Solvents and Green Chemistry

IGSS'09

Carl Lecher, Ph.D.

Assistant Professor of Chemistry

Director of the Marian University Institute for Green and Sustainable Science

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Why Are Reactions Performed Using Solvents?

- To dissolve reactants.
- To slow or increase the rate of reactions.
- To act as a heat sink or heat transfer agent.
- To prevent hot spots and run-away reactions.

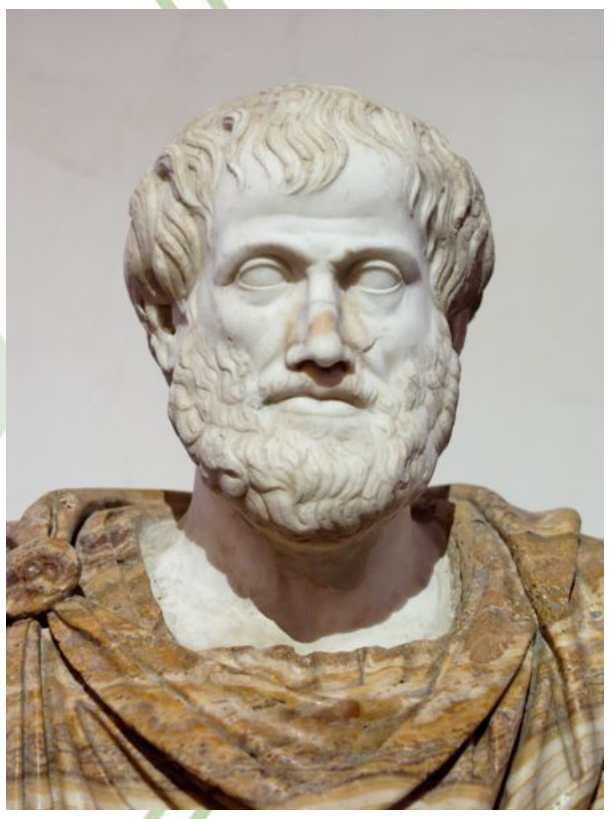
Issues with Organic Solvents

- Organic solvents are of concern to the chemical industry because of the sheer volume used in synthesis, processing, and separation.
- Organic solvents are expensive
- Organic solvents are highly regulated.
- Many organic solvents are volatile, flammable, toxic, and carcinogenic.

“No Coopora nisi Fluida”

- Aristotle believed that “No reaction occurs in the absence of solvent.”

  (This is not true!)



Solvent alternatives

A. Use of solventless reactions

B. Use of “non-organic” solvents

C. Processing technology

Advantages to Solventless Organic Reactions

- There is no reaction medium to collect, purify, and recycle.
- Reaction times can be dramatically shortened.
- Lowered energy usage.
- Considerable reduction in batch size volume.
- Less expensive.

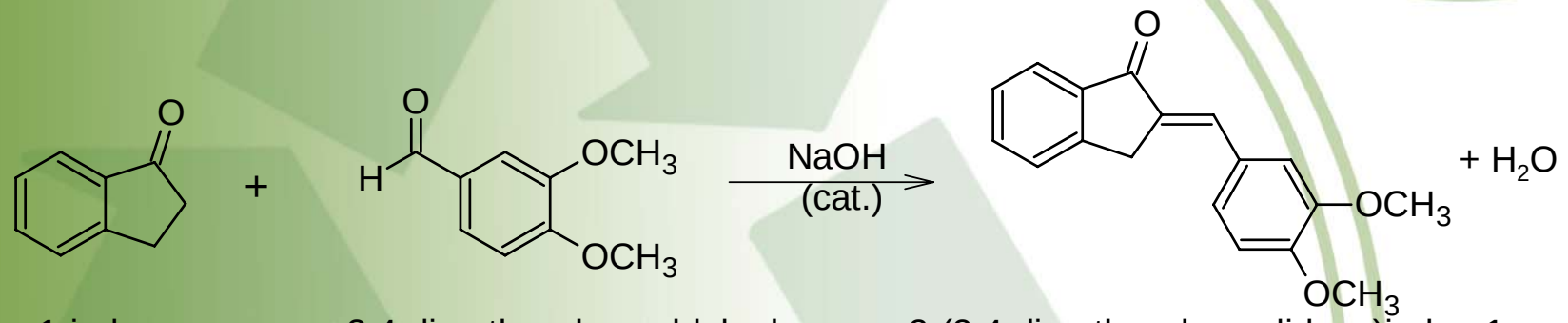
Ways to be Solvent-Free

- **Neat** – reagents react together in the liquid phase in the absence of a solvent.

- **Solid-state synthesis** – two macroscopic solids interact directly and form a third, solid product without the intervention of a liquid or vapor phase.

Neat, isn't it!

A Solventless Atom Efficient Reaction: The Crossed-Aldol Condensation



1-indanone
C_9H_8O = 132.16
m.p. 40-42°C

3,4-dimethoxybenzaldehyde
$C_9H_{10}O_3$ = 166.18
m.p. 42-45°C

2-(3,4-dimethoxybenzylidene)indan-1-one
$C_{18}H_{16}O_3$ = 280.32
m.p. 183 -185°C

Examples - Neat

- Baylis-Hillman reactions[1]
- Aldol additions[2]

1. For a review, see: Ciganek, E. *Organic Reactions*, **1997**, *51*, 201.,
2. For a review see: Tanaka, K.; Toda, F. "Solvent-Free Organic Synthesis" *Chem. Rev.* **2000**, *100*, 1025-1074.

Examples – Solid State

- Oxidations
- Reductions
- Halogenations and Hydrohalogenations
- Michael Additions and Aldol Additions
- Elimination Reactions
- [2+2], [4+2], and [6+2] Cycloaddition Reactions
- Aldol Condensation Reaction

For a review, see: Tanaka, K.; Toda, F. "Solvent-Free Organic Synthesis" *Chem. Rev.* **2000**, *100*, 1025-1074.

Limitations

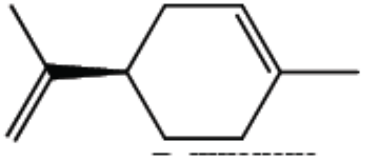
- Not all reactions will work in the absence of solvent.
- Function of catalysts.
- Exothermic reactions are potentially dangerous.
- Specialized equipment needed for some procedures.
- If aqueous quench and organic extraction are performed, this reduces green benefits.

Use of non-organic solvents

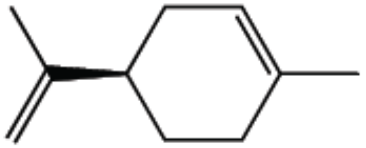
- Liquid and supercritical CO_2
- Ionic liquids
- Fluorous Phase Chemistry
- Water

Liquid CO_2 as a green extraction solvent

Traditional Method

Orange Peel $\xrightarrow[\text{and/or}\ \text{Organic solvent}]{\text{Steam distill}}$ 

Green Method

Orange Peel $\xrightarrow[\textbf{No}\ \text{organic solvent}]{CO_2(\text{liquid})}$ 

Chemical Concepts:

- Solid/liquid extraction
- Natural products (terpenes)
- Spectroscopy
- Phase transitions

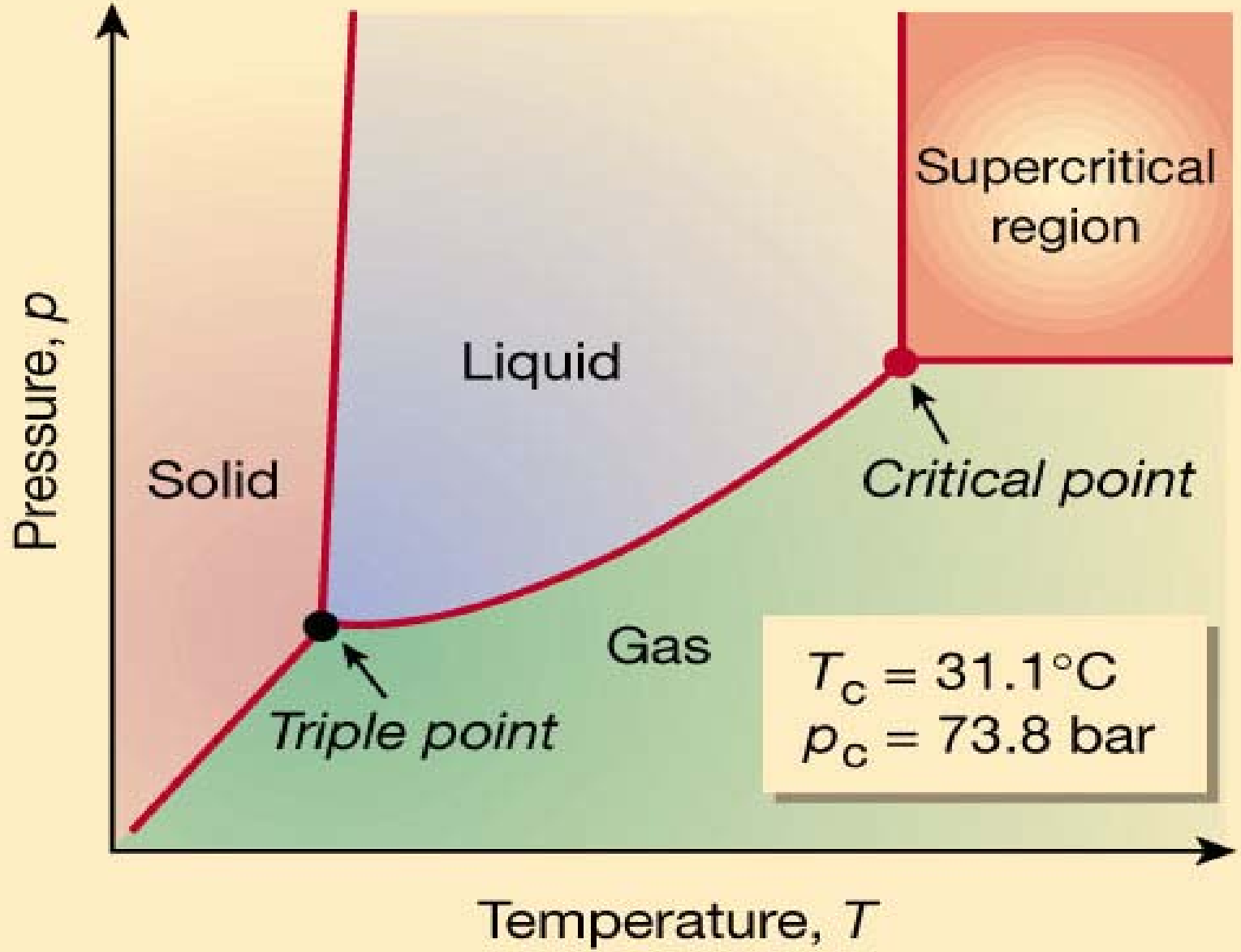
Green Lessons:

- Use of safer solvents
- Prevention of waste
- Green materials processing

McKenzie, L. C.; Thompson, J. E.; Sullivan, R.; Hutchison, J. E. "Green chemical processing in the teaching laboratory: A convenient liquid CO2 extraction of natural products," *Green Chem.* **2004**, 355-358.

Supercritical CO_2

- What does it mean to be supercritical?


Supercritical region
Liquid
Solid
Critical point
Gas
Triple point
$T_c = 31.1°C$
$p_c = 73.8$ bar
Pressure, p
Temperature, T

Properties of $scCO_2$

- Combination of properties from both the liquid and gas state.
- At liquid-like densities, $scCO_2$ exhibits low viscosity and high diffusion rates.
- High compressibility of the supercritical phase allows for solvent properties to be varied by small changes in temperature and pressure.

Properties of scCO_2

- Can be handled in standard high-pressure equipment on lab or industrial scale.
- Non-toxic, non-flammable, and inexpensive.
- Non-protic and generally unreactive.
- Product isolation to total dryness is achieved by simple decompression.
- CO_2 can be recovered and reused.

Commercial Applications of $scCO_2$

- Natural product extraction (decaffeination)
- Polymer synthesis
- Dry cleaning

Examples of $sc CO_2$ as Solvent in Synthetic Organic Chemistry

- Hydrogenation
- Hydroformylation
- Photochemical and radical reactions
- Dies-Alder cycloadditions
- Oxidations
- Palladium mediated couplings
- Biotransformations

For a review, see: Oakes, R. S.; Clifford, A. A.; Rayner, C. M. "The Use of Supercritical Fluids in Synthetic Organic Chemistry" *J. Chem. Soc*., *Perkin Trans. 1*, **2001**, 917–941.

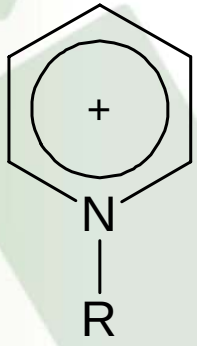
Limitations of $sc CO_2$

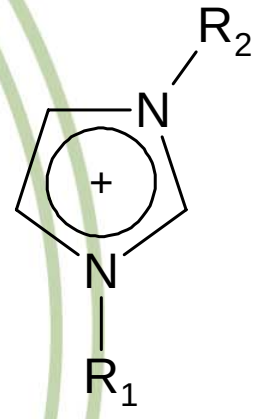
- Poor solubility of many substrates in $sc CO_2$.
- Modifiers (organic solvents) can be added to regulate solubility, but this move the process away from being green.
- CO_2-philic surfactants are being developed.
  - Are expensive and have to be separated from products.

Ionic Liquids

- Organic salts with melting points below 100°C, often below room temperature.

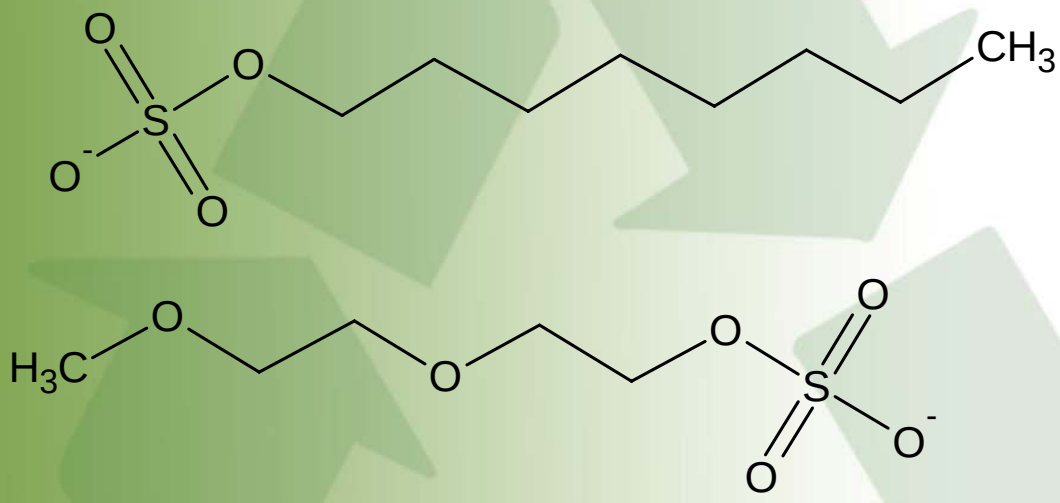
$[NR_xH_{4-x}]^+$ $[PR_xH_{4-x}]^+$

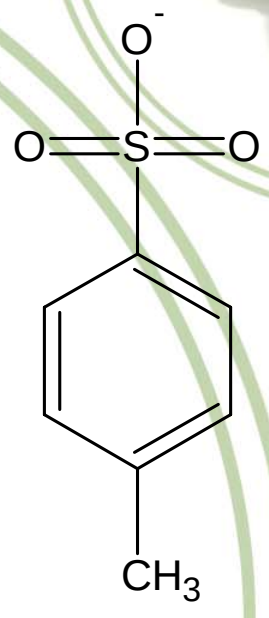




alkylammonium, alklyphosphonium, N-alkykpyridinium, and N,N'-dialkylimidazolium cations

Examples of Common Anions





octyl sulfate, 2-(2-methoxyethoxy)ethyl sulfate, and tosylate anions

BF_4^- PF_6^- SbF_6^- $CH_3CO_2^-$ HSO_4^- NO_3^- NO_2^- $AlCl_4^-$

Properties of Ionic Liquids

- Good solvents for a wide range of both organic and inorganic materials.
- Have potential to be highly polar yet non-coordinating.
- By varying cations and anions, ionic liquids can be tailored for specific applications.
- Possibility for reaction rate enhancement, higher selectivity and higher yields.

Properties of Ionic Liquids

- High thermal stability
- Often immiscible with organic solvents and/or water
- No measurable vapor pressure
- Non-flammable
- Can be recycled

- Are they safer than solvents?

Ionic liquids have been used as solvents in a variety of reactions

- Heck Reaction[1]
- Friedel-Crafts reactions[2]
- Diels-Alder reactions[3]
- Hydrogenation reactons[4]

1. Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Let.* **1999**, *1*, 997.
2. Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. *Chem. Commun.* **1998**, 2097.
3. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**,*1*, 23.
4. (a) Fisher, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett*. **1999**, *40*, 793.
   (b) Adams, C. J.; Earle, M. J.; Seddon, K. R. *Chem. Commun.* **1999**, 1043.

Other Applications of Ionic Liquids

- As biphasic systems in combination with organic solvent or water in extraction and separation technologies.
- For catalyst immobilization and recycling.
- As electrolytes in electrochemistry.

Limitations of Ionic liquids

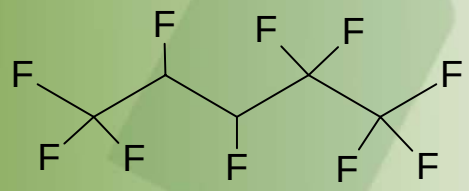
- Very expensive compared to organic solvents (100 to 1000 x).
- Have to be made, often using solvent.
- Products have to be extracted from ionic liquid using solvent.
- May have to wash with water prior to reuse.

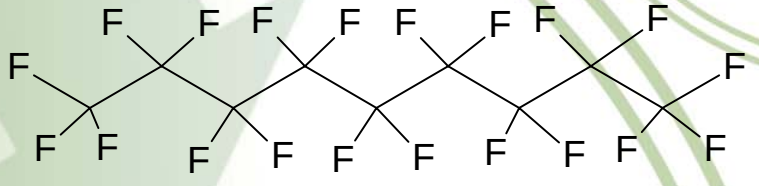
Fluorous Phase Chemistry

- What does it mean to be “fluorous”?
- What does it mean to be “perfluorinated”?

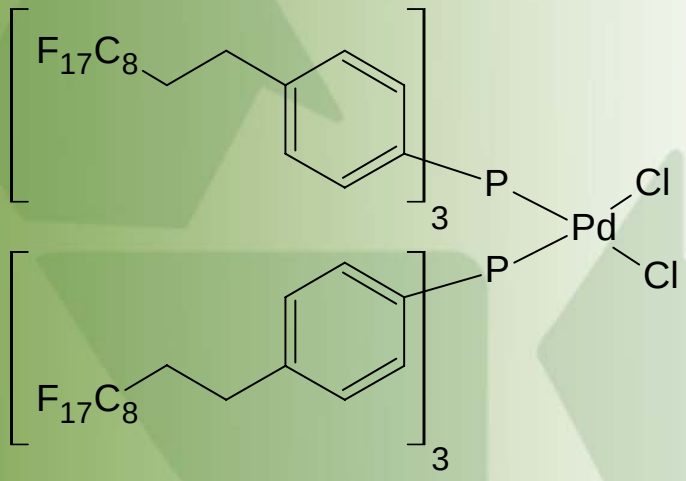
Check out all the fluorine!

Perfluorous Solvents

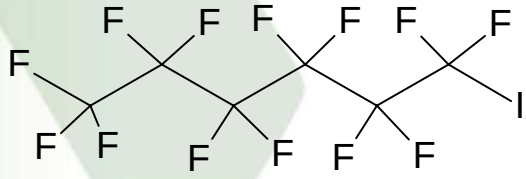


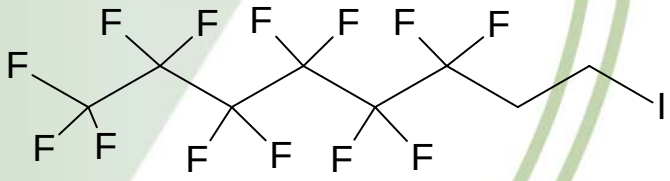


Perfluorous Catalyst



Perfluorous Tags





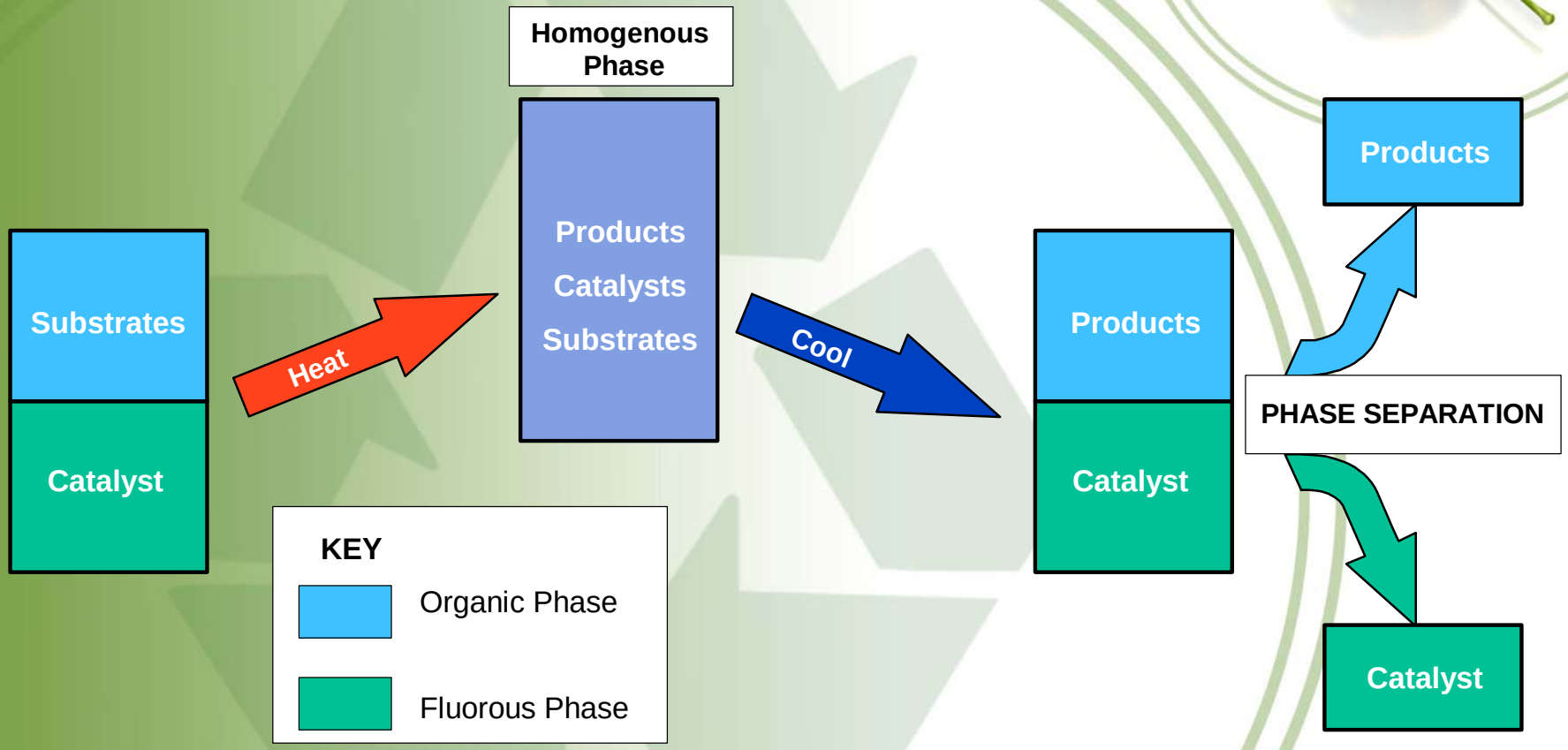
Physical Properties of Perfluorinated Organic Compounds

- High affinity for other fluorinated compounds.
- High solubility in $scCO_2$.
- Immiscible in water and most common organic solvents at room temperature.
- Forms homogenous solutions at elevated temperatures with many of these solvents.
- Chemically inert.
  - Is this good or bad?

Uses for Fluorous Chemistry

- For the recovery and recycling of fluorous catalysts and fluorous reagents.
- Fluorous biphasic organic synthesis.

Principle of Fluorous Biphase Catalysis



Advantages

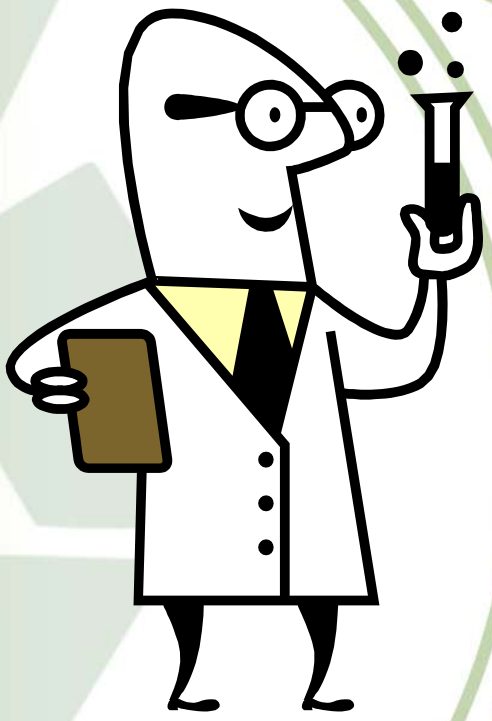
- Facile recovery of expensive catalysts.
- Complementary to other biphase chemistries.
- More facile separation.
- Design of novel catalysts and reagents.
- Alternative to the solid phase in combinatorial chemistry.
- Non-toxic?

Limitations

- Fluorous solvents and reagents are very expensive.
- 60% fluorine is usually considered the lower cutoff point for efficient fluorous extraction.
- Still requires use of a second solvent for biphase.

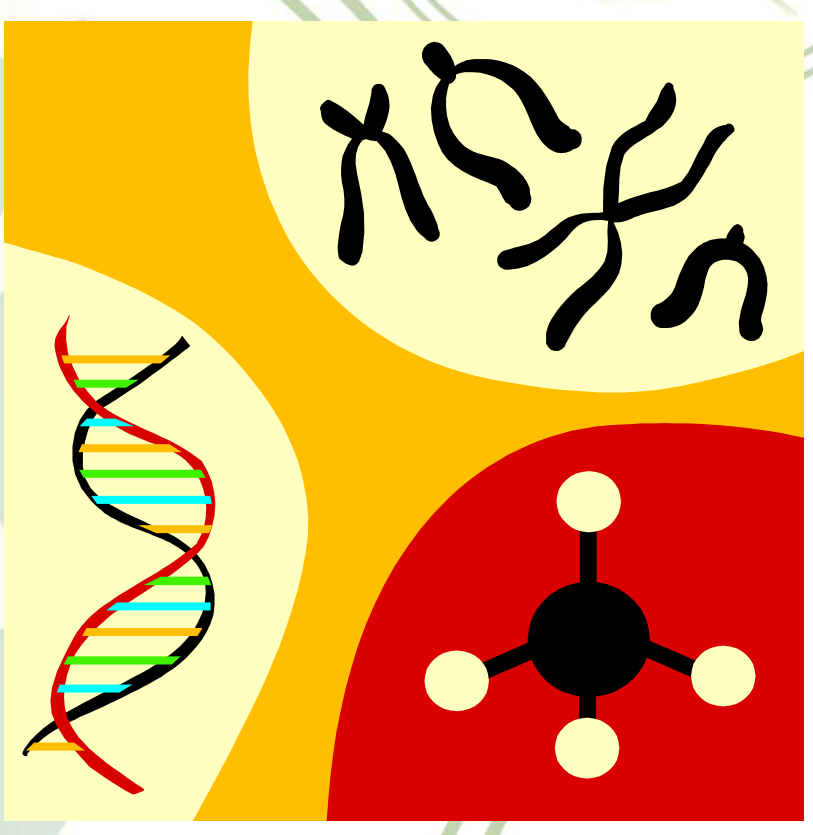
Organic Reactions in Aqueous Media

- Water – Isn't that bad for my organic reaction?

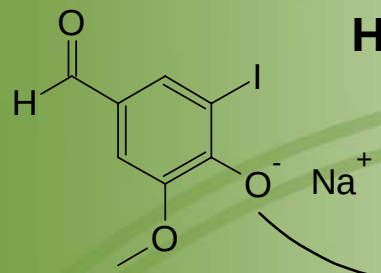


Organic Reactions in Aqueous Media

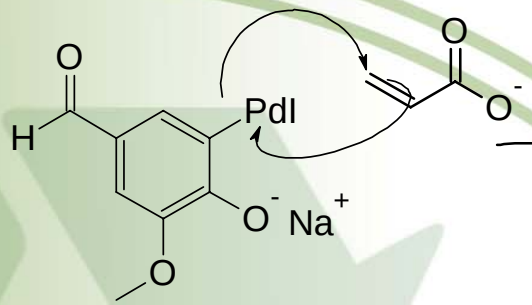
- Most of the world's chemistry occur in aqueous media.



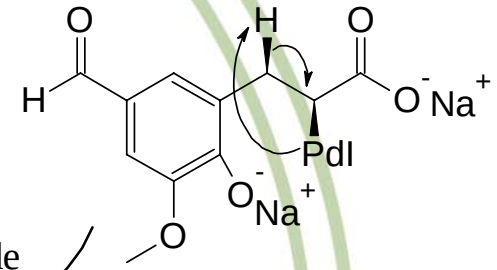
Heck Reaction in Water - new for Spring 2009



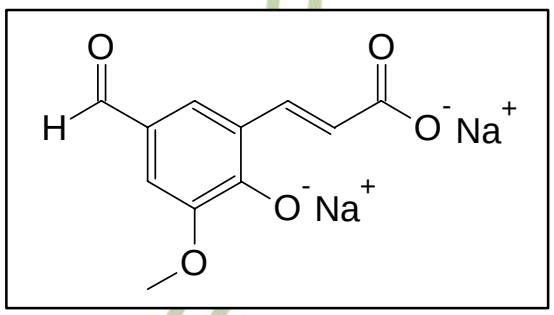
oxidative addition



olefin insertion



syn beta-hydride elimination



$I^- + HCO_3^-$

Start Here

Pd^0

Example Aqueous Reactions

- Diels-Alder reactions[1]
- Claisen-rearrangement[2]
- Aldol reactions[3]
- Allylation reactions[4]
- Oxidations[5]
- Hydrogenations[6]

1. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
2. Gajewski, J. J. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998.
3. Kobayashi, S. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998.
4. Lu, W.; Chan, T. H. *J. Org. Chem.* **2001**, *66*, 3467.
5. Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **2001**,*40*, 3455.
6. Nagel, U.; Albrecht, J. *Top. Catal.* **1998**, *5*, 3.

Why Water?

- Cost - water is the world's cheapest solvent.
- Safety – doesn't get any safer than water.
- Some reactions work better in water.

Limitations of Water as a Solvent

- Some reactions will never work in water.
- Poor solubility of most organic compounds.
- Solubility may be increased by use of organic co-solvents, pH control, surfactants, and hydrophilic auxiliaries.

Green Concerns of Water

- The product may need to be extracted into an organic solvent to purify it.
- This generates aqueous effluent containing solvent, which must be properly disposed.

Processing Technology

- The use of environmentally sound processing techniques in industrial chemical applications.

Processing Principles

- Greenness through technology
- Goal is to minimize the number of effluent streams generated and the quantity of each stream.
- Organic solvents are not necessarily bad.

Loss of Greenness

- Anytime water is used in an organic reaction, an additional waste stream is created.
  - Solvent
  - Aqueous quench / workup
  - Aqueous wash

Green Process

- A purely organic solvent-based process (with solvent-based workup), with solvent recovery, would generate little waste.
- The use of technology and good environmental practices to reduce VOCs.

Benefits of Organic Solvents

- Cheap relative to ionic liquids and fluorous solvents.
- Volatile – it takes less energy to remove solvents by evaporation.
- Solvents can be recycled by distillation, creating little waste.
- Regulated – Most countries already have industrial requirements limiting the release of VOCs.
- Chemistry is known.