# WATER AS A MEDIUM FOR ORGANIC SYNTHESIS: A GREEN CHEMISTRY

**SAAD MOULAY**

Laboratoire de Chimie-Physique Macromoléculaire
Département de Chimie Industrielle, Faculté des Sciences de L'Ingénieur,
Université Saâd Dahlab de Blida

**ABSTRACT :**

Chemistry has unraveled torrents of the world secrets and made sound achievements for the welfare of the mankind. Indeed, millions of synthetic substances have been made and, convenient routes for the synthetic purpose were developed and their mechanisms were stunningly deciphered. Organic synthesis stands as the pioneering lead in creating new chemical entities. Its astounding success in making some natural molecules of defying molecular architecture may throw some light of its supremacy. To cite but one example, it is through the organic synthesis that vitamin $B_{12}$ can now be produced on an industrial scale; to recall, the liver provides only 2-5 mg. The point is that vitamin $B_{12}$, an extremely and strikingly complicated natural molecule, is nowadays manmade.
On the other hand, the miracles of organic synthesis in entailing happiness, blessing, hope and promise are not wholly exempt of flaws, and this is undeniably a matter of fact. That is, upon hearing the term "organic", a dreadful feeling sneaks in one's body, and this stems from one's awareness of the toxicity and hazards of organics. Organic reactions involve the in-pot mixture of organic compounds and, are mostly carried out in organic media to assure a homogeneous phase. Thus, handling the organic reactants, the products and the solvents require stringent precautions in order to ward off any bit of one's body exposure. But, after the experimental work-up or the industrial manufacture operation, the product obtained is isolated not in an utterly pure form, despite an intensive purifying process; the huge amount of solvent, probably reused, is always discarded afterwards into the ground. As a consequence, the environment in its human, its air, its soil, and its waters forms is severely attacked and deleteriously affected. In this fashion, the synthetic chemist and the industrial manufacturer have been wreaking havoc in the nature whose beauty is still fading, despite the alarm ringing. But, the bountiful nature recalls the chemists to its alternatives and makes him mimic it so that to reduce the hazardousness of his synthetic pathways. One of the sustainable items that nature offers to the chemists is "water" that can be a surrogate for organic media.
In this conference, it is emphasized to look over the use of water as a medium in some synthetic reactions and techniques. Of the latter techniques are those employed in the radical polymerization of some vinyl monomers: suspension and emulsion polymerizations. Also, the polymerization of vinyl monomers in a water-based microemulsion (O/W) has been claimed. Some emulsion/polymer systems are environment favorably employed in paints.
Recent research has revealed the possibility of performing the polymerization of vinyl monomers in water-borne micromemulsions and results were even patented.
A sustaining interest has been focused within the last two decades on the use of water as a better medium for some well-known organic reactions. Indeed, the positive outcome of this research would promote the preference of water over the organic solvents and, hence, the synthetic chemist will not handle a limited amount of toxic chemicals. It is herein exemplified

by the following organic reactions: Some pericylic reactions including Diels-Alder’s and Claisen rearrangement, some aldol condensation reactions, some electrochemical syntheses, and some reactions involving organometallic reagents will be outlined.
Concluding remarks and spin-offs will be traced in the light of the illustrated examples.

# WELCOME TO JSTRE 2007

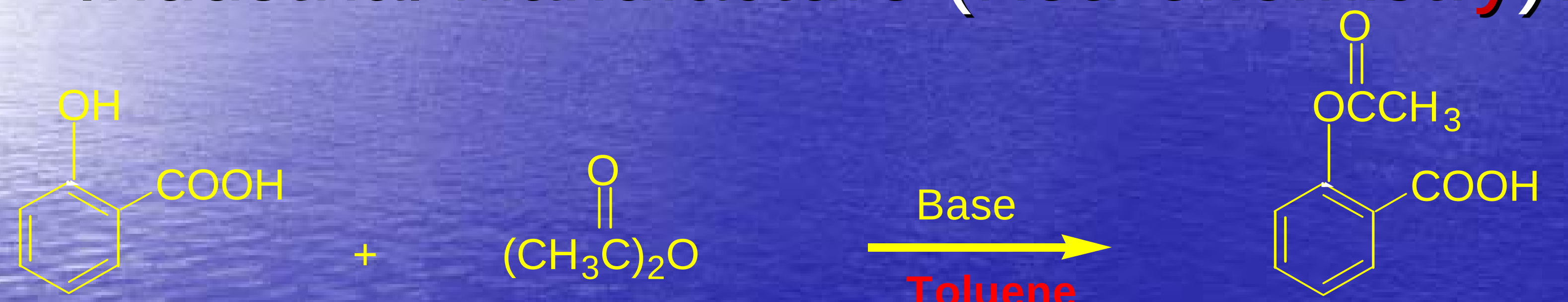
# THANKS FOR BEING HERE, TODAY

# WATER AS A MEDIUM FOR ORGANIC SYNTHESIS : A GREEN CHEMISTRY

***(Green chemistry vs. Red one).***

# ASPIRIN : The 20th century painkiller

## Conventional Synthetic Route of Aspirin Industrial Manufacture (Red Chemistry):




Salicylic acid Acetic anhydride **ASPIRIN**

(TOLUENE-CONTAMINATED ASPIRIN)

## Unconventional, Neat synthesis (Green Chemistry):

Salicylic acid + Acetic anhydride + CaO (or ZnO)

- One-pot synthesis
- No organic solvent (benzene, toluene, xylene)

E. Handal-Vega, A. P.D. Loupy, J. M. C. Garcia, *US patent 6278014*, **2001**.

# ORGANIC SOLVENTS

1. Excellent media for organic synthesis
2. Highly toxic
3. Flammable (Low flash points, $F_p$)
4. Product contamination
5. Costs associated with solvent disposal
6. Detrimental effects on the environment
7. Surge of chemophobia

Benzene, toluene, chlorinated hydrocarbons such as $CH_2Cl_2$ , $CHCl_3$, $CCl_4$ , and others.

The higher the [Cl], the greater the toxicity.

# Towards oxygenated solvents:

1. Esters: methyl acetate, ethyl acetate (nail varnish, flavoring and other applications)

2. Ethers: DEE, THF, Dioxane

3. Ketones: Acetone, MIBK, MEK

4. Alcohols: MeOH, EtOH, *i*-PrOH

# TOWARDS ENVIRONMENTALLY BENIGN AND FRIENDLY SYSTEMS

1. Supercritical fluids (SCF), (supercritical $CO_2$)
2. Solventless systems (neat: liquid reactants, solid-state reactions)
3. Ionic liquids
4. Ultrasound/Microwave systems
5. «On-water » and water-related systems

# Water: A Green, Natural and Biological Medium

1. Blood: A water-based natural emulsion, O/W;Hemoglobin (an organometallic substance) divinely dispersed in water.
2. Natural Rubber: A water-based natural emulsion,O/W; Poly(*cis*-isoprene) elegantly and homogeneously dispersed in water, in the *Hevea Brasiliensis* trunk. Latex.

3. Photosynthesis:

$xCO_2 + y\,H_2O$ + solar energy $\rightarrow C_x(H_2O)_y$

$C_x(H_2O)_y$ : Cellulose, Starch,....etc.

($H_2O$ as a reactant and a reaction medium)

4. Thousands of biological (organic) reactions in a hepatic living cell, in water.

5. Drugs are mostly organics. Nevertheless, their therapeutic effects occur in an aqueous environment.

# Man's endeavor has been to mimic the nature's lead.

***"For nature, in her designs, is the supreme master, and thriving to mimic her efficiency and elegance is a most rewarding endeavor".***

*My own belief, it is not nature but God.*

Nicolaou K.C. et al.,The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century, *Angew. Chem. Int. Ed.*, **2000**, 39, 44.

1. Delicateness in mimicking the biosynthesis.
2. Natural pathways are entirely the simplest and cleanest ones, of simpler starting materials, of milder reaction conditions, of lowest involved energy. One-pot reactions. *In vivo*
3. Relatively few synthetic pathways of similar behavior with the biosynthetic ones. Some are sluggish, heterogeneous, and require extreme reaction conditions. Usually, multi-component and multi-step reactions. *In vitro*
4. Water as a natural medium: The least and easiest component to mimic from nature.

# Water: A Greener Alternative

1. Cheap, Sustainable (economics)
2. Benign, Friendly (environment)
3. Innocuous, Harmless (health)
4. New reactivity (chemistry)

# Main Concerns of Organic Synthesis:

1. Formation of a new or the coveted compound (chemist's creativeness belief)
2. Quantitative yield
3. High Stereoselectivity (*trans:cis ratio; anti:syn ratio; endo:exo ratio; ee)*
4. High reaction rate

WATER HAS BEEN PRECLUDED FROM USE AS A MEDIUM IN ORGANIC SYNTHESIS FOR THE FOLLOWING REASONS:

- Low reaction rate
- Low yield of the desired product
- Possible water reaction: water-sensitive reactions

# WATER IN POLYMERIZATION

## *Non-Aqueous Solution Polymerization*

- Use of an organic solvent (industrial scale! : cost and toxicity aspects) (Red polym.)

- Viscosity and exothermicity can be remedied

## *Mass polymerization* *(Neat reaction)*:

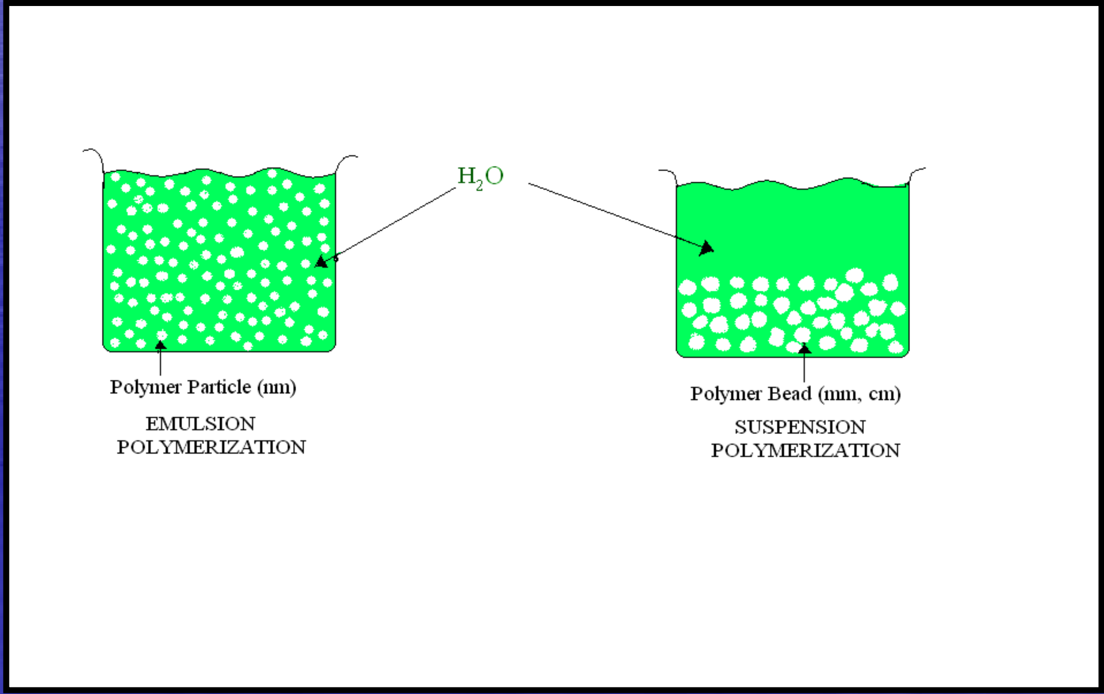
- no use of organic solvent (Green polym.)
- clean
- pure polymer

BUT

- Highly viscous (a hardship for handling)
- Highly exothermic (on an industrial scale, A BOMB !!!)

# Dispersion polymerization (Green Polymerization technique)

1. Suspension polymerization (04 ingredients).
2. Emulsion polymerization, O/W (1940s, USA, WWII); (07 ingredients). Latex.
3. Microemulsion(O/W) polymerization (Kaler et al., 2001).

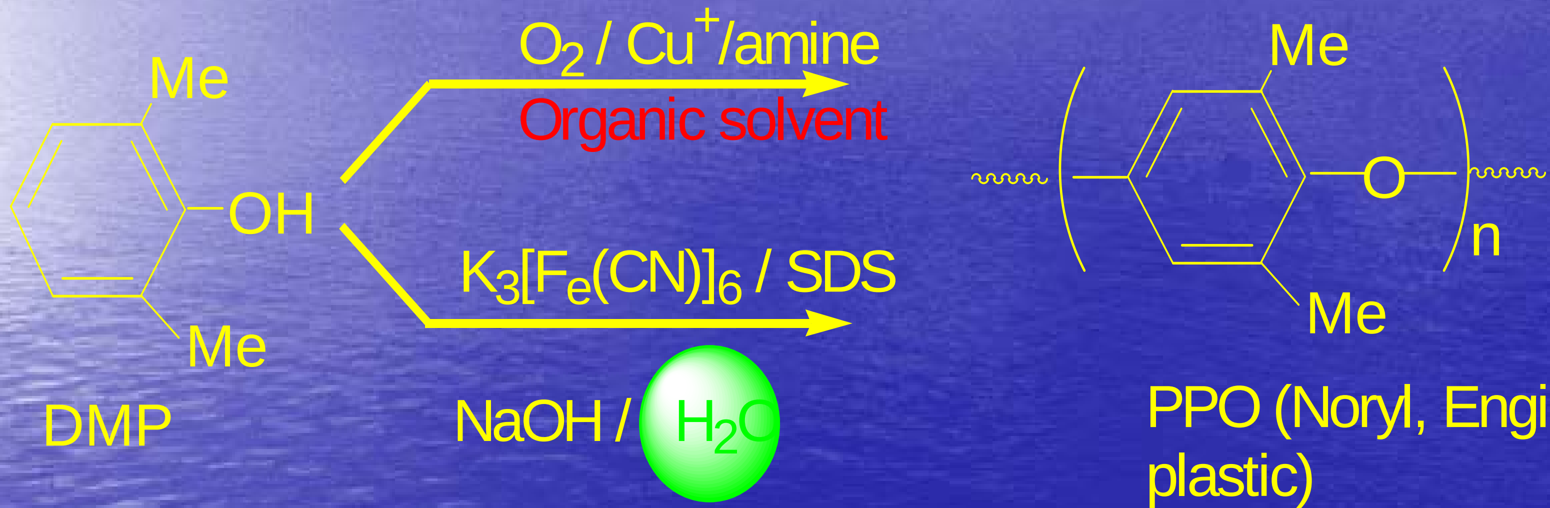


# **Water as a dispersing medium:**
## A safer work-up

Industrial applications:

- Ion-exchange resins (suspension polym.)
- Synthetic rubber (SBR), water-based paints, paper and wood sizing (emulsion polym.)

# *Oxidative Coupling Polymerization*

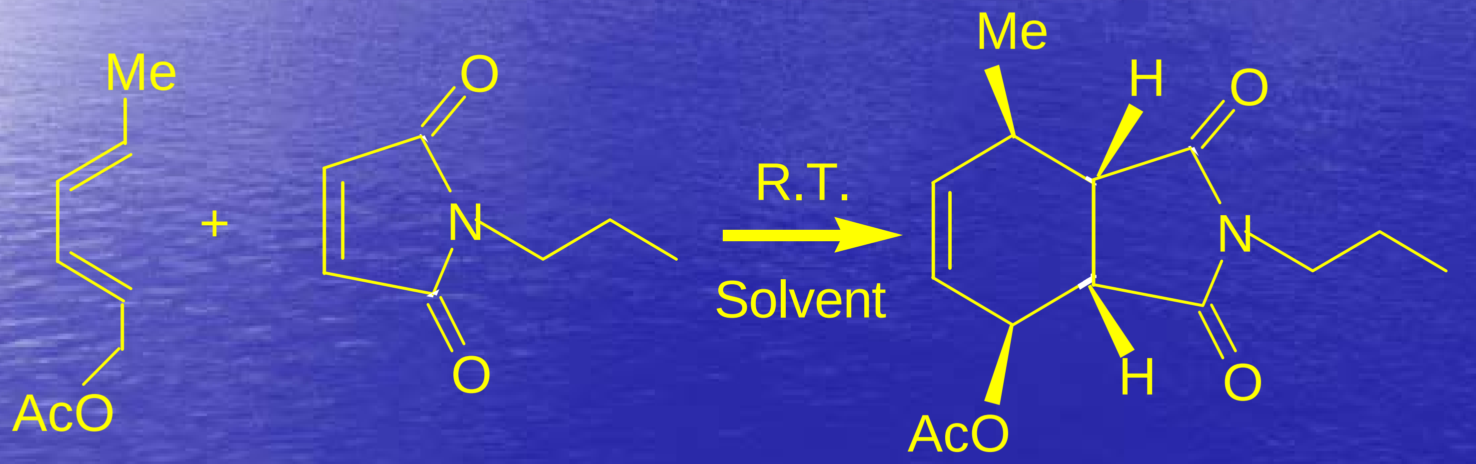



PPO (Noryl, Engineering plastic)

K. Saito et al., *Angew. Chem Soc.*, **2003**, 125, 5280.

# **WATER** IN MOLECULAR ORGANIC SYNTHESIS

1. *<u>Diels-Alder</u> (Pericyclic reaction)*




R. Breslow et al., *J. Am. Chem. Soc.*, **1980**, <u>102</u>, 7816.

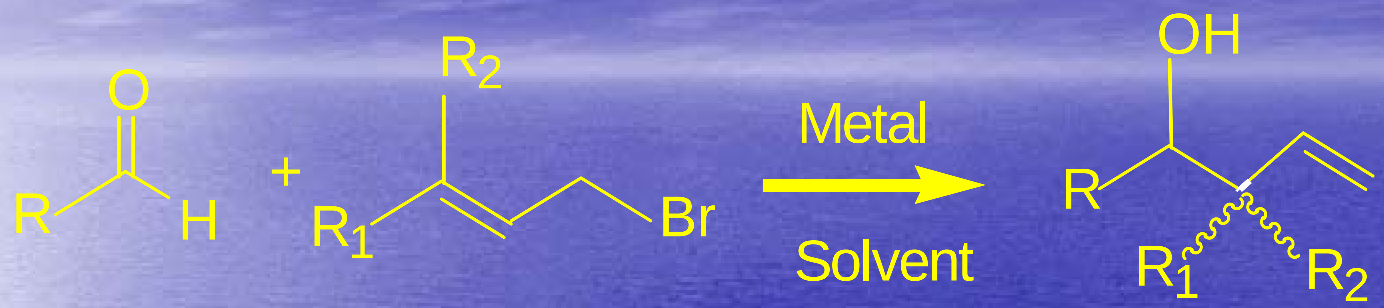
K. B. Sharpless et al., *J. Am. Chem. Soc.*, **2002**, <u>124</u>, 11971.

| Solvent | Time (h) | Yield (%) |
|---|---|---|
| Toluene | 144 (6 days) | 79 |
| $CH_3CN$ | > 144 | 43 |
| MeOH | 48 | 82 |
| $H_2O$ * | 8 | 81 |

* Suspension medium

# 2. *Reactions of Carbanions*

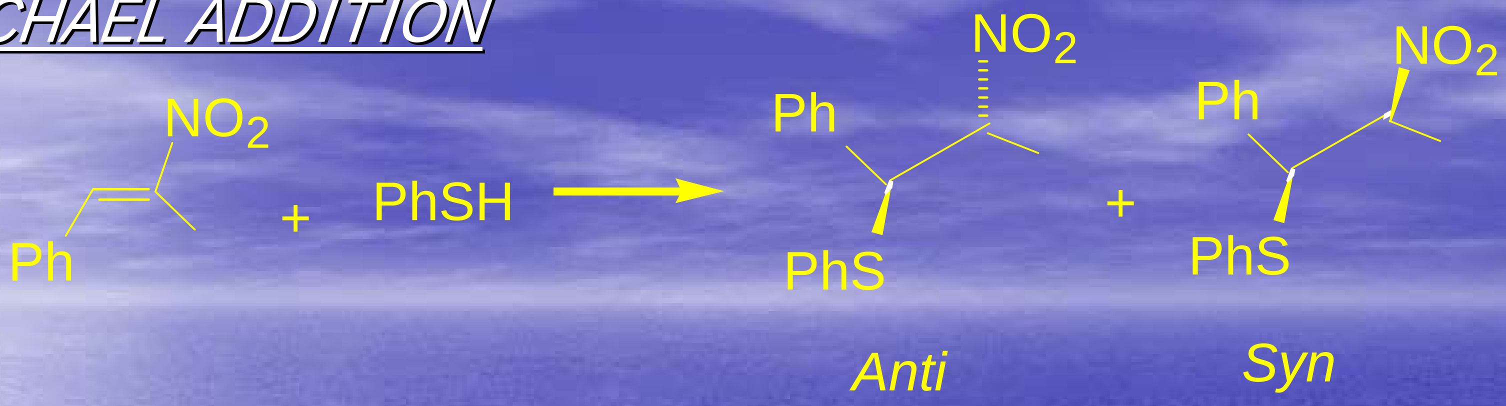
Organometallic reagents: RLi, RMgX, $R_2Cd$, $R_2Zn$, ...Etc.: Very sensitive to water (poison)




| Solvent | Time (h) | Yield (%) |
|---|---|---|
| DCM | 24 | 0 |
| DMF | 72 | 65 |
| $H_2O$ | 24 | 85 |

K. -T. Tan et al., *J. Am. Chem. Soc.*, **2003**, 125, 2958

## *MICHAEL ADDITION*

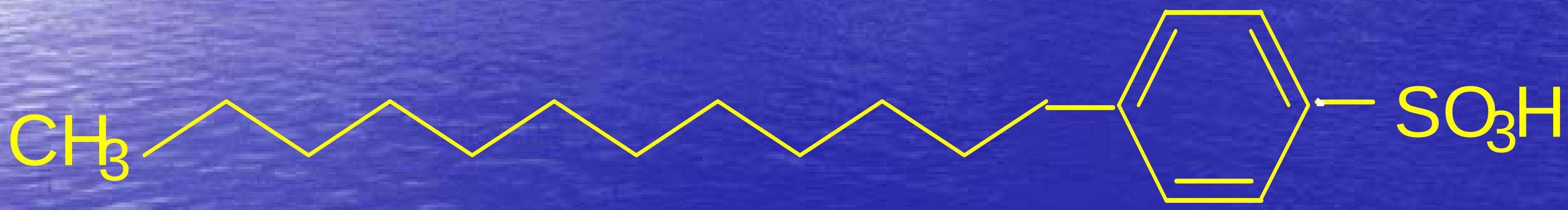



| Solvent | Base | Yield (%) | Time (h) | *Anti/Syn* |
|---|---|---|---|---|
| $CH_3CN$ [1] | $Et_3N$ | < 85 | 1 | 34:66 |
| $H_2O$ [2] | $NaHCO_3$ | 95 | 0.5 | 73:27 |

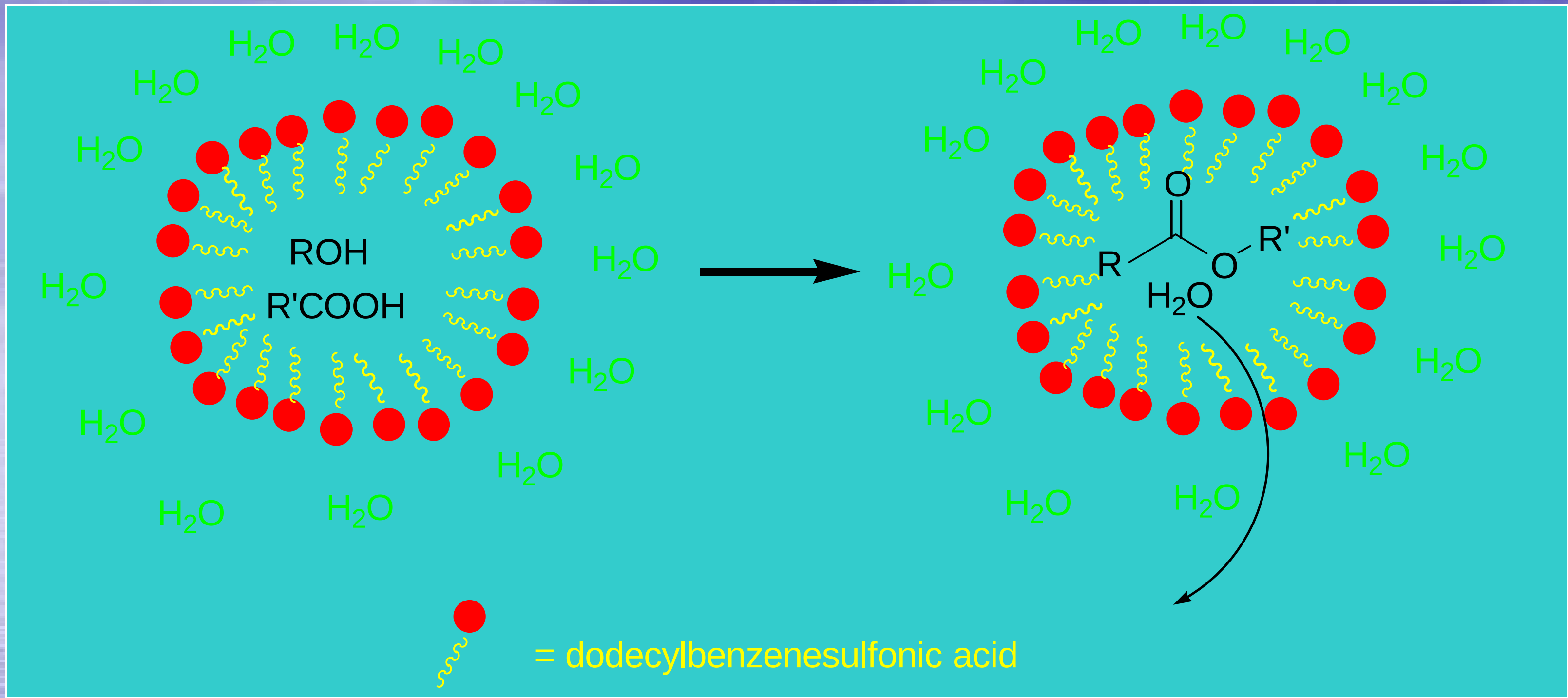

1. A. Kamimura et al., *J. Org. Chem.*, **1990**, 55, 2437.
2. F. M. da Silva et al., *J. Braz. Chem.Soc.*, **2001**, 12, 135.

# *3. Esterification reactions*


Bronstëd Acid-Surfactant Combined catalyst (BASC):




Dodecylbenzenesulfonic acid (DBSA)



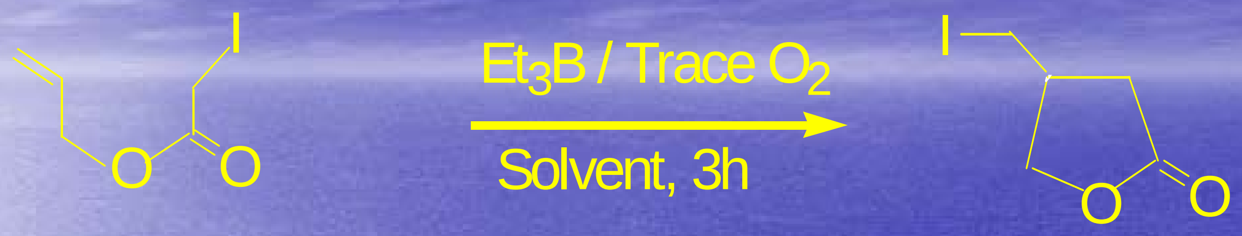

$$CH_3(CH_2)_{10}COOH + Ph(CH_2)_3OH \xrightarrow[H_2O,\ 40\ °C,\ 48\ h]{DBSA} CH_3(CH_2)_{10}COO(CH_2)_3Ph$$

89%

S. Kobayashi et al., *J. Am. Chem. Soc.*, **2002**, 124, 11971*; ibid.,* 5640.

# *3. Radical Reactions*

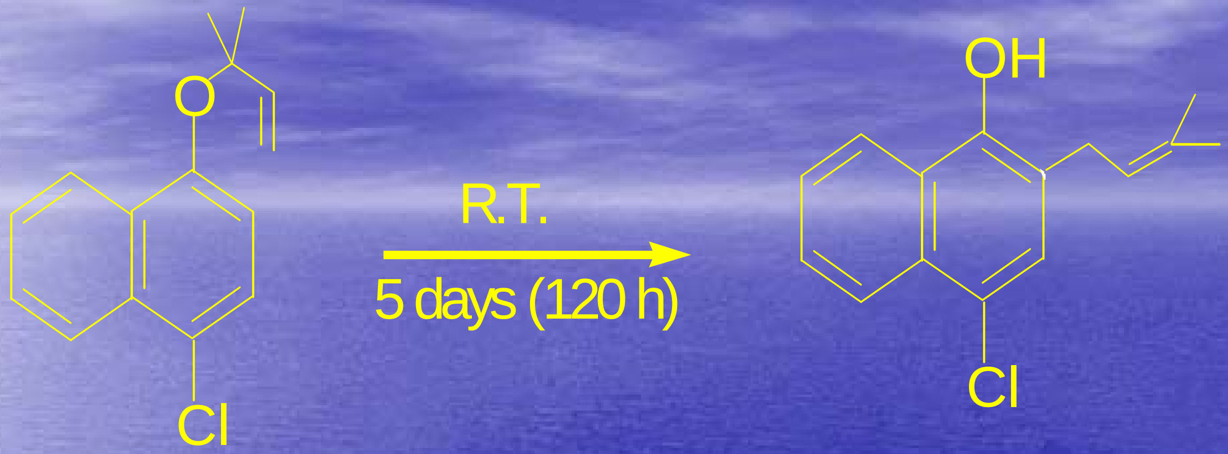
## Atom-transfer radical cyclization




| Solvent | Yield (%) | Solvent | Yield (%) |
|---|---|---|---|
| Hexane | 0 | DMF | 13 |
| Benzene | 0 | DMSO | 37 |
| THF | 0 | $H_2O$ | 78 |

T.Nakamura et al., *J. Am. Chem. Soc.*, **2000**, 122, 11041.

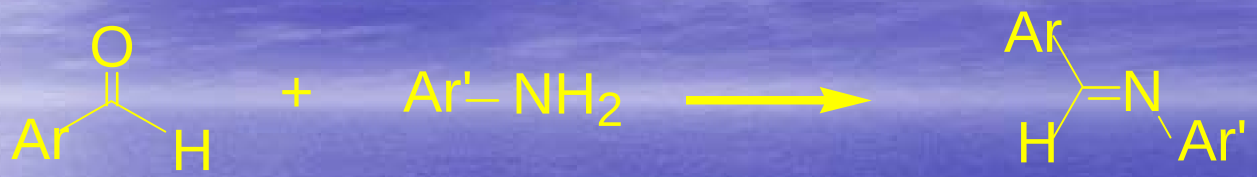
# 4. Claisen Rearrangement




| Solvent | Yield (%) | Solvent | Yield (%) |
|---|---|---|---|
| Toluene | 16 | MeOH | 56 |
| $CH_3CN$ | 27 | | |
| DMF | 21 | $H_2O$ | 100 |

K. B. Sharpless et al., *J. Am. Chem. Soc.*, **2002**, 124, 11971.

# 5. Aldehydes-Amines Condensation

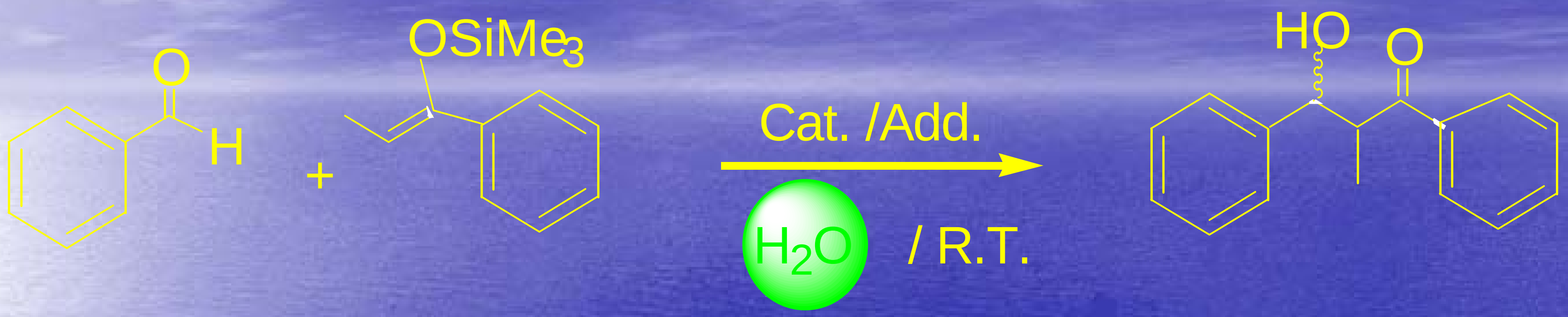



Aromatic aldehydes　　anilines　　Schiff's bases, imines

| Solvent | Yield (%) | Time | Catalyst |
|---|---|---|---|
| Benzene | 47-95 | Several hours | Acid |
| $H_2O$ | 86-98 | 0.5-3 h | Neat |

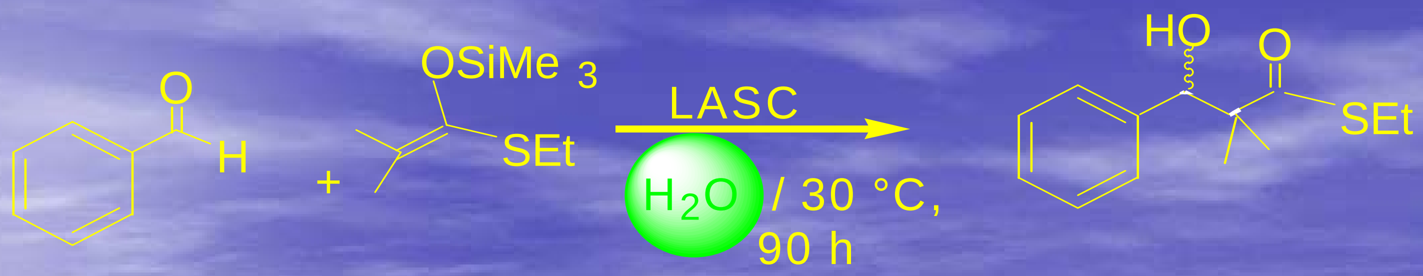
K. Tanaka et al., *Green Chemistry*, **2000**, 2, 272.

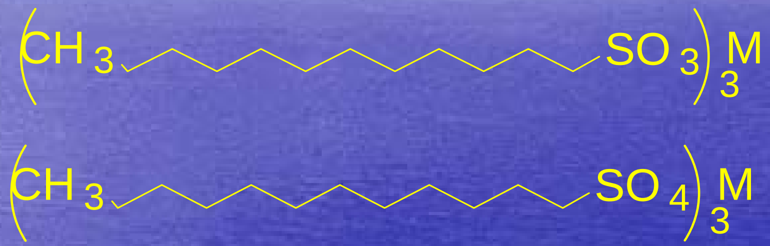
# 6. *Aldol Condensation*




| Catalyst/additive | Yield (%) |
|---|---|
| $Sc(OTf)_3$ / - | 3 |
| $Sc(OTf)_3$ / SDS | 88 |
| $Sc(DS)_3$ | 92 |

S. Kobayashi et al., *Acc. Chem. Res.*, **2002**, 35, 209.




LASC = Lewis Acid -Surfactant Combined Catalyst

| LASC | Yield (%) |
|---|---|
| $Sc(C_{12}H_{25}SO_3)_3$ | 90 |
| $Yb(C_{12}H_{25}SO_3)_3$ | 85 |

S. Kobayashi et al., *Pure Appl. Chem.*, **2000**, 172, 1373.

03/04/2007

# 7. Electrosynthesis


4-(-bromobutyl)-2-cyclohexen-1-one

1- decalone (*Trans* + *Cis*)

| Medium | Yield (%) | Stereoselectivity ratio (*trans:cis*) |
|---|---|---|
| DMF | Low | 3:1 |
| $H_2O$-based Microemulsion (O/W) | 90 | 93:7 |

J. M. Rusling, *Pure Appl. Chem.*, **2001**, 73, 1895.

# WORTHY CONCLUDING STATEMENTS

- EVER-INCREASING AND SUSTAINING HOPE, BASED ON THE WEALTH OF EXPERIMENTAL RESULTS FROM LITERATURE.

- WOULD THE 21ST CENTURY BE A CENTURY OF «ORGANIC REACTIONS IN WATER»??? !!!!

- THE EVERY CHEMIST'S WISH,... BUT A STRIVE TO FULFILL IT IS COMPULSORY.

- ORGANIC SYNTHESIS MUST BE FINE-TUNED TO THE NATURE, AND NOT THE OPPOSITE (THE OPPOSITE IS NOT, BY ALL MEANS, EVEN A MATTER OF FACT!!!!).

- ONLY IN THIS WAY CAN CHEMISTS PRIDE THEMSELVES AS HUMAN BENEFACTORS.

- A DECLINE OF THE PUBLIC ANXIETY TOWARDS CHEMISTRY, CHEMICALS, AND RELATED ITEMS: A RESET OF THE PUBLIC RELIANCE ON CHEMISTRY. TOWARDS A "CHEMOPHILIA"

- Narrowing the biochemistry /chemistry gap.

# FOR A FURTHER READING


1. C.,-J. Li and L. Chen, « *Organic Chemistry in Water* », Chem. Soc. Rev., **2006**, 35, 68-82.

2. K. B. Sharpless et al., « *On Water, Unique Reactivity of Organic Compounds in Aqueous Suspension* », Angew. Chem. Int. Ed., **2005**, 44, 3275-3279.

3. R. Breslow, Acc. Chem. Res., **2004**, 37, 471.

4. Niklaas Jan Buurma, «*Water, a Unique Medium for Organic Reactions »,* Ph.D Thesis, University of Groningen, **2003**.

5. R. Breslow, « *Hydrophobic Effects on Simple Organic Reactions in Water* », Acc. Chem. Res., **1991**, 24, 159-164.

# THAT'S ALL, FOLKS……