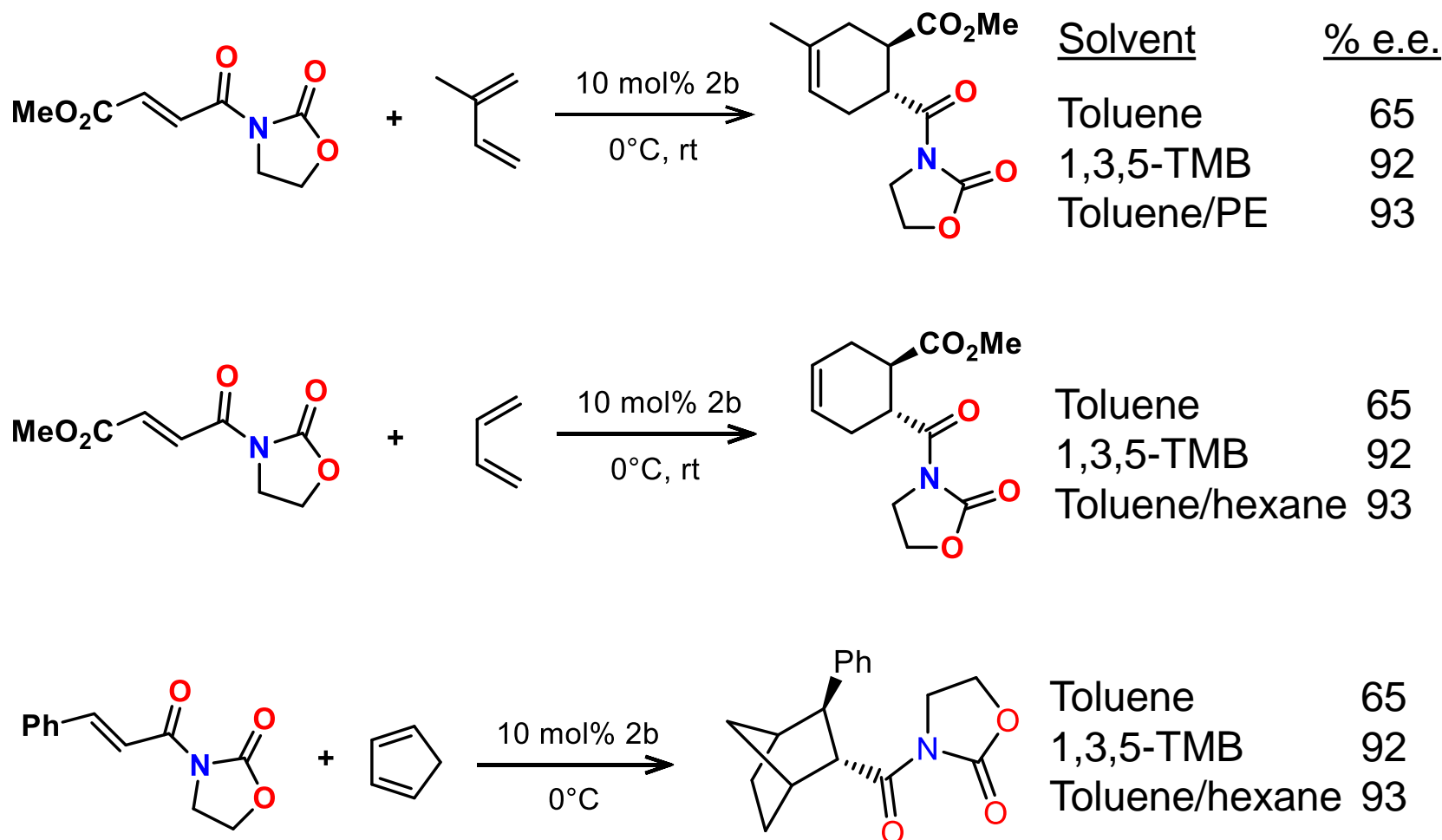
# Homolysis vs. Heterolysis.





# Effect on Enantio-selectivity.

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## Solvent Replacement in Synthetic Chemistry.

- ❖ **Not a simple problem – usually cannot simply replace one solvent with another.**
- ❖ As reaction media:
  - Solvents have a substantial effect on reactions, allowing a degree of control not possible in its absence
  - Can affect:
    - Rates of reaction
    - Chemo-, regio- and stereoselectivity
    - Outcome of reaction – may not work at all, or may do something totally different!
    - workup of reaction mixtures
- ❖ If can be exploited then may give extra incentive for adoption of new technology.



## Solvent Types (Volatile Organic - VOC).

**Hydrocarbons:** toluene, xylene, hexane, cyclohexane, heptane

**Amines:** pyridine, quinoline, triethylamine

**Chlorinated:** dichloromethane, dichloroethane, trichloroethane, chloroform, chlorobenzene, dichlorobenzene

**Ketones:** acetone, methylethylketone, MIBK

**Alcohols:** methanol, ethanol, n-propanol, IPA, t-butanol, n-butanol, higher alcohols, glycols, glycol ethers

**Esters:** ethyl acetate, isopropyl acetate, butyl acetate, ethyl lactate

**Ethers:** diethyl ether, TBME, THF, dioxane, dibutyl ether, dioxolane, dialkoxy methanes (acetals), anisole, dialkoxyethanes, alkoxyethanols

**Acids and Derivatives:** acetic acid, formic acid, acetonitrile,

**Dipolar aprotics :** DMSO, sulfolane, HMPA, urea, DMF, DMAc, NMP + other amides

**Water**





## Problems with VOC's.

### Direct

- Varying toxicity depending on VOC nature, exposure method and duration.
  - E.g. DMF (teratogen),  $\text{CHCl}_3$  (suspect carcinogen).
- Flammability (fire hazards).
- Peroxide formation (usually ethers).

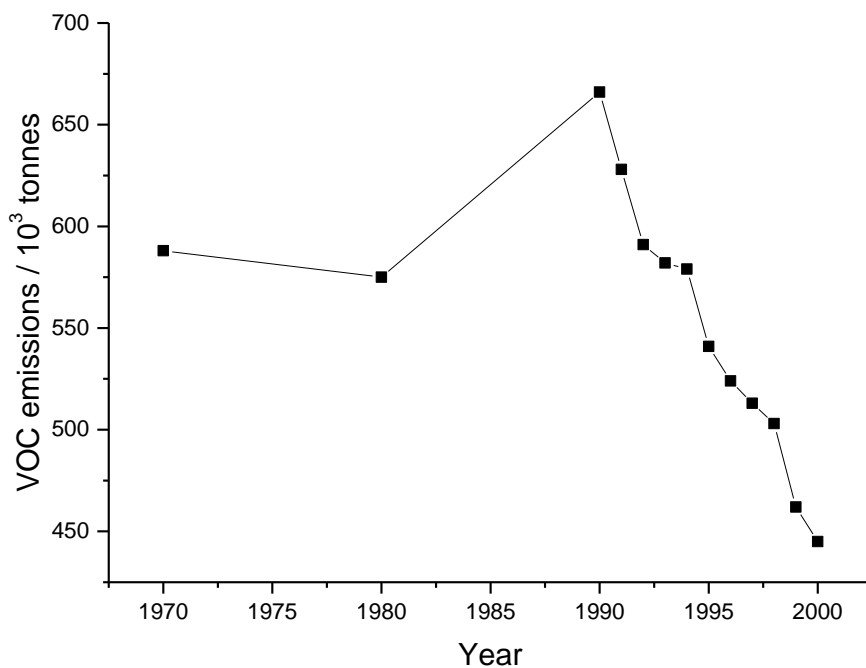
### Indirect

- Ozone depletion
  - Chlorofluorocarbons (CFC's) now phased out
    - E.g.  $\text{CF}_3\text{Cl}$  (lifetime in atmosphere 640 years, GWP 14,000)
    - $\text{CCl}_4$  – now banned (35 years, GWP 1400)
- Global warming potential (GWP)
  - Does not have to be ozone depleting to have GWP
    - E.g. HFC134a ( $\text{CH}_2\text{FCF}_3$ ) used in refrigerants and air conditioning units, 14yrs, GWP 1300
- Environmental persistence.

Use of less volatile solvents may improve environment as long as they do not lead to problems elsewhere.



- VOC solvents are extensively used in organic synthesis (6,000,000,000 Euro in 2006).
- In 2010 solvent use was the largest source of VOCs in the atmosphere (27% of the total).

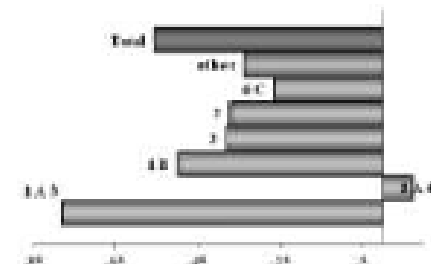
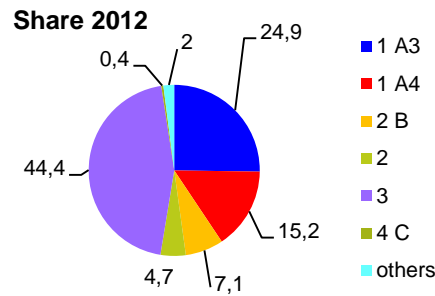
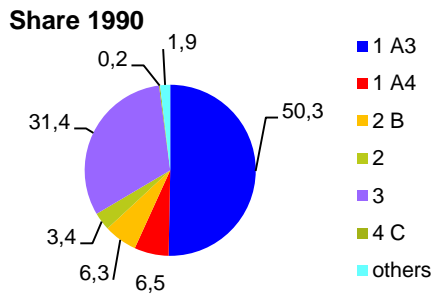
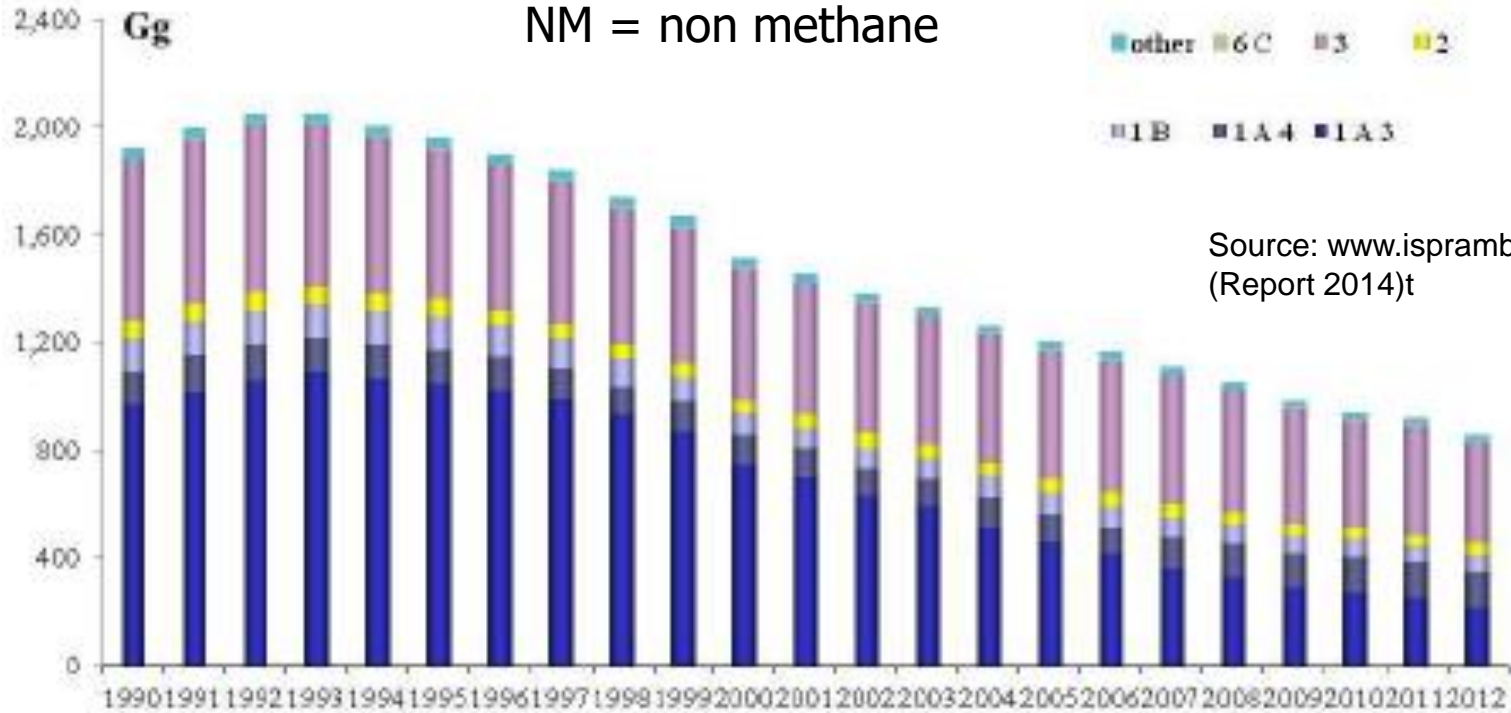


Emissions are on the decline from 1990 but still represent five million tonnes p.a. in Europe.

*Source: DEFRA Atmospheric emissions estimate 2006*



# (NM)VOC Emission Trend, percentage share by sector and variation 1990-2012 in ITALY.





## Environmental Laws on Solvents.

### EU Law

- The VOC Solvents Emissions 1999/13/EC Directive (amended with Directive 2004/42/EC) is the main policy instrument for the reduction of industrial emissions of volatile organic compounds (VOCs) in the European Union. Now [Industrial Emissions Directive \(2010/75/EU\)](#)

### Italian Laws

- D.P.R. 24/05/1988 N°203 ; Modified D.M.A. 12/07/1990 (elenco degli inquinanti volatili pericolosi)
- Water Law

### US Laws

- Clean Air Act and amendments (hazardous air pollutants list)
- Clean Water Act
- Toxics Release Inventory
- Toxic Substances Control Act

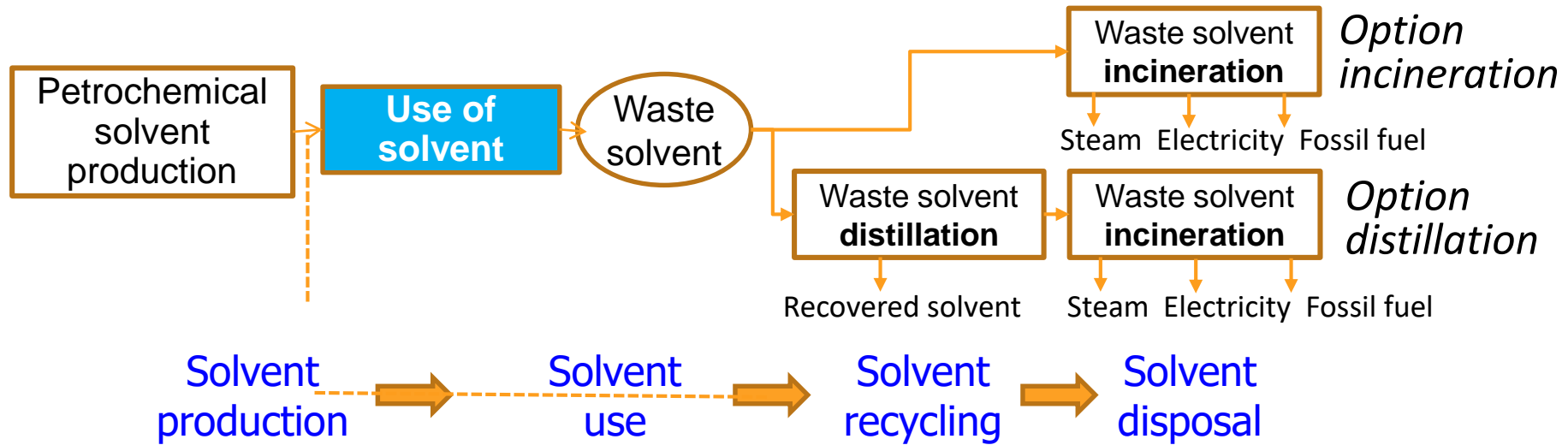
But also: Montreal Protocol; Kyoto Protocol.



## What Are the Concerns for Solvents?

- ❖ Inherent toxicity
- ❖ Flammability
- ❖ Explosivity
- ❖ Stratospheric ozone depletion
- ❖ Atmospheric ozone production
- ❖ Secondary atmospheric pollutant production
- ❖ Global warming potential.

# System Model of the Solvent Assessment Using the Life-Cycle Assessment Method.



**Table 1** Specification of solvent treatment processes used in this work. These assumptions reflect general conditions in the chemical industry according to the opinion of an expert panel

Parameter	Assumptions	Comment
Incineration technology	Hazardous waste incinerator	Model description see ref. 19
Distillation technology	Batch distillation	Detailed description see ref. 20
Use of energy and ancillaries	Average use batch distillation	According to statistical analysis <sup>20</sup>
Production of energy and ancillaries	Average European production	Data were taken from ref. 16
Solvent recovery	Average solvent recovery of 90%	According to the opinion of an expert panel ref. 21
Residue treatment	Incineration	Most commonly used technology for organic solvents ref. 22

## Total CED of a Treatment Option.

**Table 2** Results of the life-cycle assessment of the 26 organic solvents. The total CED of a treatment option is calculated based on these results: CED (Option Distillation) = CED (Solvent Production) + CED (Solvent Distillation); CED (Option Incineration) = CED (Solvent Production) + CED (Solvent Incineration)

Solvent	CAS-No.	Solvent production CED per kg solvent/MJ-eq.	Solvent distillation CED per kg solvent/MJ-eq.	Solvent incineration CED per kg solvent/MJ-eq.
Acetic acid	64-19-7	55.9	-34.9	-15.5
Acetone	67-64-1	74.6	-53.6	-33.9
Acetonitrile	75-05-8	88.5	-79.6	-29.7
Butanol (1-)	71-36-3	97.3	-74.6	-39.9
Butyl acetate	123-86-4	121.6	-95.9	-34.1
Cyclohexane	110-82-7	83.2	-63.4	-53.5
Cyclohexanone	108-94-1	124.7	-99.7	-40.4
Diethyl ether	60-29-7	49.8	-31.9	-40.2
Dioxane	68-12-2	86.6	-63.8	-27.6
Dimethylformamide	68-12-2	91.1	-67.6	-25.9
Ethanol	64-17-5	50.1	-31.2	-31.7
Ethyl acetate	141-78-6	95.6	-72.0	-27.6
Ethyl benzene	100-41-4	85.1	-64.9	-49.8

CED = Cumulative Energy Demand

## Total CED of a Treatment Option (2).

**Table 2** Results of the life-cycle assessment of the 26 organic solvents (*cont.*). The total CED of a treatment option is calculated based on these results: CED (Option Distillation) = CED (Solvent Production) + CED (Solvent Distillation); CED (Option Incineration) = CED (Solvent Production) + CED (Solvent Incineration)

Solvent	CAS-No.	Solvent production CED per kg solvent/MJ-eq.	Solvent distillation CED per kg solvent/MJ-eq.	Solvent incineration CED per kg solvent/MJ-eq.
Formaldehyde	50-00-0	49.3	-28.8	-15.9
Formic acid	64-18-6	73.9	-50.1	-4.7
Heptane	142-82-5	61.5	-43.7	-54.5
Hexane	110-54-3	64.4	-46.7	-55.2
Methyl ethyl ketone	108-10-1	64.2	-44.6	-37.6
Methanol	67-56-1	40.7	-21.7	-22.2
Methyl acetate	79-20-9	49.0	-29.2	-22.8
Pentane	109-66-0	73.2	-54.5	-55.3
Propyl alcohol ( <i>n</i> -)	71-23-8	111.7	-87.3	-36.5
Propyl alcohol ( <i>iso</i> -)	67-63-0	65.6	-46.1	-36.5
Tetrahydrofuran	109-99-9	270.8	-230.7	-37.5
Toluene	108-88-3	80.0	-60.0	-49.3
Xylene	1330-20-7	72.5	-53.1	-49.9



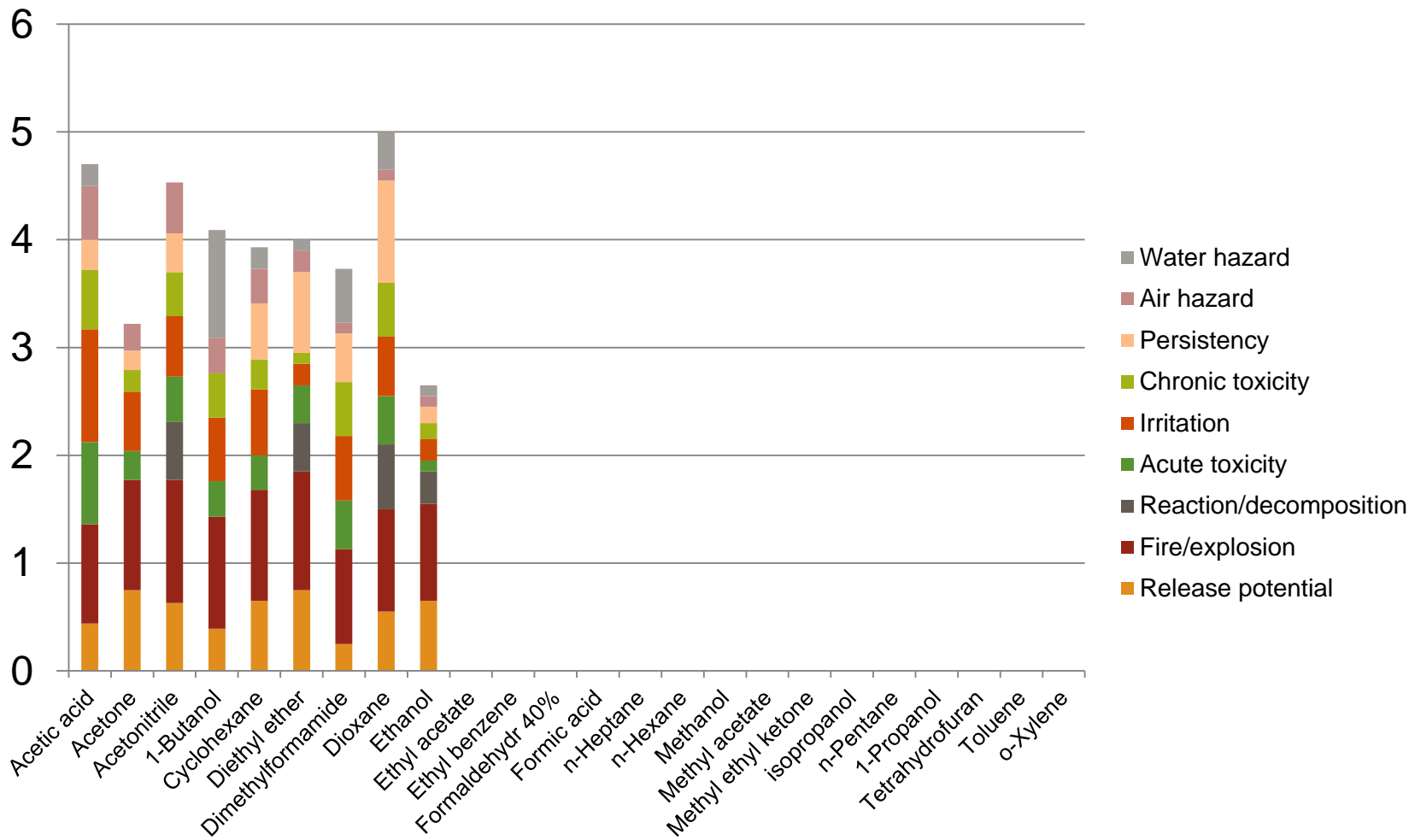


# Suitability of Molecular Solvents.

Most acceptable				Lest acceptable			
Aqueous solvents	Oxygenated solvents	Aliphatic hydrocarbons	Aromatic hydrocarbons	Dipolar aprotic solvents	Chlorinated solvents	Ozone depleters	Toxic and carcinogenic solvents
Water	Alcohols	<i>n</i> -Alkanes	Xylene	Dimethyl sulfoxide	Methylene chloride	Fluorochloroalkanes	Benzene
	Ethers	Cycloalkanes	Toluene	(Dimethyl formamide)	Chloroform		Carbon tetrachloride
	Esters		Mesitylene		1,2-Dichloroethane		
	Ketones						
	Organic carbonates						



# Results of an Environmental, Health and Safety (EHS) Assessment for 26 Common Solvents.



Green Chem., 2007, 9, 927–934

## Current Approaches to Solvent Replacement.

- **Not a simple problem** – usually cannot simply replace one solvent with another.
- **Consider process as a whole**, not just one aspect (solvents used in work-up and purification not just reaction medium).
- Many aspects must be considered and their relative importance determined quantitatively (**metrics**).
  - Where does the solvent come from?
  - What is the process used to prepare the solvent never mind about its intended use?
    - Energy
    - Hazardous processes
    - Raw material
    - By-products
    - Toxicity

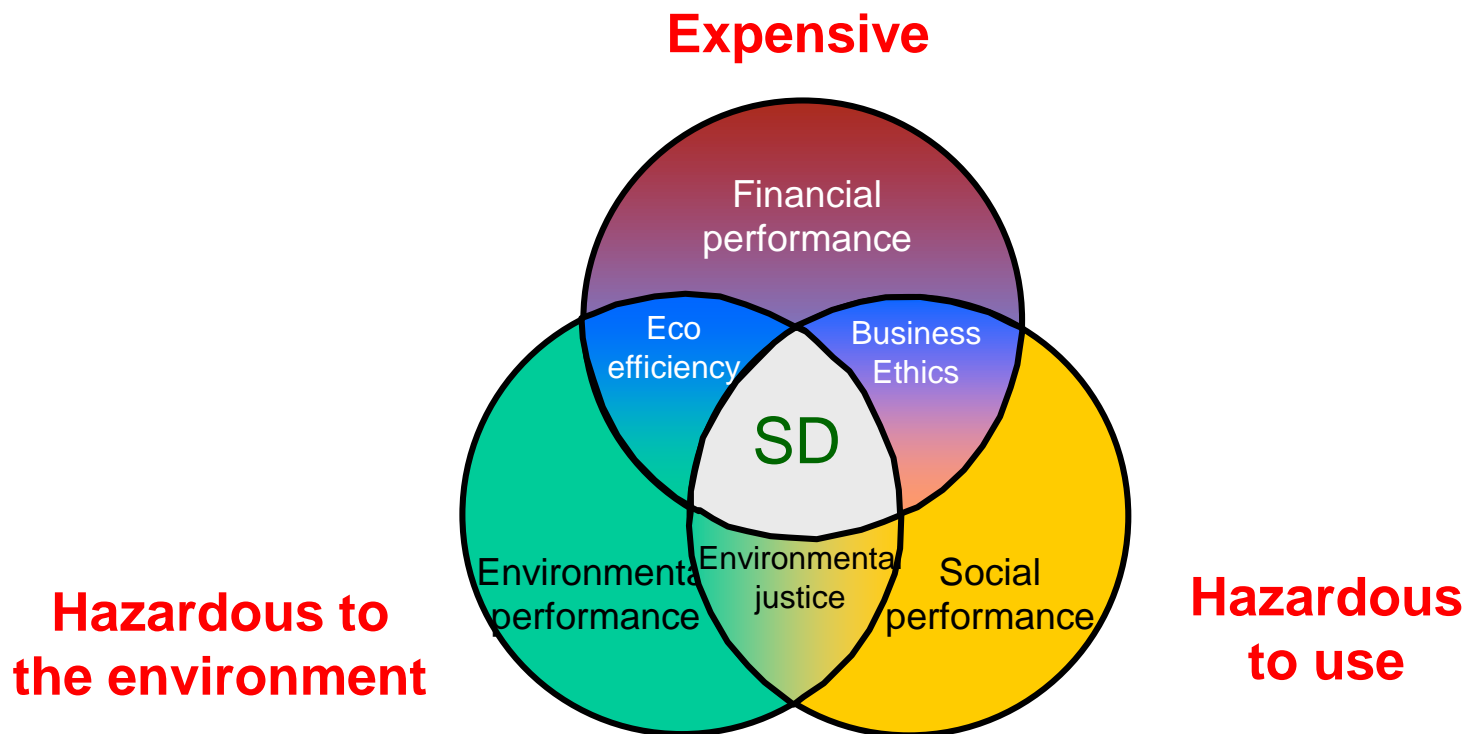
❖ **Less Hazardous**

❖ **Human Health**

❖ **Environmental (Local and Global)**



# Sustainable Solvent Development.



*Solvent optimization can give numerous benefits!*



## Undesirable Solvents.

Red Solvent	Flash point (° C)	Reason
<b>Pentane</b>	-49	Very low flash point, good alternative available.
<b>Hexane(s)</b>	-23	More toxic than the alternative heptane, classified as a HAP in the US.
<b>Di-isopropyl ether</b>	-12	Very powerful peroxide former, good alternative ethers available.
<b>Diethyl ether</b>	-40	Very low flash point, good alternative ethers available.
<b>Dichloromethane</b>	n/a	High volume use, regulated by EU solvent directive, classified as HAP in US.
<b>Dichloroethane</b>	15	Carcinogen, classified as a HAP in the US.
<b>Chloroform</b>	n/a	Carcinogen, classified as a HAP in the US.
<b>Dimethyl formamide</b>	57	Toxicity, strongly regulated by EU Solvent Directive, classified as HAP in the US.
<b>N-Methylpyrrolidinone</b>	86	Toxicity, strongly regulated by EU Solvent Directive.
<b>Pyridine</b>	20	Carcinogenic/mutagenic/reprotoxic (CMR) category 3 carcinogen, toxicity, very low threshold limit value (TLV) for worker exposures.
<b>Dimethyl acetate</b>	70	Toxicity, strongly regulated by EU Solvent Directive.
<b>Dioxane</b>	12	CMR category 3 carcinogen, classified as HAP in US.
<b>Dimethoxyethane</b>	0	CMR category 2 carcinogen, toxicity.
<b>Benzene</b>	-11	Avoid use: CMR category 1 carcinogen, toxic to humans and environment, very low TLV (0.5 ppm), strongly regulated in EU and the US (HAP).
<b>Carbon tetrachloride</b>	n/a	Avoid use: CMR category 3 carcinogen, toxic, ozone depletor, banned under the Montreal protocol, strongly regulated in the EU and the US (HAP).



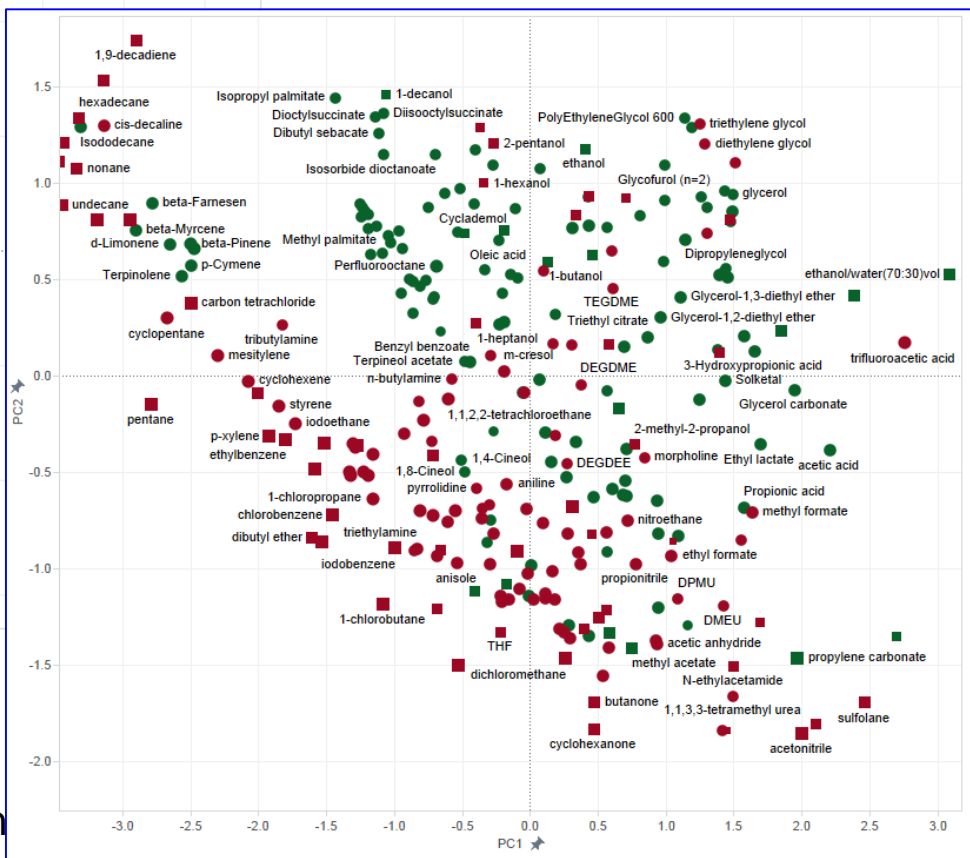
## Solvent Replacement Table.

Undesirable Solvent	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether or diethyl ether	2-MeTHF or <i>tert</i> -butyl methyl ether
Dioxane or dimethoxyethane	2-MeTHF or <i>tert</i> -butyl methyl ether
Chloroform, dichloroethane or carbon tetrachloride	Dichloromethane (??)
Dimethyl formamide, dimethyl acetamide or N-methylpyrrolidinone	Acetonitrile
Pyridine	Et <sub>3</sub> N (if pyridine is used as a base)
Dichloromethane (extractions)	EtOAc, MTBE, toluene, 2-MeTHF
Dichloromethane (chromatography)	EtOAc/heptane
Benzene	Toluene

“Green chemistry tools to influence a medicinal chemistry and research chemistry based organization”  
Dunn and Perry, et. al., Green Chem., 2008, 10, 31-36.



# Solvent Substitution by Green Alternatives.



expansion



## Strategies of Solvents Replacement.

- Avoid or minimise solvents in first place
- Use less toxic solvents
- Use renewable solvents (not derived from petrochemicals)
- Avoid VOC's
  - Aquatic toxicity
  - Ultimate biodegradability
  - EU Environmental classification
  - Acute human toxicity
  - Vapor pressure
  - Octanol/Water Partition Coefficient (OWPC)
  - Source/Supplier
  - Photochemical Ozone Creation Potential (POCP) (Reserved)

**PLUS Other Significant Concerns!**





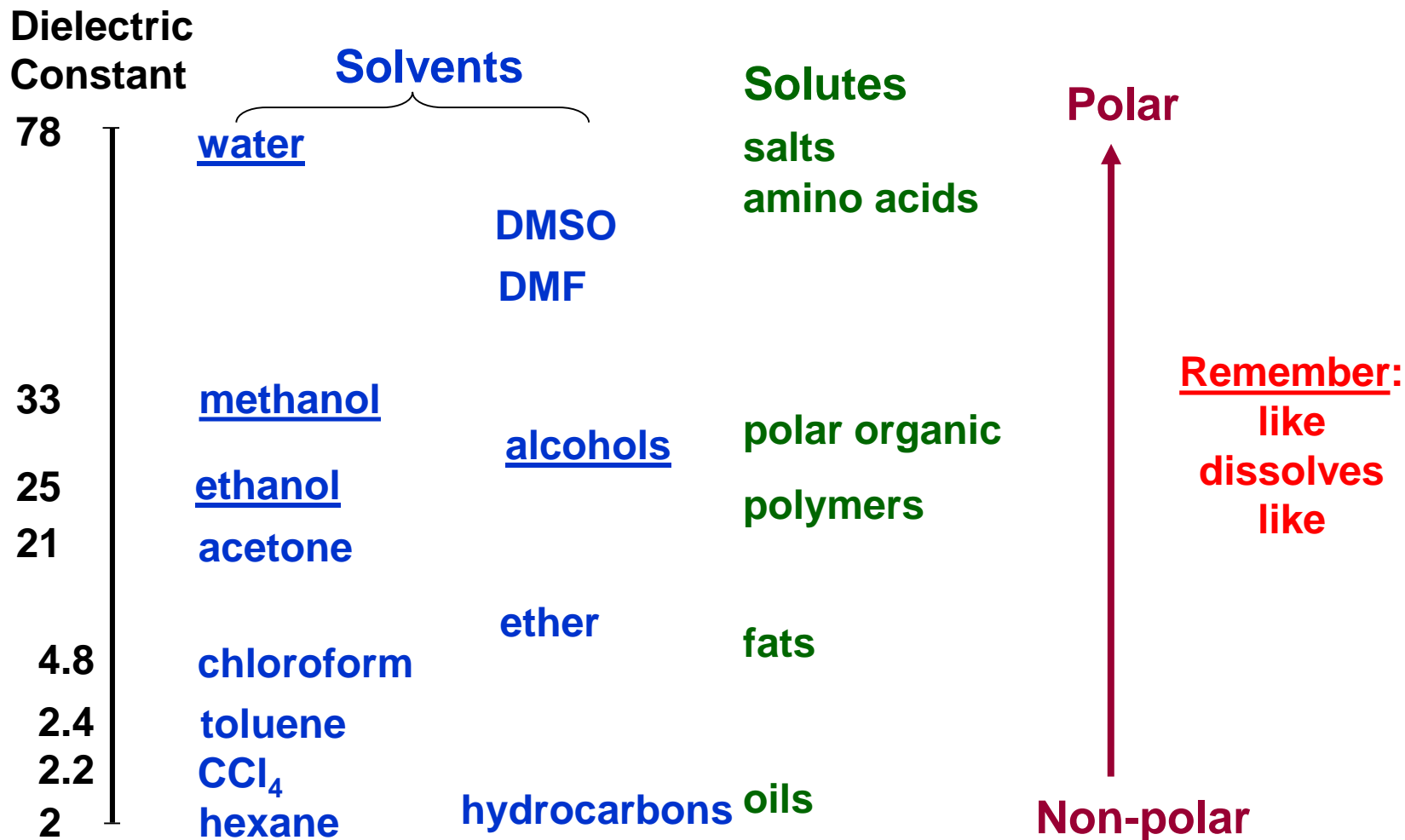
## Is the Source Sustainable?

Comparing solvents the following need to be considered:

- Where does it come from?
- Is the source sustainable?
- There are alternatives (in particular if it is possible avoid its use)?
- Where will it end up?
- How can its effect be neutralized, if toxic-volatile?
- How cost its recycling?
- How much energy can be recovered from its combustion?



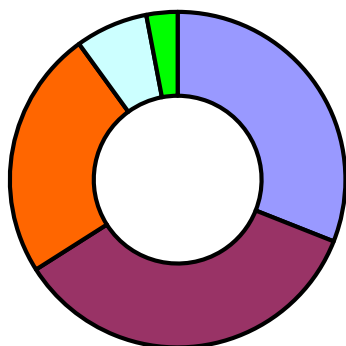
# What Solvent do we Need?





# Solvent Use in Research.

## Solvent Use - "Perkin Trans 1" Journal



- Chlorinated
- Dipolar aprotic
- Other Harmful
- Accetable
- Eco-compatible

## Solvent Use "Green Chemistry" Journal



- Clorinated
- Dipolar aprotic
- Other Harmful
- Accetable
- Eco-Compatible



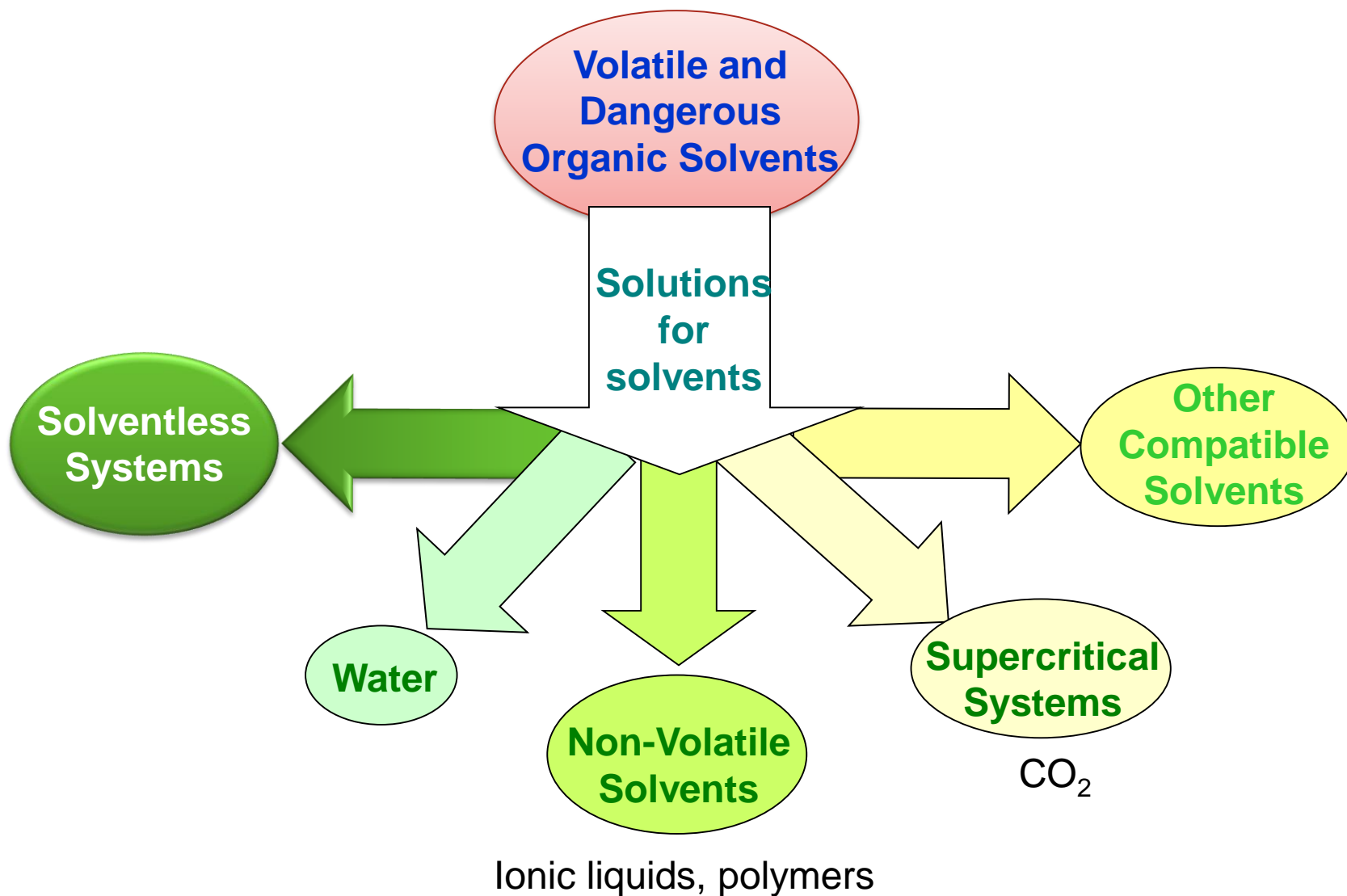
## Benign Solvents.

Replacement of VOC solvents is highly desirable and several efforts has been developed to reach this goal.

Alternatives:

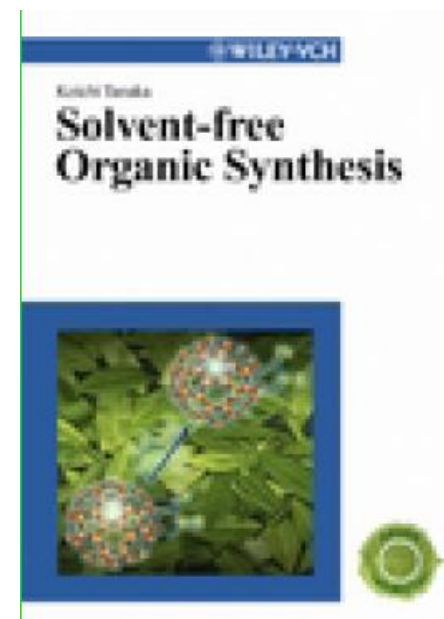
- No solvent
- Water and aqueous solvents
- Supercritical fluids (carbon dioxide, water, ethane, etc.)
- Ionic liquids
- Polymeric/immobilized/derivatized solvents
- Other compatible solvents (ethyl lactate).

***All have advantages and disadvantages which need to be considered when assessing suitability for replacement.***



## 'Solventless' Chemistry.

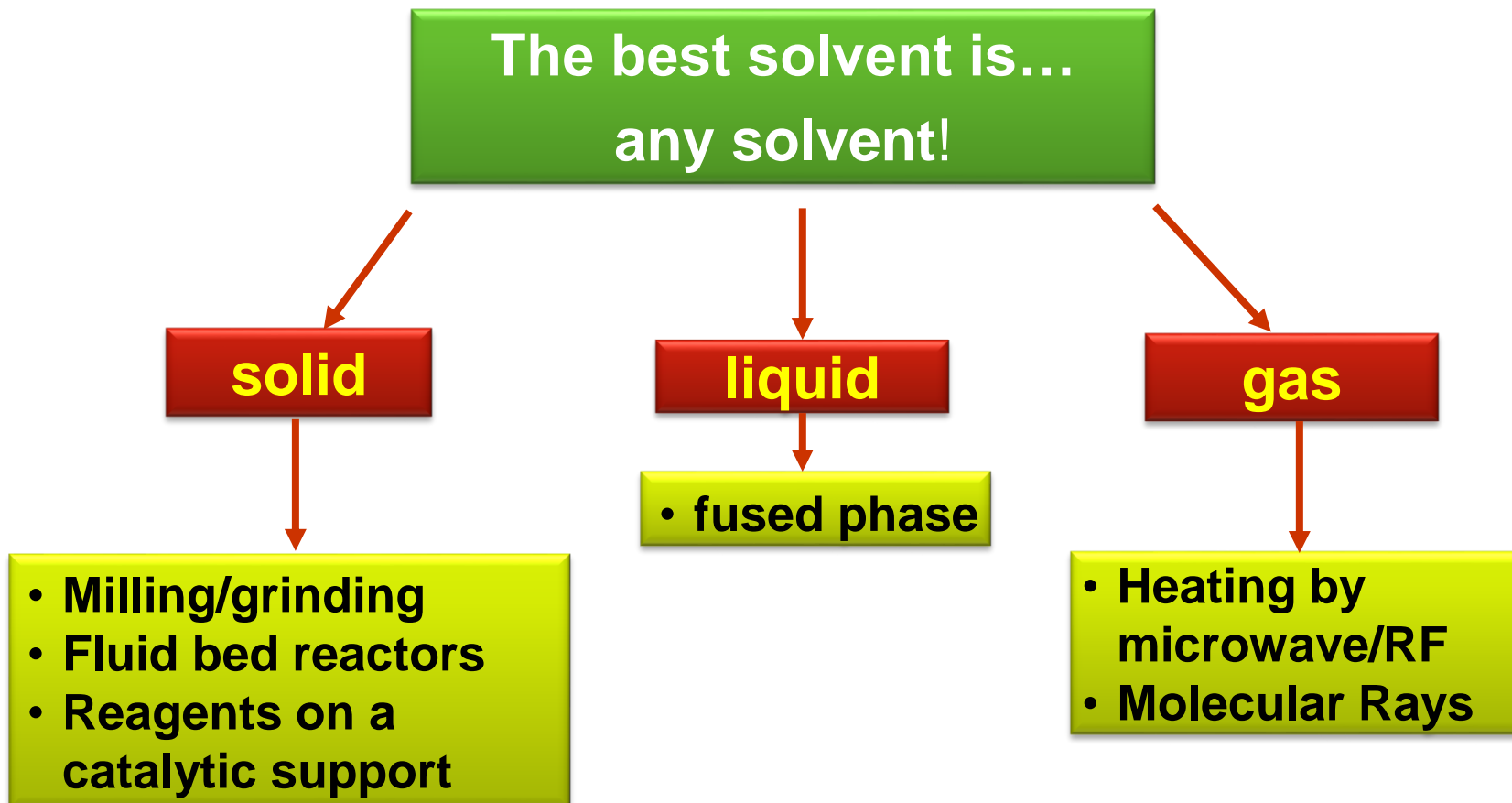
- Has been around for many years
- Provides one of the simplest solutions to the problem of solvents
- Not many reactions amenable to solventless approach, particularly on large scale
- Exothermic reactions can be dangerous on large scale – need close collaboration with chemical engineers to overcome such problems
- Efficient mixing can be a problem, particularly when have solid reagents or products
- Some technologies (milling, solid reactors, etc.) can help
- Solvents still often required for extraction, separation and purification of products



Koichi Tanaka

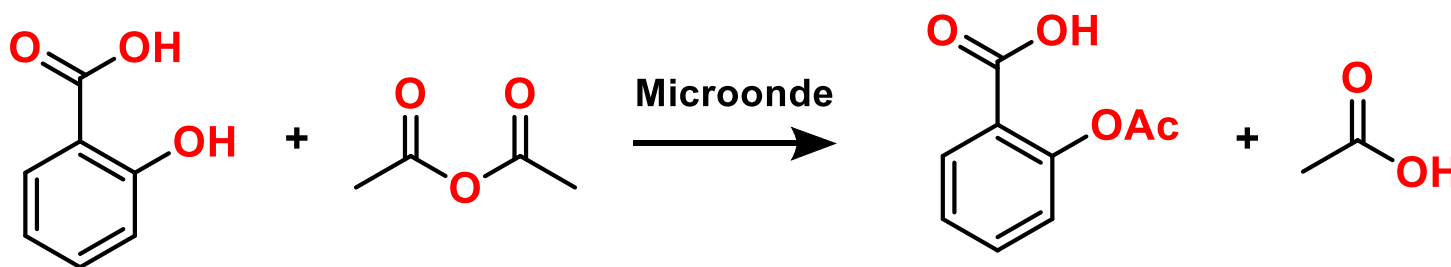


## Reactions without Solvent.



## Solventless Synthesis of Aspirin.

- When reagents are liquids or when one reagent is liquid and able to disperse almost in part the other reagents it is useful to verify if exist conditions in which the reaction occurs without solvent.
- In some cases, supply energy by microwaves is particularly advantageous, i.e. in the synthesis of aspirin:

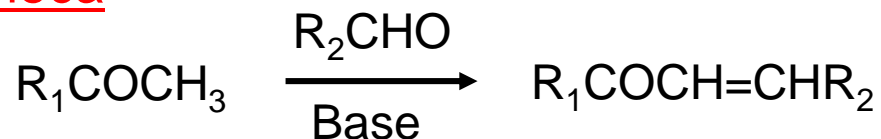


Bose, Stevens Institute of Technology

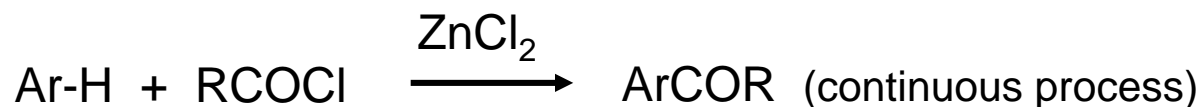


## No Solvent – Examples.

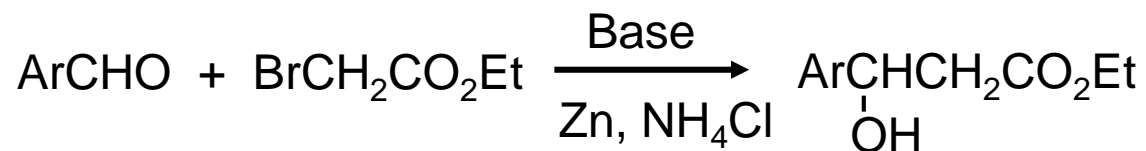
### Zeneca



### Friedel-Crafts



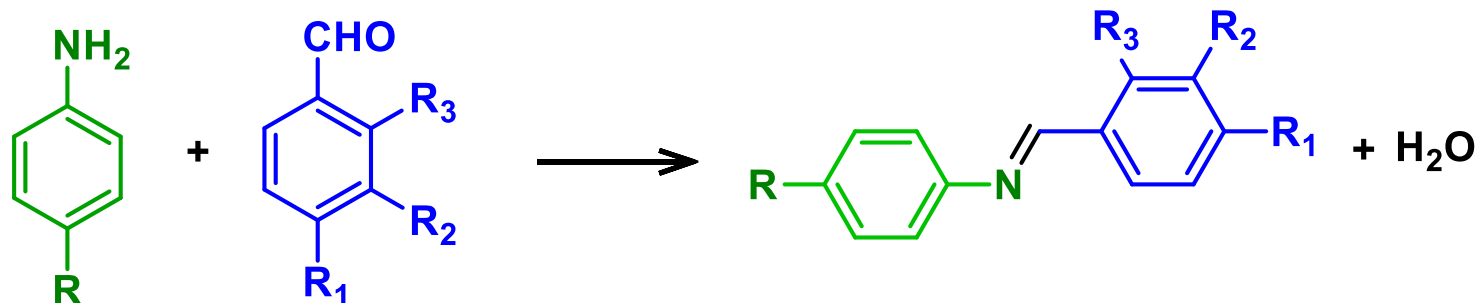
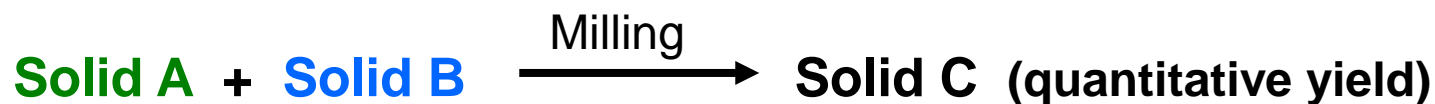
### Reformatsky



*Org. Synt.* Yield 61-64%

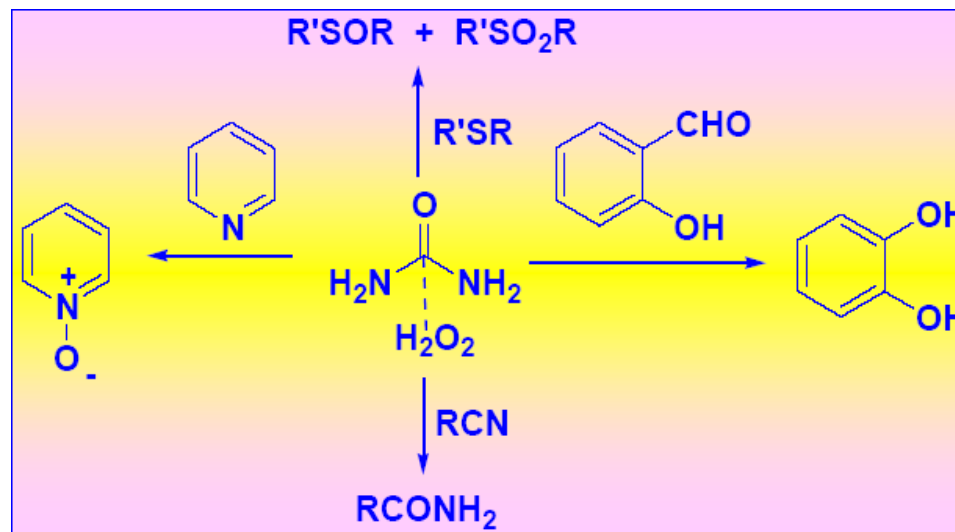
K. Tanaka *J. Org. Chem.* **1991**, 56, 4333

# Reactions by Mechanical Milling.

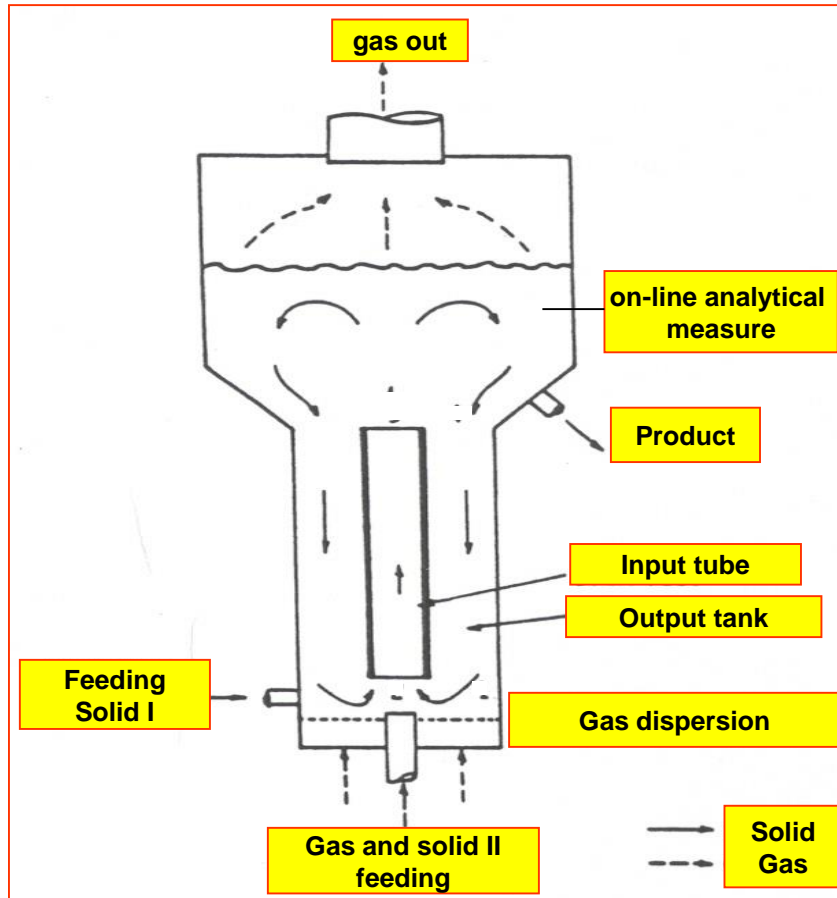


Solid-State General  
Oxidation with 1:1  
Urea/ $\text{H}_2\text{O}_2$  Complex

R. S. Varma and K. P. Naiker,  
*Org. Letters*, 1999, 1, 189.



# Example: Solid-Solid Reaction in Fluid Bed.



## Opportunity

**Definition of reagents mixing conditions**

- purity and homogeneity of product (QA)

**Data on solid/solid interface are essential:**

- Dimension and particle shape
- Surface chemistry
- Inter-particle forces and interactions

**Safe control of reactor**

- Thermodynamic and heat transf.
- Avoid run-a-way reactions

**Robust in situ analytical technique.**



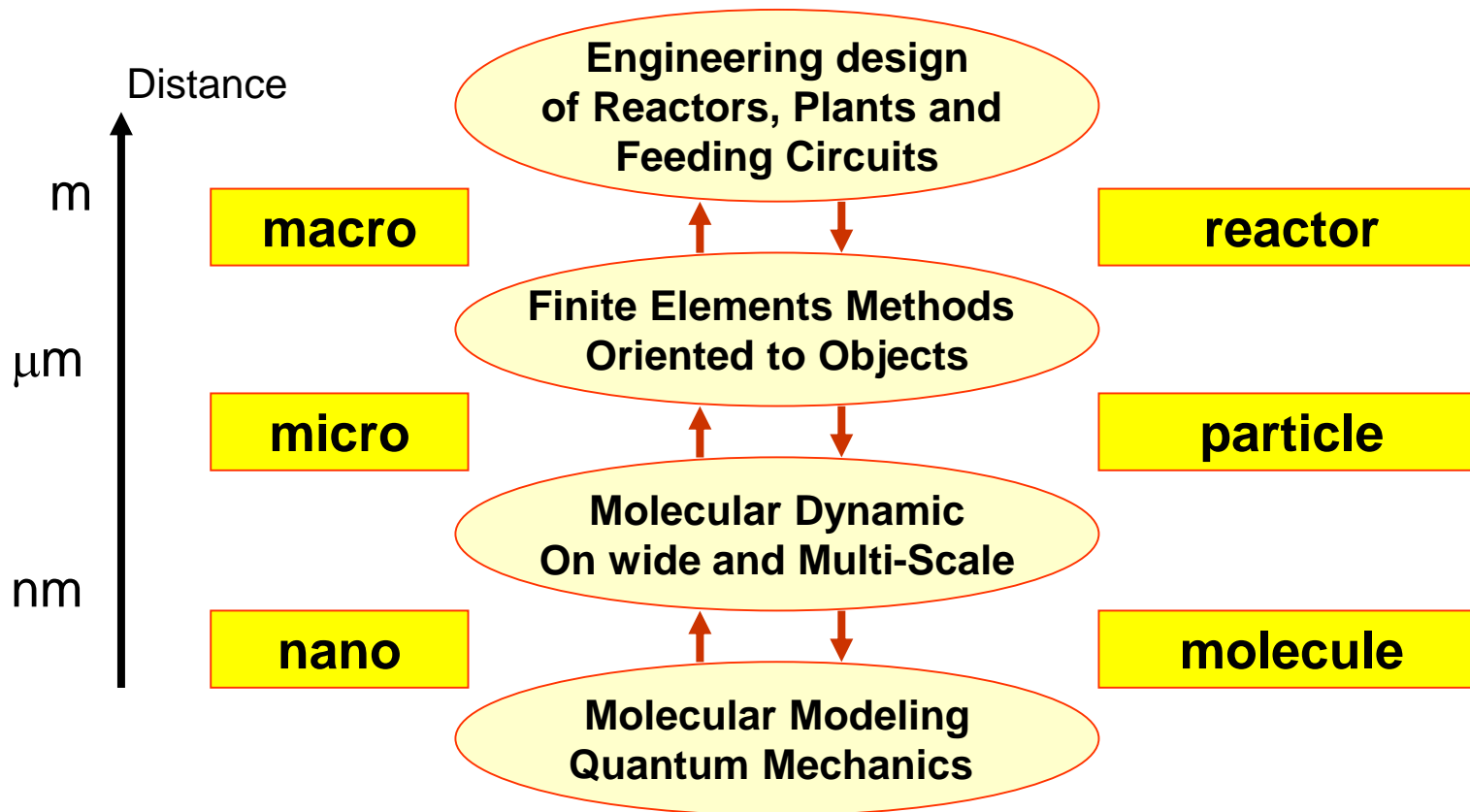
## Solvent less Conditions.

### DryView™ Imaging Systems:

- Photothermographic imaging technology
- Uses no wet chemistry
- Creates no effluent
- Requires no post-process steps such as drying
- Applicable to all industries that process panchromatic film products (medical radiography, printing, industrial radiography, and military reconnaissance).



# Solid-Solid Reactions : Need a Modeling on Several Scales.



**Chemists and Engineers Collaboration – Essential!**



## References on Solvent Free Processes.

- K. Tanaka and F. Toda "Solvent-Free Organic Synthesis" *Chem. Rev.* 2000, 100, 1025-1074.  
Crushed grapes give wine by fermentation, but dried grapes do not result in wine.
- Koichi Tanaka, "Solvent-free Organic Synthesis" 2003 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. ISBN: 3-527-30612-9; Wiley-VCH; Second, Completely Revised and Updated Edition | March 2, 2009 | English | ISBN: 3527322647 |
- Nasir Baig RB, Rajender S Varma: Solvent-free synthesis in An Introduction to Green Chemistry Methods, 2013, Pages 18-38  
Doi: 10.4155/ebo.13.4



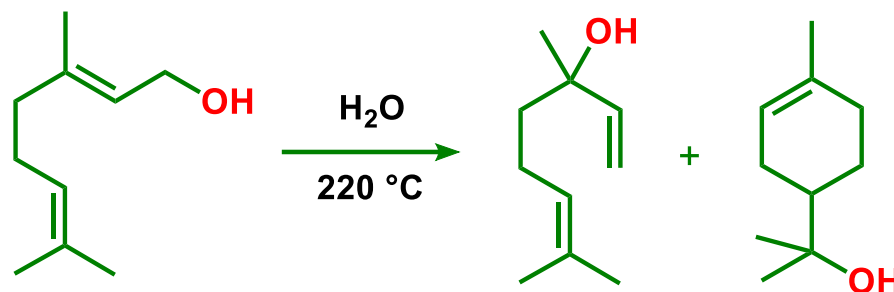
## Molecular Solvents – Water.

- One of the most obvious alternatives to VOCs.
- Cheap, readily available, plentiful and versatile – the solvent of choice!
- Useful for certain types of reaction but limited because of:
  - Poor solubility for organic non polar substrates (surfactants and emulsions can aid)
  - Compatibility with reagents (active in redox and acid-base reactions)
- Clean up of aqueous waste difficult
- Useful in biphasic processes with other solvents
- Separation is energy intensive and time consuming
- Reactive towards oxidant and reducing agents.

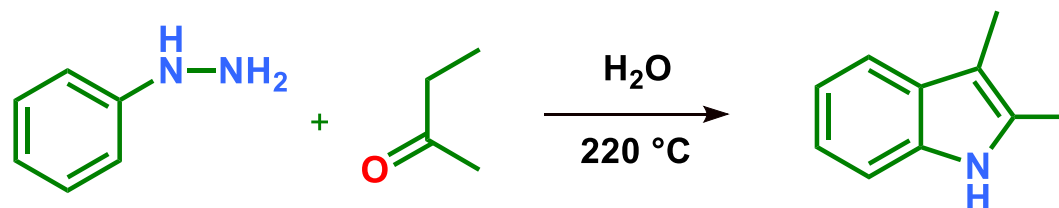


## Water - Benign Solvent.

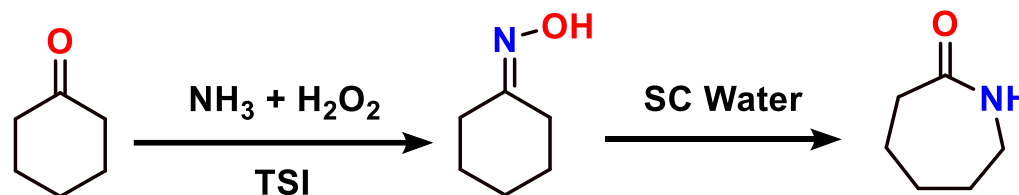
### High temperature isomerization of Geraniol using Water



### High temperature synthesis of 2,3-Dimethyl-Indole in Water



### High temperature synthesis of caprolactam in SC Water

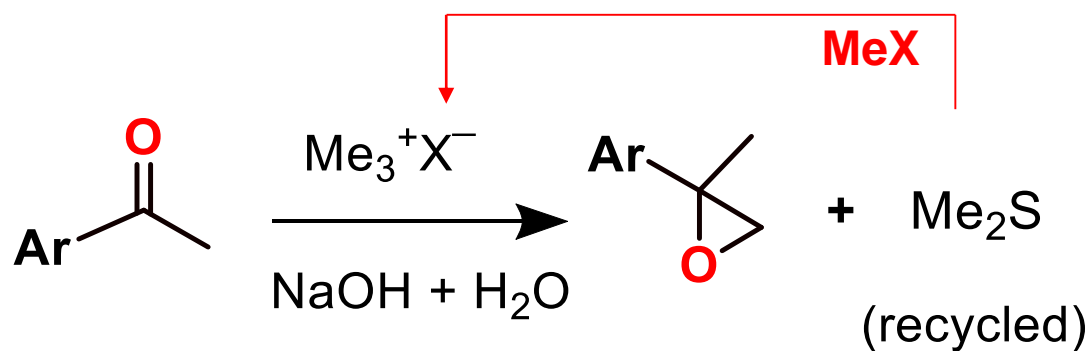




## Water - Benign Solvent (2).

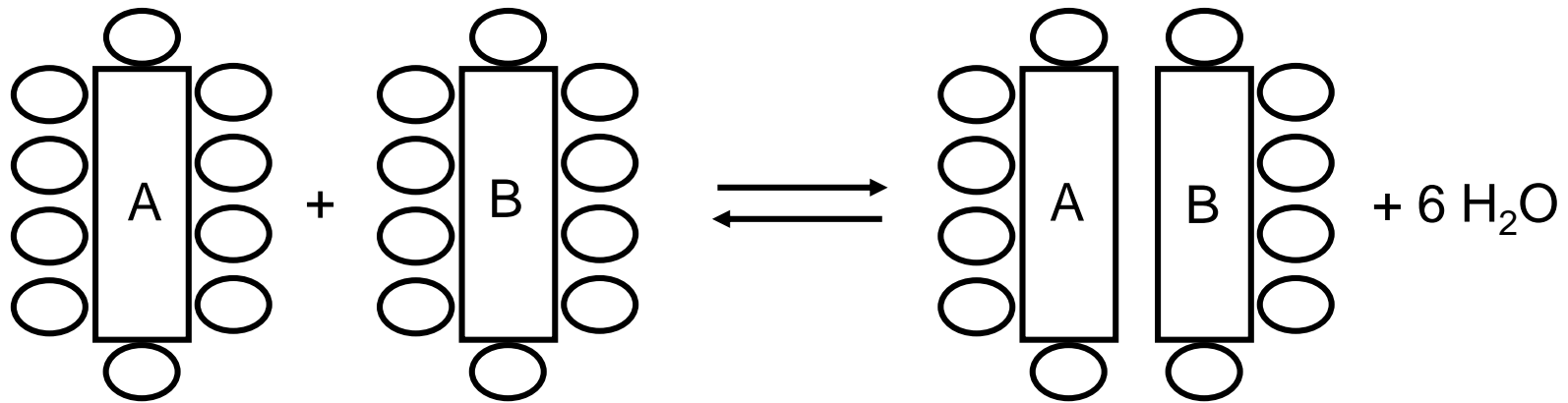
- Enzymes/microorganism reactions
- Suspensions
- PTC and other 2 phase processes
- Analogues of anhydrous chemistry (e.g. sulphur ylid, organometallic)

### Zeneca Agrochem





## The Hydrophobic Effect.

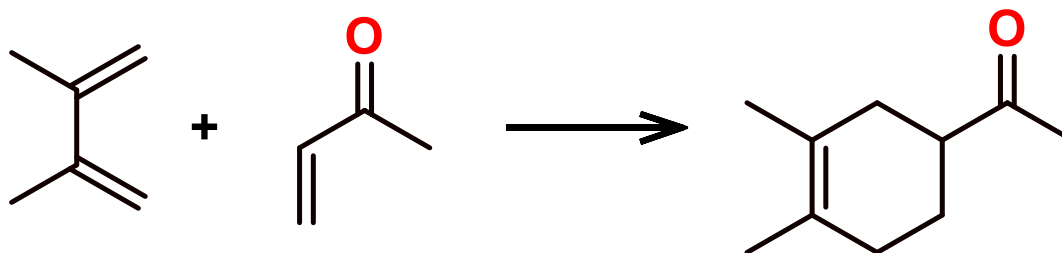


Formation of a hydrophobic interaction between two hydrocarbon molecules A and B. (The circles represent water molecules).

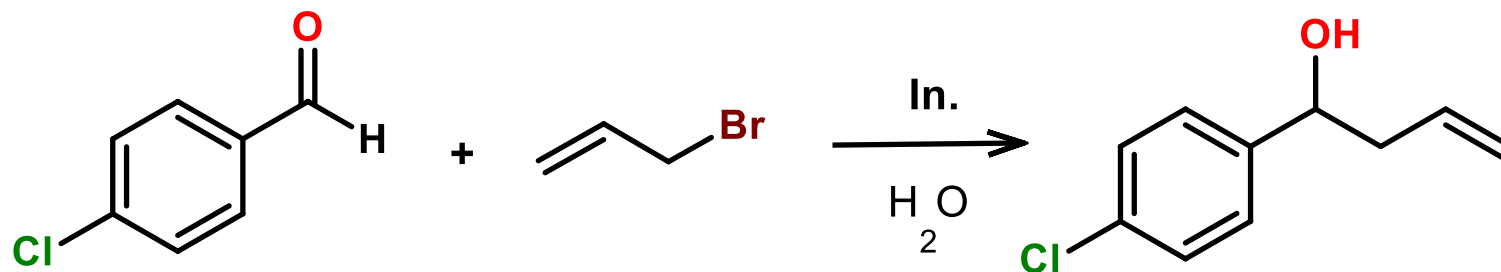
*REACTIONS IN WATER SHOW GREAT POTENTIALITY'*  
(in supercritical conditions also hydrocarbons are soluble !)



Aqueous Conditions for the Diels-Alder Reaction:

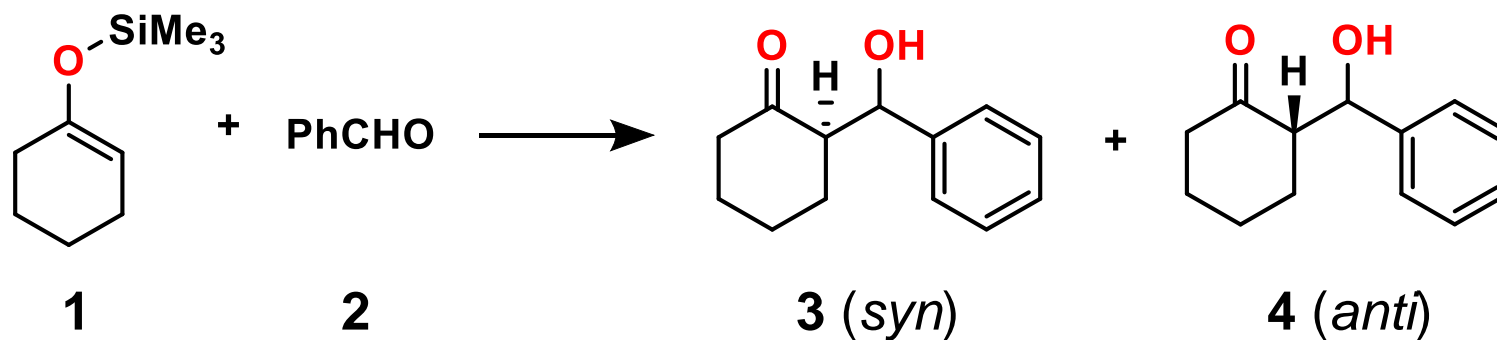


Aqueous Conditions for Metal-Mediated Reactions:





# Mukaiyama Reaction.



(A. Lubneau, *J. Org Chem.* 1986, 51, 2142)

- Reaction ACCELERATED in water
- No catalyst required
- Rate and selectivity similar to reactions conducted under pressure

Similar findings with Diels-Alder reaction with 2 insoluble substrates in water.

(R. Breslow, *Tetr. Lett.* 1984, 1239)



- **Reviews:**

A. Lubineau *Chem. Ind.* 1996, 123

*Synthesis* 1994, 9, 741

P. Grieco *Chem. Rev.* 1993, 93, 2023

*Aldrichimica Acta* 1991, 6, 159

R. Breslow *Acc. Chem. Res.* 1991, 6, 159





## Miscellaneous Solvent Ideas.

- **Mixed solvent**
  - control solubility of product accurately via ratio difficult to recover.
- **No solvent**
  - liquid reagents (at a chosen temperature)
  - highly volume efficiency (high productivity by volume)
  - safety issues if exothermic.



## Solubility of Water in Solvents.

Solvent	g/L	M	- log $K_D$
Water	1000	56	
Ethyl acetate	33	1.8	1.5
Diethyl ether	15	0.8	1.8
Diisopropyl ether	9	0.5	2.0
Methylene chloride	2	0.1	2.7
Chloroform	0.7	0.04	3.1
Toluene	0.5	0.03	3.3
Carbon tetrachloride	0.1	0.005	4
Hexane	0.1	0.005	4

## Molecular Organic Solvents.

- + Dissolve a wide range of solutes – depending on dielectric constant
- + Volatile solvents are less energy intensive for product separation
- + Non volatile solvents such as glycols (ethylene and propylene glycols and their PEG telomers, glycerol, etc.) are increasingly being used as benign solvents
  - Often toxic
  - Generally expensive,
  - flammable
  - All VOCs are controlled by legislation.

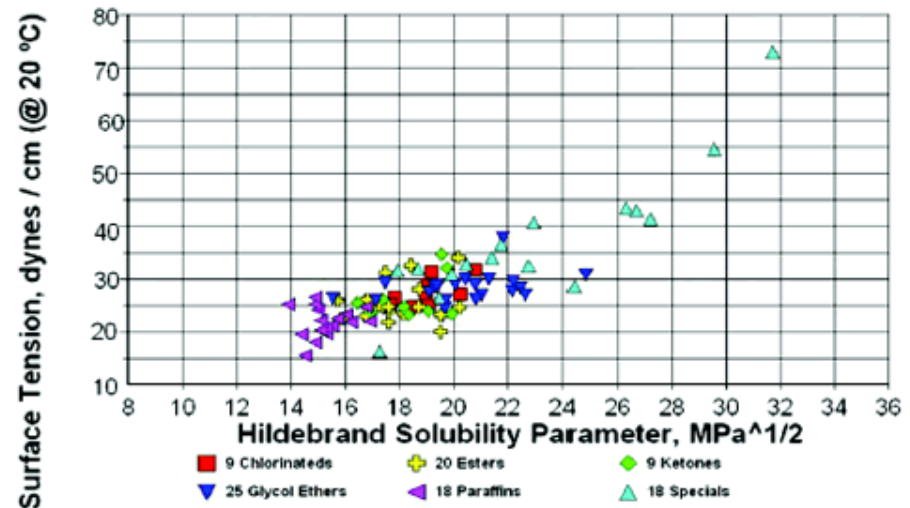
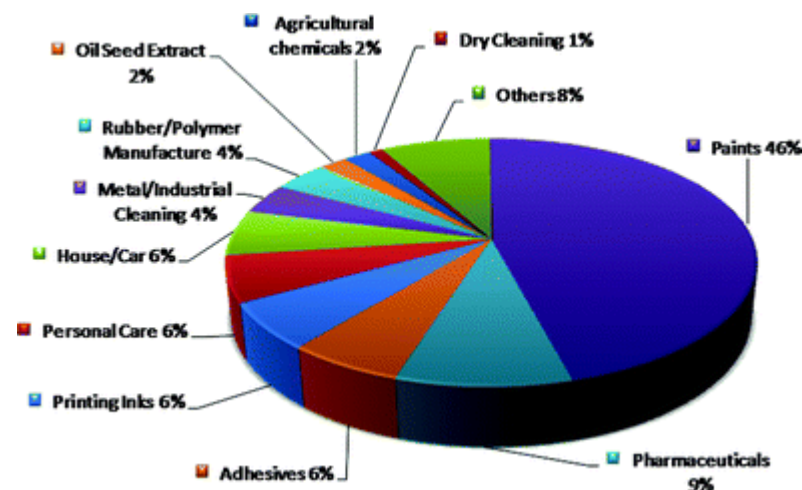
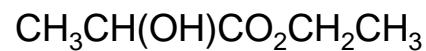
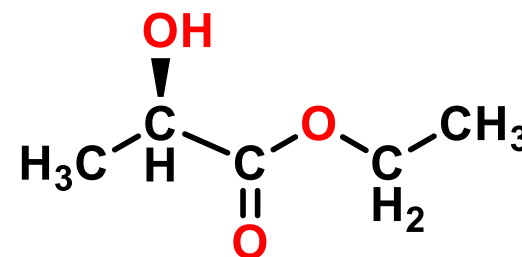


Figure 1: Total Solubility Parameter vs Surface Tension



## Esters of Lactic Acid.

- Low cost, high purity lactate esters, e.g. **ethyl lactate**, for use as "green solvents" environmentally benign.
- Attractive solvent properties:
  - Biodegradable,
  - Easy to recycle,
  - Non-corrosive,
  - Non-carcinogenic
  - Non-ozone depleting
  - Good solvent for variety of processes
- Made from renewable sources (carbohydrates), such as corn or food-processing wastes.
- potential to replace approximately 80% of the petroleum-derived solvents now in use.
- Commonly used in the paint and coatings industry.



<http://www.er.doe.gov/epic/html/GreenSolvents.htm>



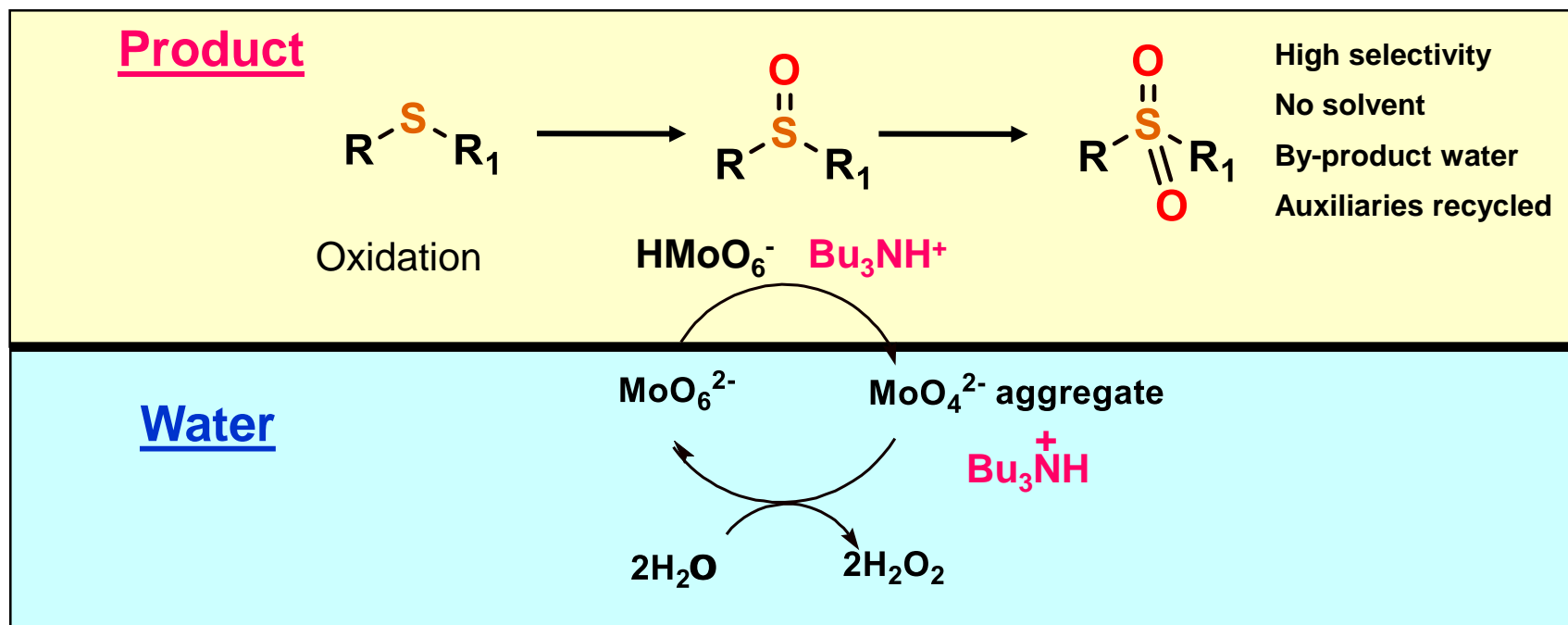
## Alternative Solvent Systems/Mixtures.

### ➤ Isomet

- Mixture of isoparaffinic hydrocarbon, propylene glycol monomethyl ether, and isopropyl alcohol
- Replaces Typewash (mixture of methylene chloride, toluene, and acetone)
- Excellent performance in postage stamp and overprinting presses
- Acceptable properties (cleaning ability, solvent evaporation rate, odor, environmental compliance, and cost).

## Biphasic Systems.

- Uses two immiscible solvent and aims to keep the catalysts and reagents in separate phases – easier separation.
- Generally based on aqueous/organic systems (i.e. in  $\text{H}_2\text{O}_2$  oxidation).
- Phases are made homogeneous by stirring, ultrasound or heating.





## Neoteric Solvents.

- Aim is to design new fluids which have tuneable properties.
- Some already in large scale usage, others have the potential to become valuable sustainable solvents.
- The term cover:
  - ionic liquids (LMQA)
  - supercritical fluids,
  - liquefied gas,
  - gas expanded liquids,
  - eutectic solvents, and
  - polymeric solvents.



## Liquefied Gases.

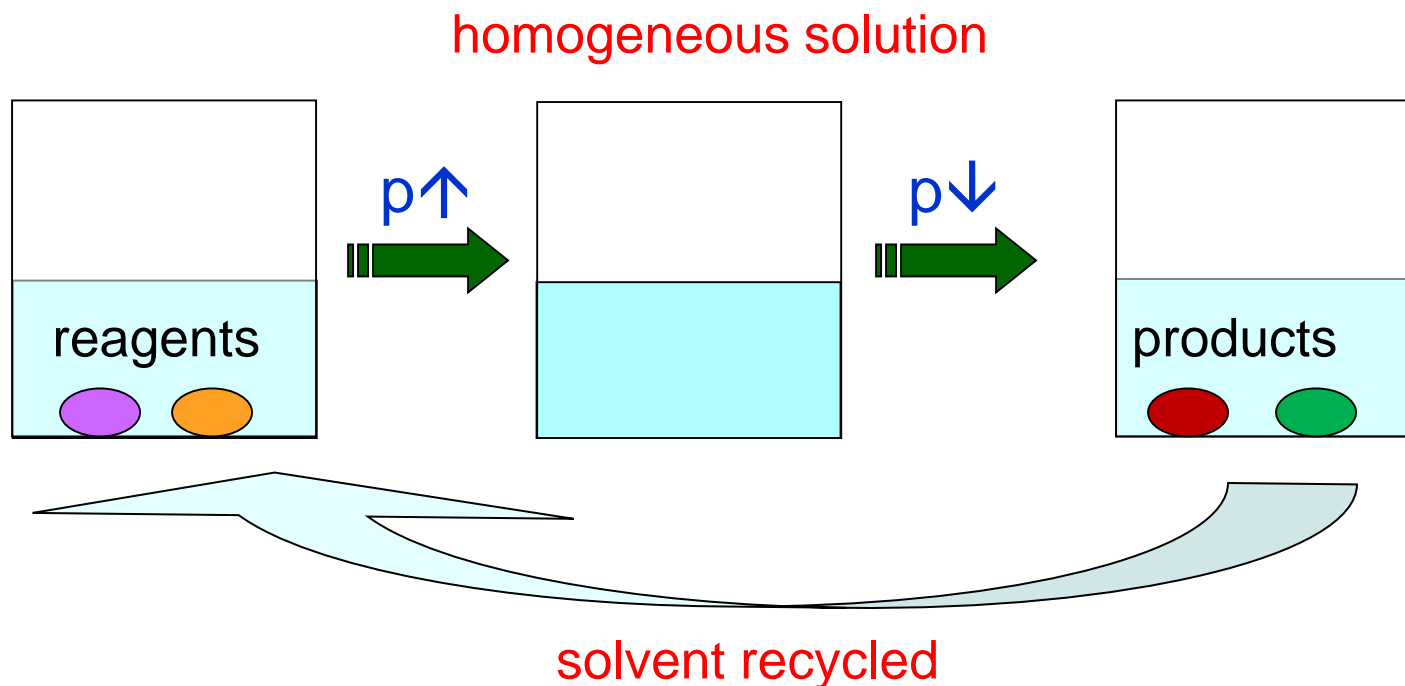
- Liquefied gases are gases that become liquid at normal temperatures when they are pressurized inside a gas cylinder. The cylinder is initially filled as a liquid. The liquid then evaporates to a gas and saturates the head space above the liquid and maintains liquid-vapor equilibrium. As gas is released from the cylinder, enough liquid evaporates to the head space, thus keeping the pressure in the cylinder constant. Examples of liquefied gases include ammonia, carbon dioxide, chlorine, methane, natural gas, propane, and CHC.
- Currently used primarily for extraction also used as aerosol propellants.
- Carried out on an industrial scale (low pressures c.a. 4 bar).
- Use HFCs (non ozone depleting, non-toxic, non-flammable, but they are greenhouse gases with long lifetimes).

*[www.ineosfluor.co.uk](http://www.ineosfluor.co.uk)*

*[www.advancedphytonics.co.uk](http://www.advancedphytonics.co.uk)*

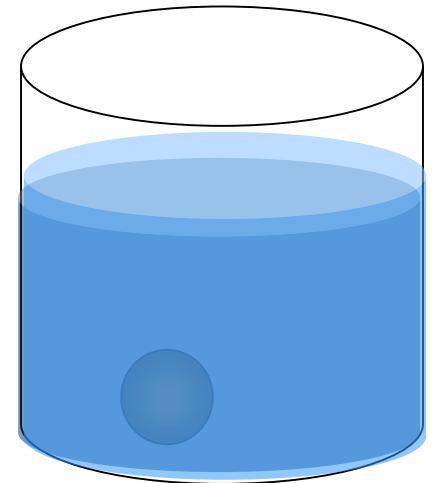
## Liquefied Gases.

- Gas-liquid transitions can be controlled by pressure – more energy efficient.
- Useful when solvent residues are an issue.



## Gas Expanded Liquids (GXLs).

- A GXL is a mixed solvent composed of a compressible gas (such as  $\text{CO}_2$  or ethane) dissolved in an organic solvent.
- Aim to change the properties of a liquid by pressurizing with a gas – generally small pressure changes.
- Large potential for non-toxic tunable solvent, e.g.  $\text{CO}_2/\text{H}_2\text{O}$ .
- Class I liquids, such as water, have insufficient ability to dissolve  $\text{CO}_2$  and to expand. Class II liquids such as methanol, hexane, and most other traditional organic solvents, dissolve large amounts of  $\text{CO}_2$ , expand appreciably, and undergo significant changes in physical properties.





## Solvent Effects (References).

1. **Solvent Effects in Organic Chemistry**  
C. Reichardt VCH, 1989, 2<sup>nd</sup> Ed.
2. **Solvent Recovery Handbook**  
I. Smallwood, E. Arnold June 1993 (ISBN 0-340-57467-4)
3. **Industrial Solvents Handbook**  
E.W.Flick, Noyes Data Corporation 1985 (2<sup>nd</sup> Ed.) ISBN 0-8155-1010-1
4. **Hansen Solubility Parameters: A user's handbook, II Ed.**  
C.Hansen, (2007). Boca Raton, Fla: CRC Press
5. **Green Solvents I and II - Properties and Applications in Chemistry**  
Mohammad, Ali, Dr., Inamuddin (Eds.) 2012, XVIII, 430 p.
6. **Alternative Solvents for Green Chemistry (2)**, F. Kerton, R. Marriott 2013.
7. Hutchenson, K., et al.; ACS Symposium Series; ACS, DC, 2009