

# GREEN CHEMISTRY

Laurea Magistrale in Scienze Chimiche

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6 CFU – AA 2017-2018





Green Chemistry 08

# **SOLVENTS IN GREEN CHEMISTRY IV**

# Solvents in Green Chemistry



**Use safer solvents and auxiliaries**



# LIQUID POLYMERS

INTRODUCTION





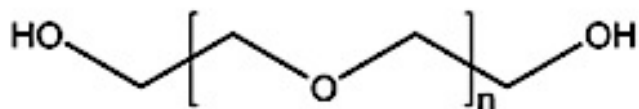
# Introduction

Low molecular weight polymers or those with low glass-transition temperatures can be used as nonvolatile solvents.

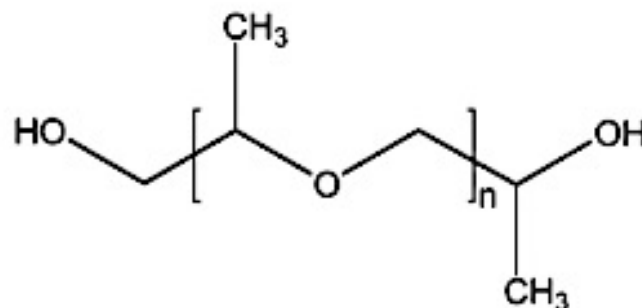
*Poly(ethyleneglycols)* – PEGs

*Poly(propyleneglycols)* – PPGs

have been used in a range of applications



PEG



PPG



# Properties



- They show interesting phase behaviour and allow the benefits of a heterogeneous and homogeneous system to be employed by adjusting an external variable such as temperature.
- PEGs are available in a wide range of molecular weights and complete toxicity profiles are available.
- PEGs and PPGs are water soluble and, therefore, many of their applications involve aqueous solutions. The higher the molecular weight of the polymer, the lower its solubility in aqueous solution.

# Properties

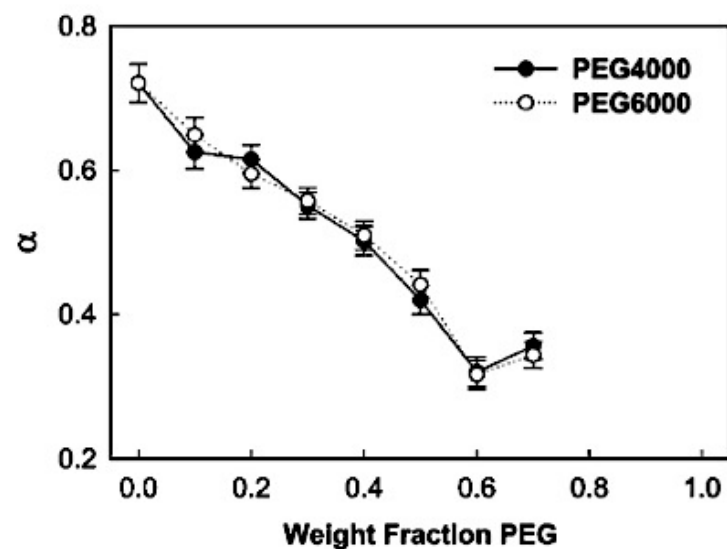
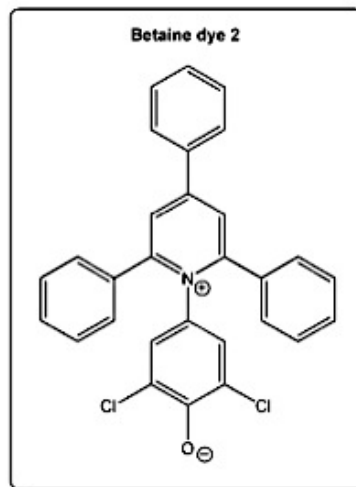
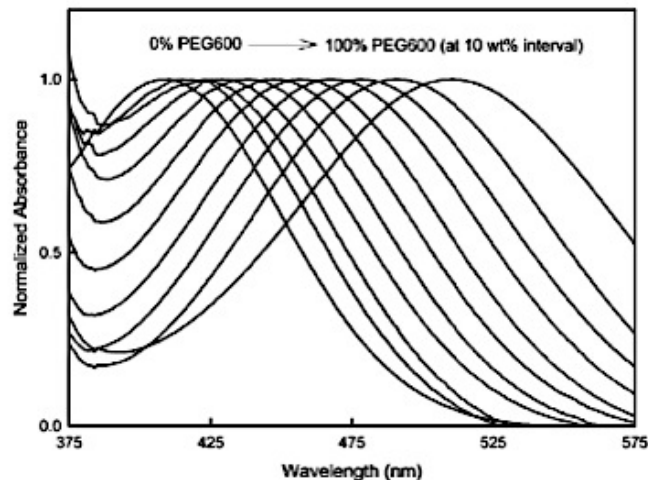


- **PPG is less hydrophilic than PEG of a comparable molecular weight.**
- **PEG has low flammability and low (to zero) vapour pressure.**
- **In contrast to many other alternative solvents, PEG is known to be biodegradable, biocompatible and, therefore, nontoxic.**
- **PEG can be recovered and recycled from solutions by extraction or direct distillation of the volatile component.**

# Properties



PEG acts as a cosolvent and imparts an apparent decrease in solution polarity and/or hydrogen-bond donating (HBD) acidity, which leads to an increase in solubility of organic molecules

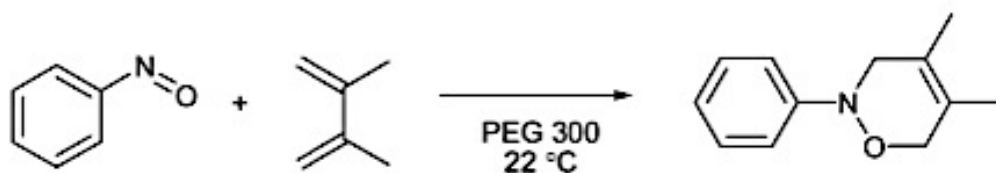




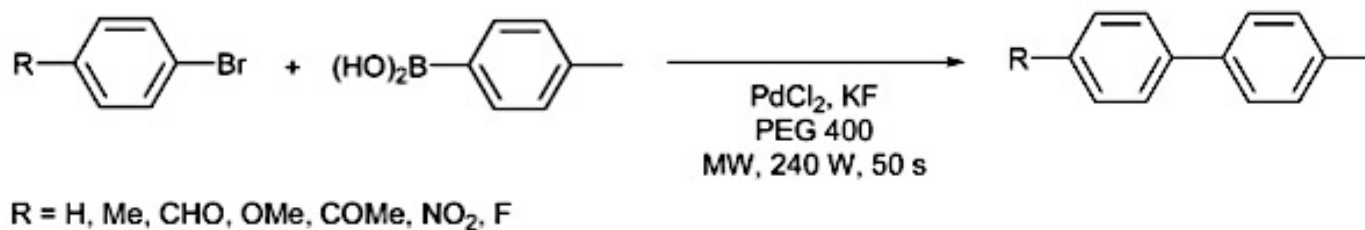
# PEG and PPG in Organic Synthesis



## Diels-Alder Reaction



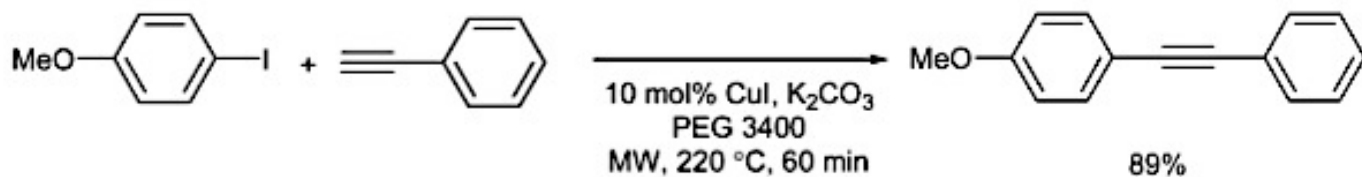
## Suzuki Cross-coupling Reaction



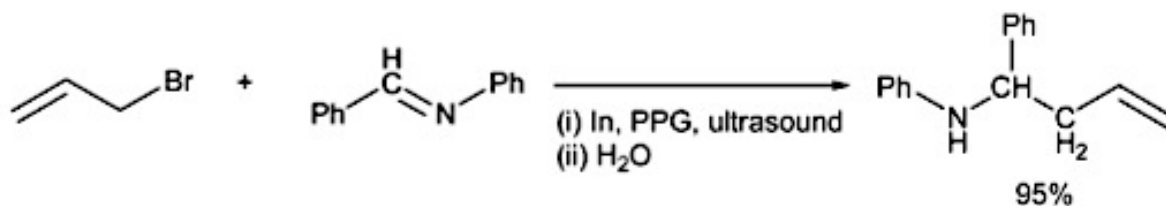
# PEGs and PPGs in Organic Synthesis



## Copper-catalyzed Sonogashira Reaction



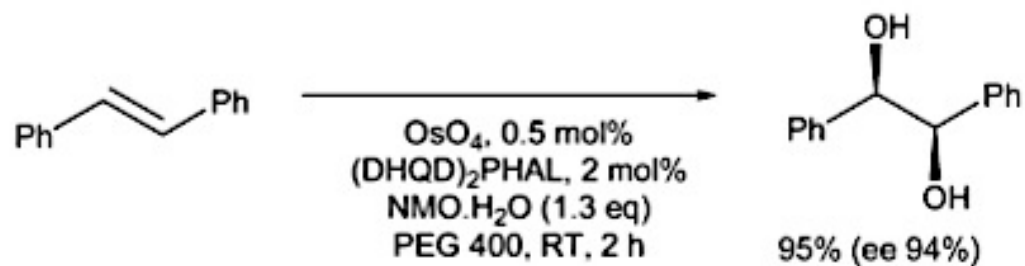
## Synthesis of Homoallylic Amines



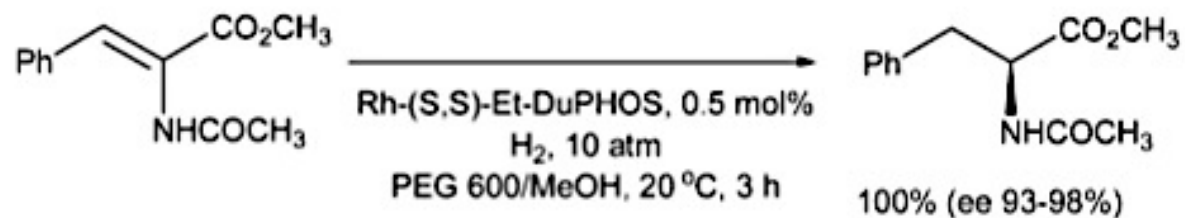
# PEG and PPG in Organic Synthesis



## Catalytic Asymmetric Dihydroxylation



## Catalytic Asymmetric Hydrogenation



# PEG and PPG in Organic Synthesis

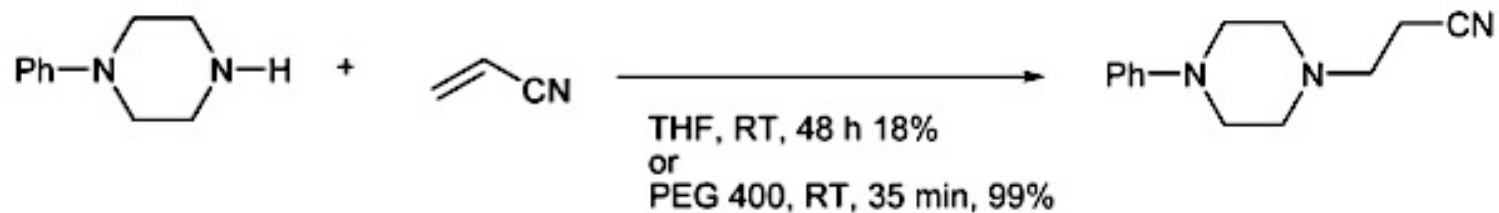


**Table 9.1** Some catalytic oxidations using  $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$  in PEG 200.

<i>Reaction</i>	<i>Substrate</i>	<i>Product (selectivity,%)</i>
<b>Oxydehydrogenation of alcohols</b>	Benzyl alcohol	Benzaldehyde (100)
	4-Bromobenzyl alcohol	4-Bromobenzaldehyde (100)
	1-Phenyl ethanol	Styrene (66), acetophenone (26), benzaldehyde (8)
<b>Oxydehydrogenation of dienes</b>	$\alpha$ -Terpinene	4-Cymene (100)
	Limonene	4-Cymene (80), $\gamma$ -terpinene (11), $\alpha$ -terpinolene (9)
<b>Oxidation of sulfides</b>	4-Vinylcyclohexene	Ethylbenzene (100)
	Tetrahydrothiophene	Sulfoxide (73), sulfone (27)
	Dibutyl sulfide	Sulfoxide (61), sulfone (39)
<b>The Wacker reaction</b>	Thioanisole	Sulfoxide (77), sulfone (23)
	Propene	Acetone (100)



# PEG and PPG in Organic Synthesis

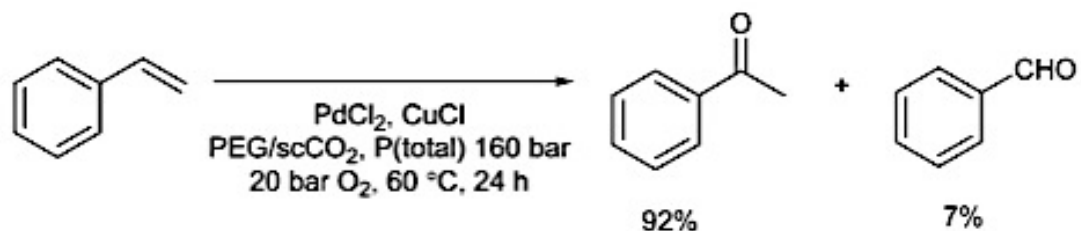


**Figure 9.6** Example of a Michael addition reaction of an amine to a conjugated alkene.

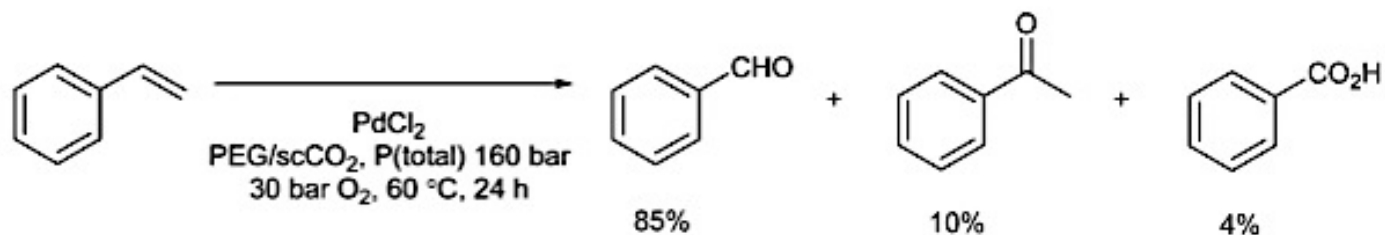
# PEG and PPG in Organic Synthesis



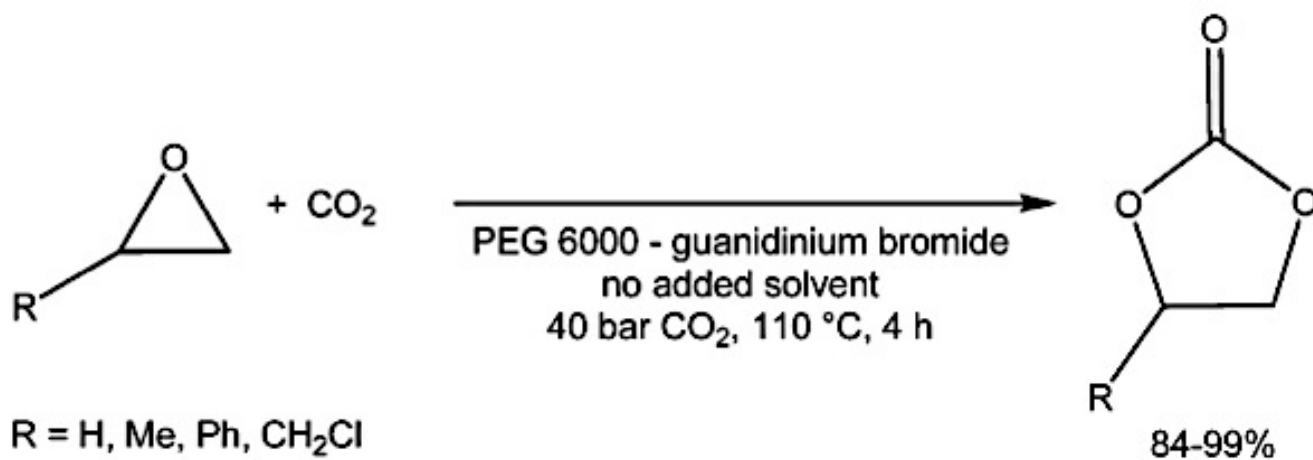
## Wacker oxidation to acetophenone



## Aerobic oxidation to benzaldehyde



# PEG and PPG in Organic Synthesis



**Figure 9.8** Functionalised PEG in 'solventless' catalytic synthesis of cyclic carbonates from CO<sub>2</sub> and epoxides.

# TUNABLE AND SWITCHABLE SOLVENT SYSTEMS

INTRODUCTION





# Introduction



**A significant advantage that these solvents have over many other media is that they can be tailor-made for a particular process and particular properties can be turned on and off as desired. Unfortunately, this means that in most cases they are going to be considerably more expensive than simple alternatives such as water. Often, the switch in these systems is the introduction of a gas such as carbon dioxide, although, the pressures involved are typically lower than those used for supercritical conditions, many users would still be wary about using and containing these gases.**

# Gas-Expanded Liquids



- **Gas-expanded liquids (GXLs) and particularly carbon-dioxide-expanded liquids (CXLs) are relatively new and promising alternative reaction media.**
- **They offer several advantages over traditional solvents and compared with supercritical carbon dioxide, lower pressures and therefore, less energy is needed to utilise them.**
- **However, clearly another liquid is needed when CXLs are used and this is usually a petroleum-sourced VOC. Due to the safety advantages of carbon dioxide over other compressible gases that are used in this field, e.g. ethane, this discussion focuses on CXLs.**

# Gas-Expanded Liquids



**Table 10.1** Summary of advantages of CXLs over conventional reaction media and scCO<sub>2</sub>.

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**1. Process advantages**

- (a) Ease of removal of the CO<sub>2</sub>
- (b) Enhanced solubility of reagent gases
- (c) Fire suppression capability of CO<sub>2</sub>
- (d) Milder process pressures (tens of bars) compared to scCO<sub>2</sub> (typically over 100 bar)

**2. Reaction advantages**

- (a) Higher gas miscibility compared to ambient condition organic solvents
- (b) Enhanced transport rates due to the properties of dense CO<sub>2</sub>
- (c) Between 1 and 2 orders of magnitude greater rates than in neat organic solvents or scCO<sub>2</sub>

**3. Environmental advantages**

- (a) Substantial replacement of organic solvents with benign dense phase CO<sub>2</sub>
-

# Gas-Expanded Liquids

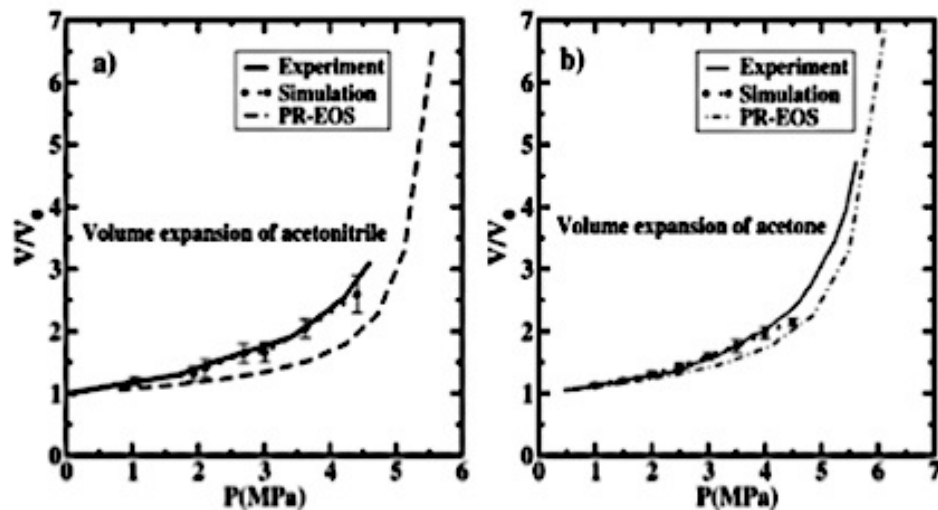


**Table 10.2** A comparison of different liquid classes and their expansion behaviour under carbon dioxide pressure at 40 °C.

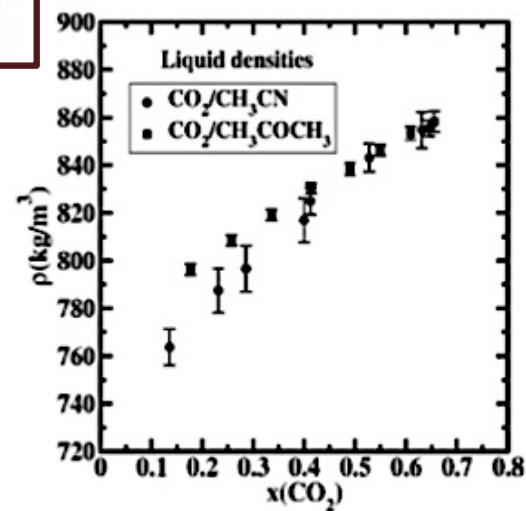
<i>Class</i>	<i>Solvent</i>	<i>P, bar</i>	<i>Volumetric expansion, %</i>	<i>wt% CO<sub>2</sub></i>	<i>mol% CO<sub>2</sub></i>
I	H <sub>2</sub> O	70	na	4.8	2.0
II	acetonitrile	69	387	83	82
III	PEG-400	80	25	16	63



# Gas-Expanded Liquids



Expansions in volume of solvents (a – acetonitrile and b – acetone) in the presence of carbon dioxide of varying pressures, 1 MPa = 1 bar.



Densities of gas-expanded acetonitrile (●) and acetone (■), with varying carbon dioxide mol fraction. [Reprinted with permission from

# Gas-Expanded Liquids



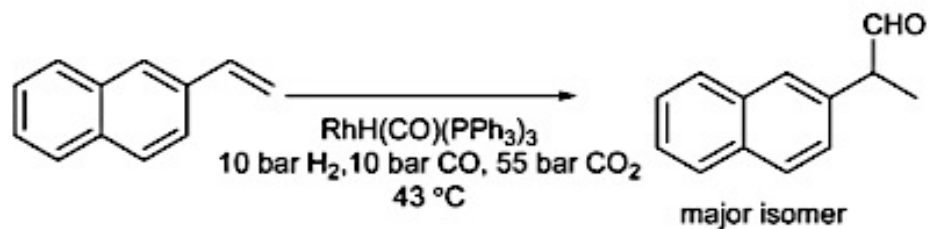
**Table 10.3** Phase behaviour results for some binary mixtures of solvents initially and upon exposure to 50 bar carbon dioxide.

<i>Miscible and remain miscible</i>	<i>Miscible and become immiscible</i>	<i>Immiscible and become miscible</i>
DMSO- <i>n</i> -PrOH, EtOH or MeOH	ROH-Acetone, Cyclohexane, Toluene, Et <sub>2</sub> O or CH <sub>2</sub> Cl <sub>2</sub>	Cyclohexane-DMSO, DMF, CH <sub>3</sub> CN or MeOH
EtOH-MeOH	Cyclohexane-Acetone, Toluene, THF, Et <sub>2</sub> O or CH <sub>2</sub> Cl <sub>2</sub>	
Acetone-CH <sub>3</sub> CN	Toluene-Acetone, DMSO, DMF, THF or Et <sub>2</sub> O	Et <sub>2</sub> O-DMSO
	THF- Acetone, CH <sub>3</sub> CN, DMSO, DMF, Et <sub>2</sub> O or CH <sub>2</sub> Cl <sub>2</sub>	

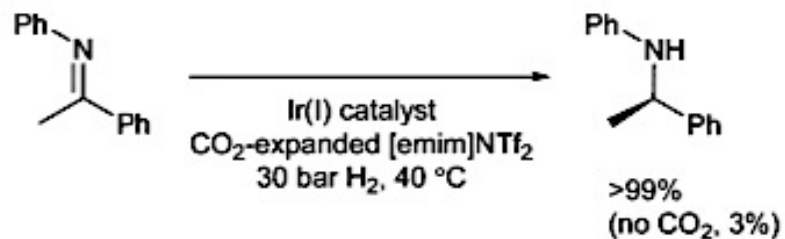
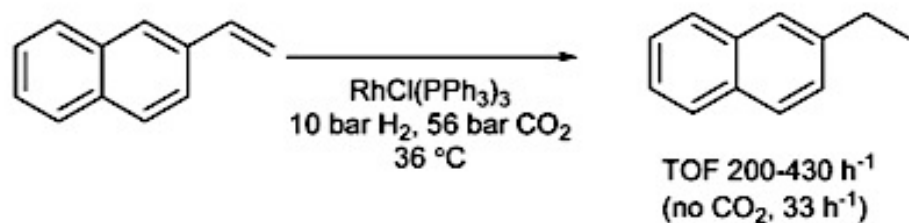
# Gas-Expanded Liquids



## Homogeneous Hydroformylation



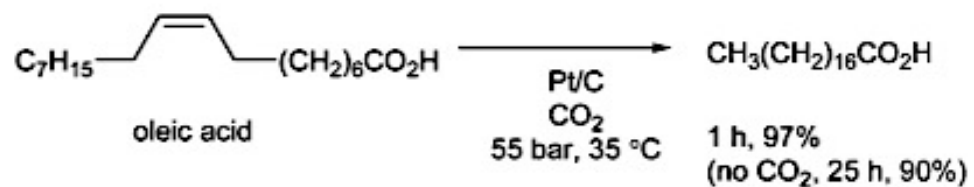
## Homogeneous Hydrogenation



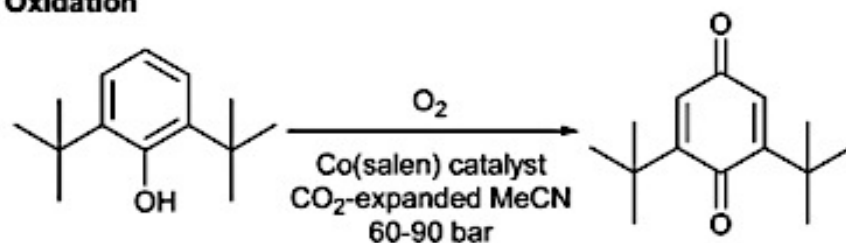
# Gas-Expanded Liquids



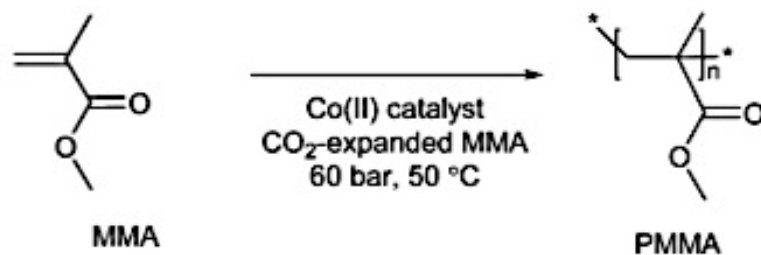
## Heterogeneous Hydrogenation



## Oxidation

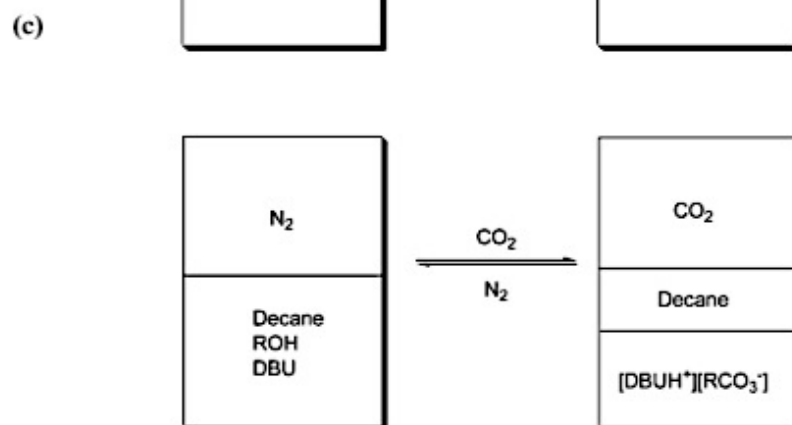
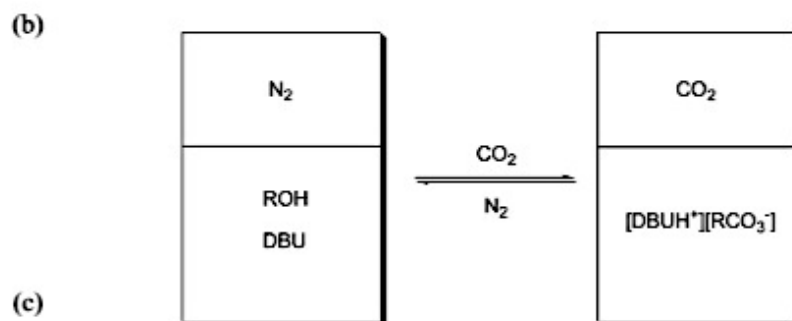
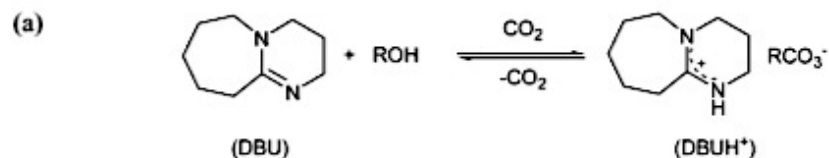


## Polymerization





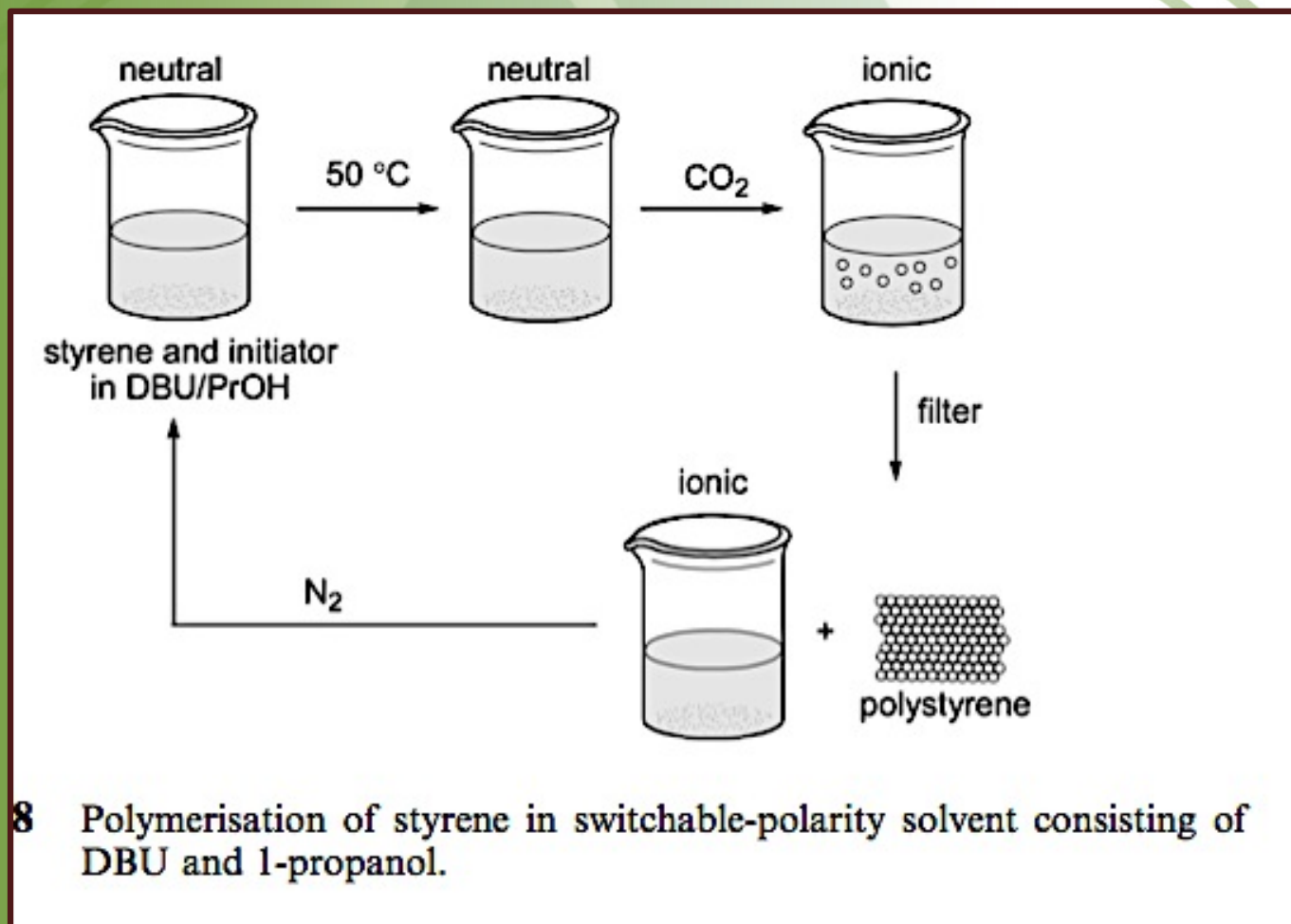
# Solvents of Switchable Polarity



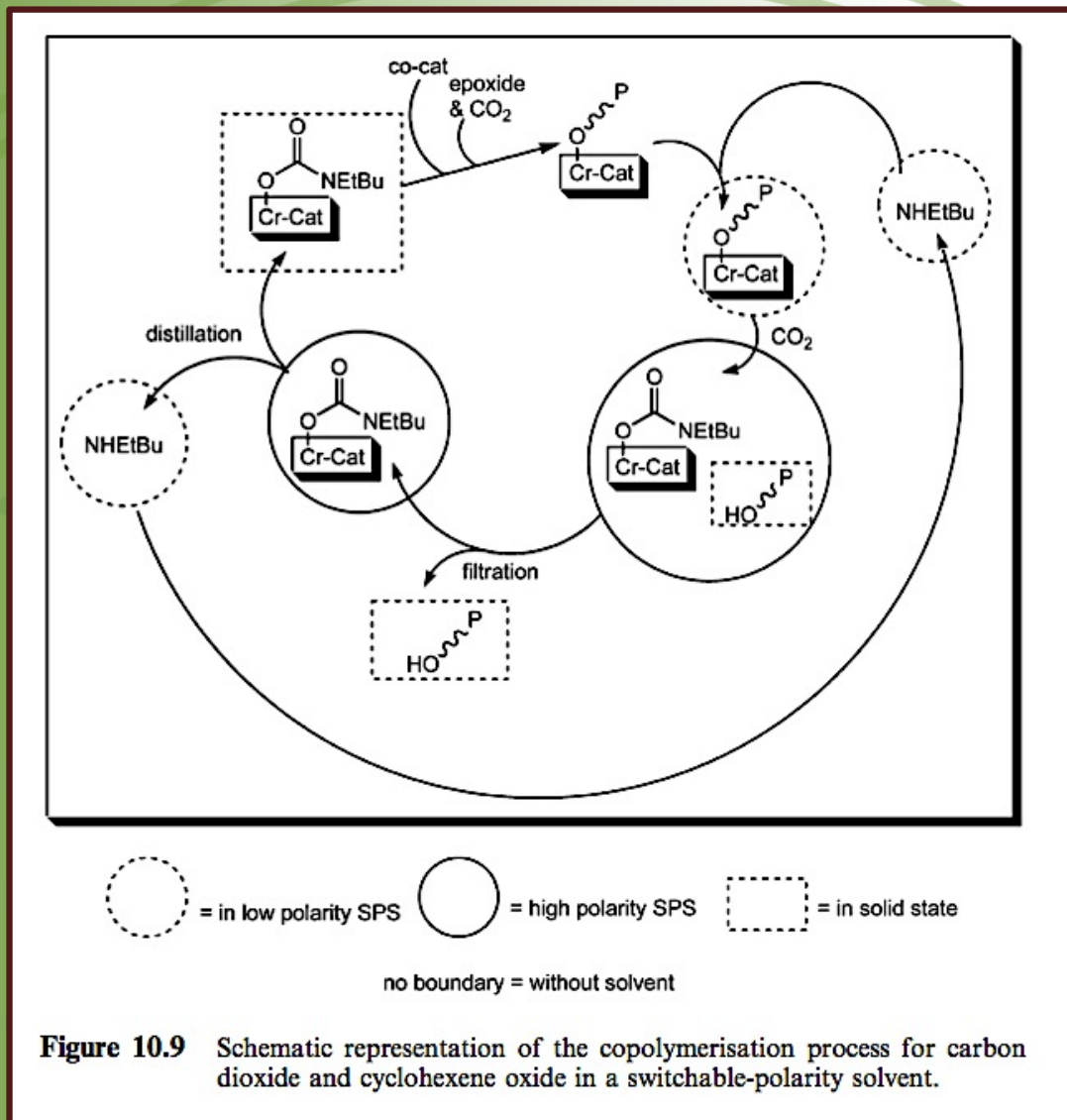
Switchable-polarity solvents such as this have the potential to remove the requirement for changing solvents after each step of a reaction and therefore, they could significantly reduce the amount of solvent needed in a chemical process.

The 'switching' of a switchable solvent. (a) Reversible protonation of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) in the presence of an alcohol and carbon dioxide. (b) Polarity switching in reaction a. (c) Miscibility of decane with the alcohol/DBU mixture (nonpolar) under nitrogen and separation of decane from the 'ionic liquid' (polar) under carbon dioxide.

# Solvents of Switchable Polarity



# Solvents of Switchable Polarity



# Solvents of Switchable Polarity

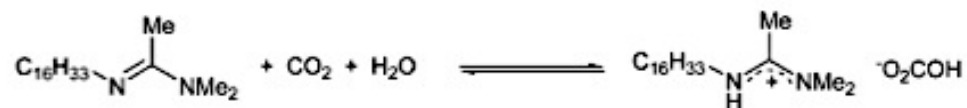


**Table 10.4** Summary of solubility studies using N-ethyl-N-butylamine-based SPS.

<i>Soluble in both forms of SPS</i>	<i>Soluble in ionic form of SPS</i>	<i>Soluble in NHEtBu</i>	<i>Insoluble in both NHEtBu and ionic form of SPS</i>
Benzylbenzamide Ibuprofen	Tetraethylammonium <i>p</i> -toluenesulfonate	Tetracosane	Cellulose Benzyltriethylammonium chloride
Toluene Styrene Decane Water	Sodium <i>p</i> - toluenesulfonate	Stilbene	(Vinylbenzyl) trimethylammonium chloride



# Switchable Surfactants

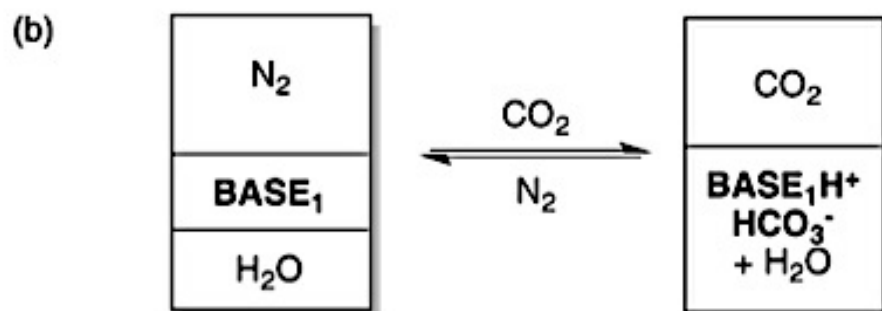
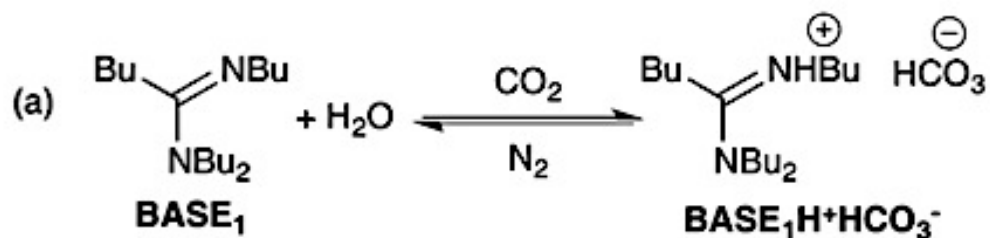


**Scheme 10.1** Switchable surfactant formation from long-chain alkyl amidine and carbon dioxide and water.

**Table 10.5** Potential applications of temporary or switchable surfactants.

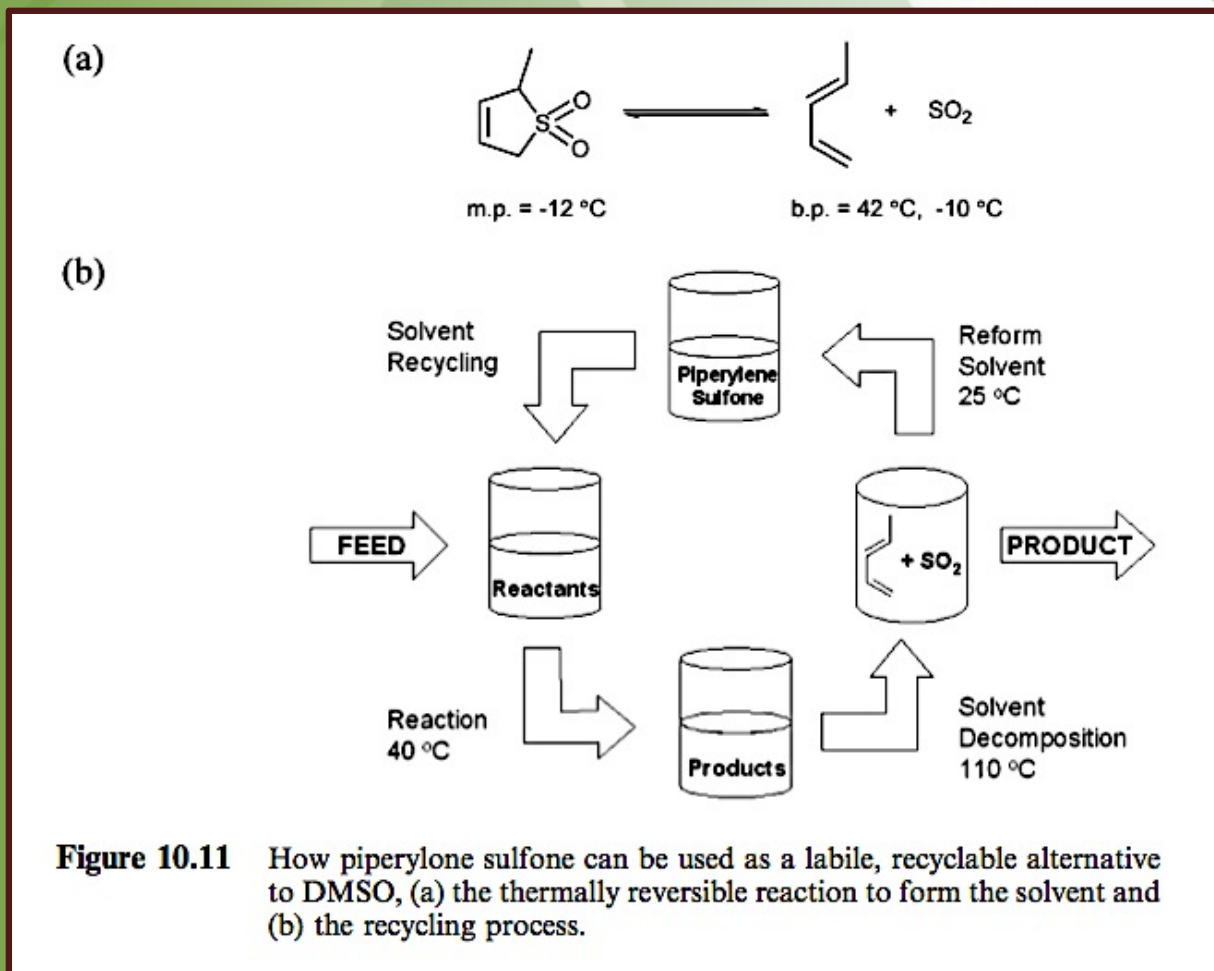
1. Emulsion polymerisations
2. Preparation of nanoparticles
3. Cleaning and degreasing of equipment/metals
4. Enhanced oil-recovery (EOR)
5. Oil:oil-sand separation
6. Viscous-oil transportation
7. Cosmetic emulsions

# Switchable Hydrophilicity Solvents



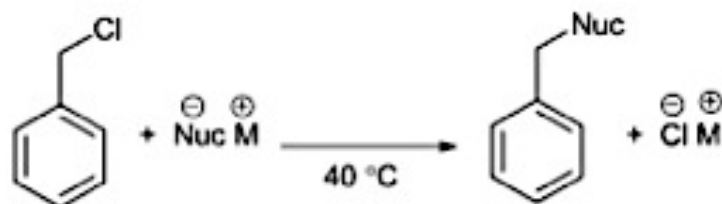
**10** The 'switching' of a switchable hydrophilicity solvent: (a) Reversible reaction of *N,N,N'*-tributylpentanamidine (BASE<sub>1</sub>) with water and carbon dioxide. (b) Reversible phase separation (miscibility) of *N,N,N'*-tributylpentanamidine (BASE<sub>1</sub>) and water, upon exposure of the mixture to carbon dioxide or nitrogen.

# Solvents of Switchable Volatility

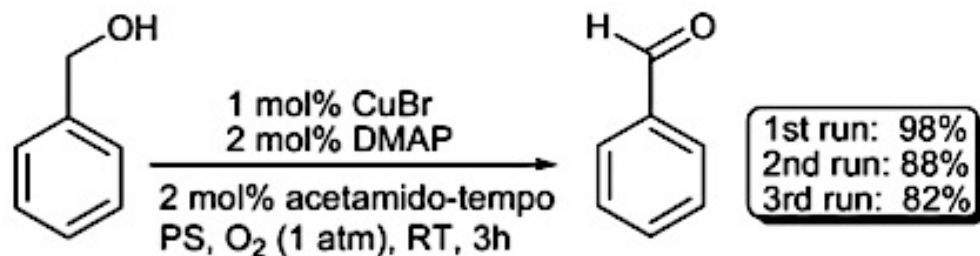


**Figure 10.11** How piperylene sulfone can be used as a labile, recyclable alternative to DMSO, (a) the thermally reversible reaction to form the solvent and (b) the recycling process.

# Solvents of Switchable Volatility



$\ominus \oplus$   
Nuc M = Potassium thioacetate, DMSO = PS:  $k > 1800 \times 10^4 \text{ l mol}^{-1} \text{ s}^{-1}$   
= Caesium acetate, DMSO:  $k = 22.7 \times 10^4 \text{ l mol}^{-1} \text{ s}^{-1}$ , PS:  $k = 0.35 \times 10^4 \text{ l mol}^{-1} \text{ s}^{-1}$



DMAP = 4-dimethylaminopyridine

**Scheme 10.3** Recycling and reuse of copper catalyst and solvent in the aerobic oxidation of benzyl alcohol.



# **WATER**

## **INTRODUCTION**



# Introduction

Beyond using no added solvent in a reaction or process, **water** is probably the greenest alternative we have.



**Table 3.1** Physical properties of water compared with acetone and ethanol.

	<i>Water, H<sub>2</sub>O</i>	<i>Acetone, (CH<sub>3</sub>)<sub>2</sub>C=O</i>	<i>Ethanol, CH<sub>3</sub>CH<sub>2</sub>OH</i>
Melting point/°C	0	-94.7	-113.9
Boiling point/°C	100	56	78
Triple point/°C	0.01	-94.3	-123
Critical point, <i>T<sub>c</sub></i> /°C and <i>P<sub>c</sub></i> /bar	374/221	235/48	241/63
Density at 25 °C/g cm <sup>-3</sup>	1.00	0.78	0.78
Latent heat of vaporization/ kJ g <sup>-1</sup> K <sup>-1</sup>	2.26	0.518	0.846
Specific heat capacity/ J g <sup>-1</sup> K <sup>-1</sup>	4.19	2.44	2.15
Hildebrand solubility para- meter/(MPa) <sup>0.5</sup>	47.9	19.7	26.2
Dielectric constant	78.30	20.7	24.3
Dipole moment	1.85	2.88	1.69
<i>E<sub>T</sub><sup>N</sup></i>	1.000 (defined)	0.654	0.355
<i>α</i>	1.17	0.08	0.86
<i>β</i>	0.47	0.43	0.75
<i>π*</i>	1.09	0.71	0.54
Donor number	1.46	0.44	0.82
Acceptor number	54.8	12.5	37.9

# Properties



**Table 3.2** Summary of the advantageous properties of water as a solvent.

<b>Safety advantages</b>	Non-flammable Non-toxic
<b>Reaction and process advantages</b>	Low cost A density of $1 \text{ g cm}^{-3}$ provides a sufficient difference from most organic substances for easy biphasic separation It is polar, so relatively easy to separate from apolar solvents or products; polarity may also influence (and improve) reactions Very high dielectric constant and therefore, favours ionic reactions High thermal conductivity, high specific heat capacity and high evaporation enthalpy High solubility of many gases, especially $\text{CO}_2$ Highly dispersible and high tendency towards micelle formation in presence of suitable additives
<b>Environmental advantages</b>	Renewable Widely available in suitable quality (close to zero transportation costs) Odourless and colourless, making contamination easy to recognize



# Properties

- For homogeneous aqueous systems, the improvements are generally attributed to some combination of polarity effects, hydrophobic interactions, and hydrogen bonding.
- In heterogeneous systems, hydrogen bonding interactions across the water-organic phase boundary become important.





# Properties



## Polarity Effect

- A reaction that proceeds via a transition state that is more polar than its initial state will be faster in polar solvents that can stabilize the developing charges (e.g., an  $S_N1$  reaction of *t*-butyl bromide).
- Conversely, a reaction that passes through a less polar transition state will be slower in polar solvents owing to preferential stabilization of the initial state (e.g., an  $S_N2$  reaction with an anionic nucleophile).
- Water is a highly polar solvent with a dielectric constant ( $\epsilon_r$ ) of 80.1 .

# Properties



## Hydrophobic Effect

Water is a protic polar solvent but the results observed in organic protic polar solvents (ethanol, methanol) were close to the hydrocarbon solutions, so these observations were attributed to a particular property of water, the **hydrophobic effect**

This effect stems from the repulsive interactions between hydrophobic molecules and water, which lead to the formation of **hydrophobic aggregates** that allow the reduction of the contact surface with water. In the meantime, in order to maintain the network of **hydrogen bonds**, which is responsible for its high cohesive energy density, water wraps itself around this aggregate.

This organization acts as an internal pressure and thus accelerates reactions with negative activation volume, like cycloadditions

# Properties

## Hydrophobic Effect

A common test for the hydrophobic effect involves addition of different salts to aqueous reactions. Salts with small cations and anions (e.g., LiCl, NaCl) are known to decrease the solubility of organic species in water (an effect known as salting out). An explanation for this behavior is believed to be contraction of the solvent volume accompanying dissolution of these salts. As water molecules rearrange themselves to surround the dissolved ions, the network of hydrogen bonds contracts, leaving less empty space to accommodate the dissolved hydrocarbons.



# Properties

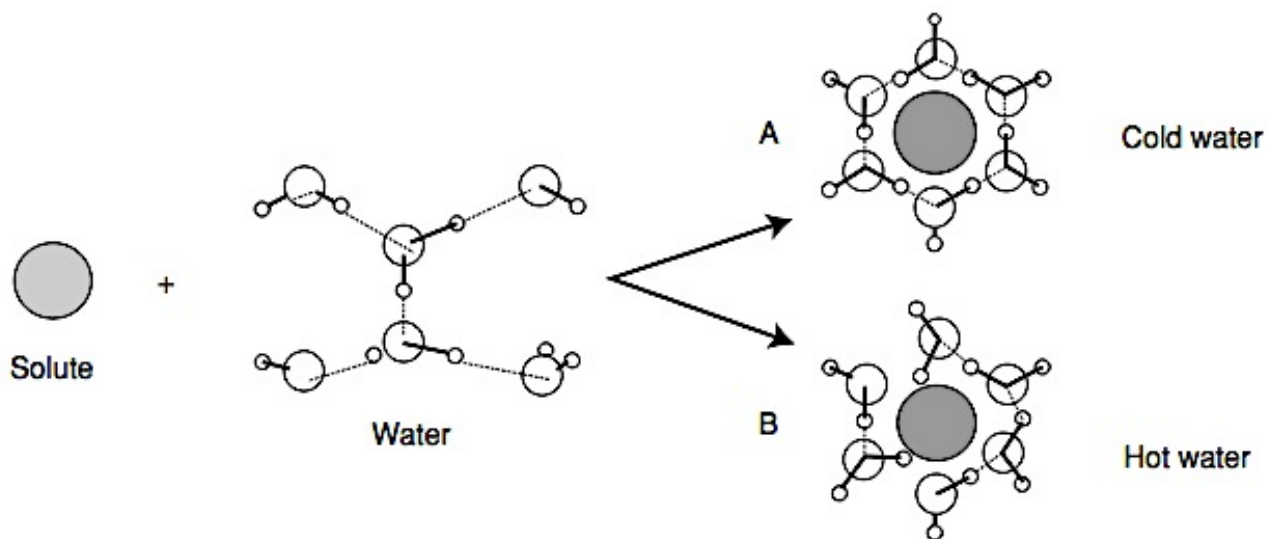
## Hydrophobic Effect

The end result is an effective increase in the hydrophobic effect. Conversely, salts where one or both of the ions are large (e.g.,  $\text{C}(\text{NH}_2)_3\text{Cl}$ ,  $\text{LiClO}_4$ ,  $\text{C}(\text{NH}_2)_3\text{ClO}_4$ ) have the opposite effect. These salts increase the water solubility of nonpolar species and are said to act as “salting in” agents. The molecular cause of this effect is not fully understood. One explanation is that the larger ions of these salting in agents break up the hydrogen bonding network, making it easier to form a cavity for the nonpolar substance. Alternatively, the large ions could be directly improving the solubility of nonpolar substances by acting as a bridge between the hydrocarbon and water molecules.



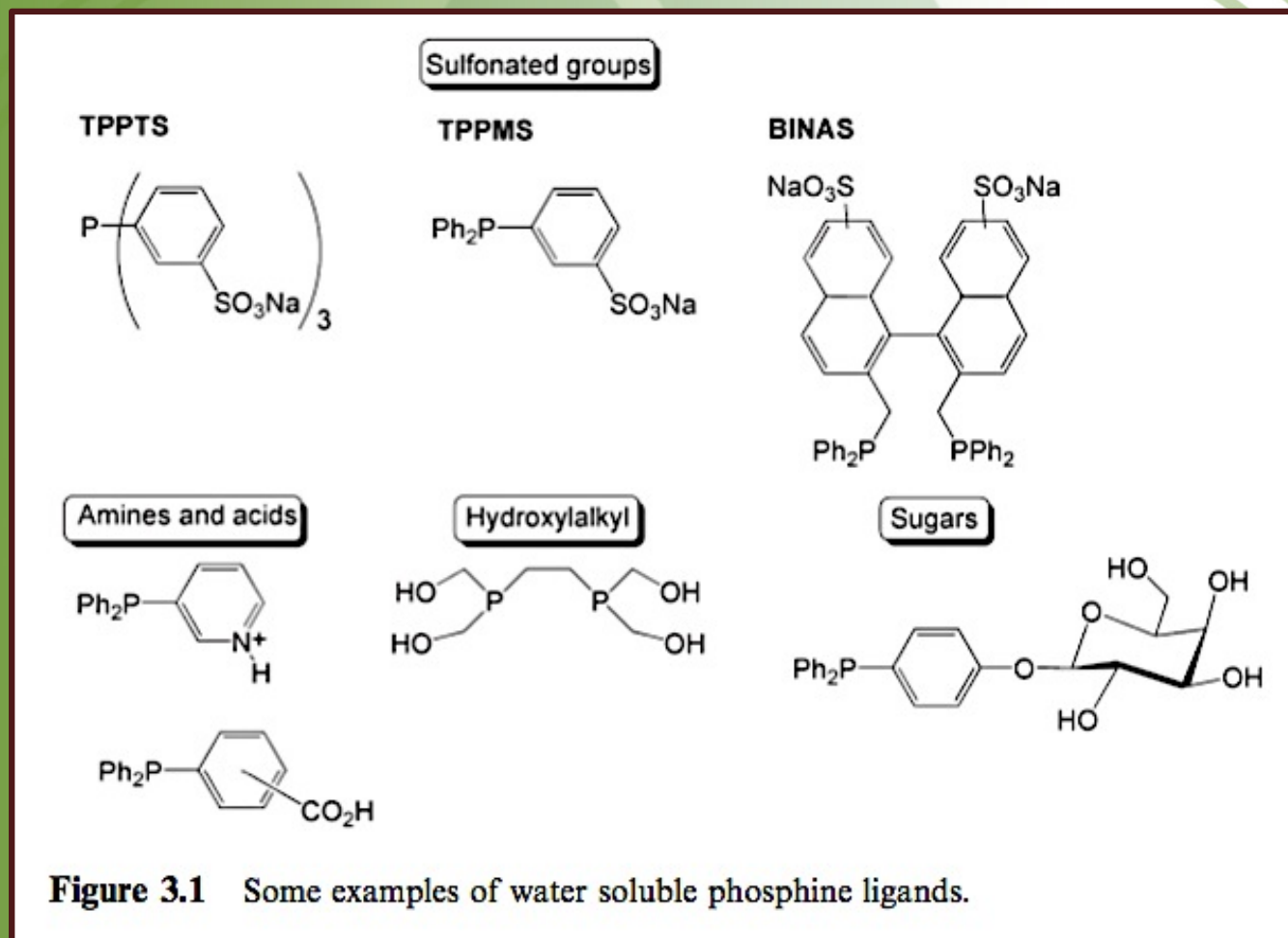


# Properties

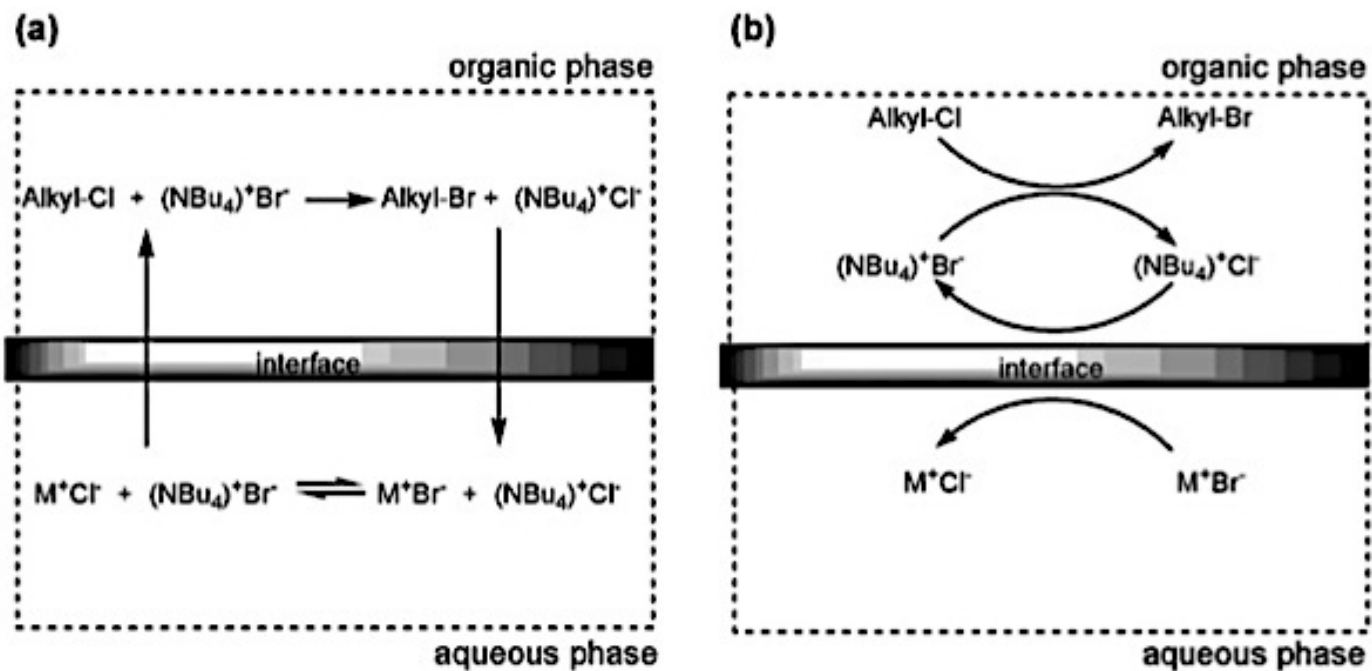


**Figure 2.5** Preferred tangential orientation of the O—H bonds of water relative to an apolar molecular surface. At higher temperatures the hydration shell becomes less organized. Reproduced with permission from Southall et al. (2002).<sup>78</sup> Copyright 2002 American Chemical Society.

# Biphasic Systems



# Biphasic Systems



**Figure 3.2** (a) A shuttling mechanism and (b) an interfacial mechanism for a simple anion displacement reaction.

# Biphasic Systems

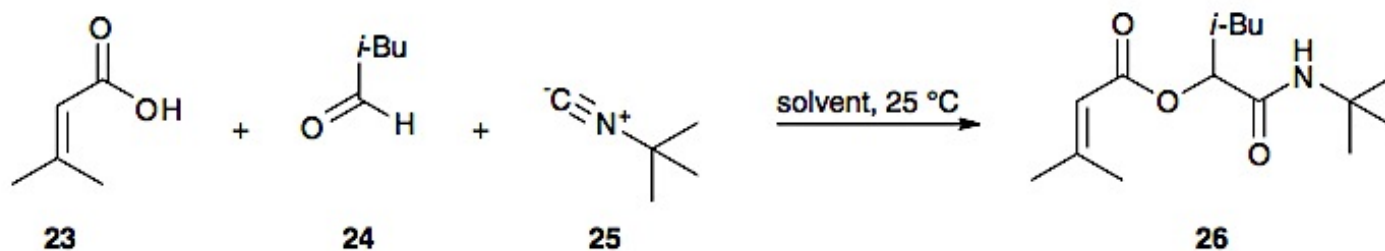


**Table 3.3** Summary of advantages and disadvantages of phase transfer catalysis.<sup>1</sup>

<i>Advantages</i>	<i>Disadvantages</i>
Reduced need for organic solvents	Catalyst required, which may be toxic
Relatively inexpensive auxiliaries required, e.g. $(\text{NBu}_4)^+\text{Cl}^-$	Difficult to separate; emulsions may form
Improved separation possible	Catalyst can be hard to recover
Increased reaction rates and productivity	Vigorous mixing required
Improved selectivity, due to lower operating temperatures	Contaminated waste water can be tough to purify



# Chemical Synthesis



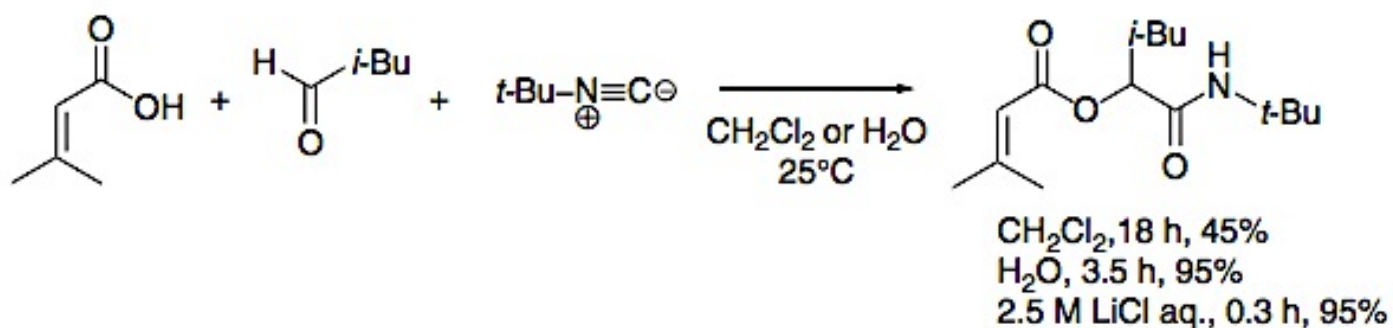
Solvent	Time (h)	Conversion (%)
Dichloromethane	18	50
Dimethylformamide	24	15
Methanol	24	0
Water	3.5	100

**Scheme 10.7** Solvent effect on the Passerini reaction.

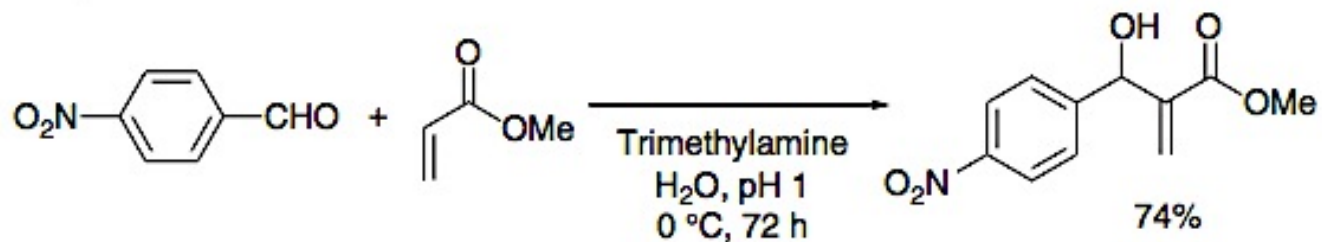
# Chemical Synthesis



## Passerini Reaction



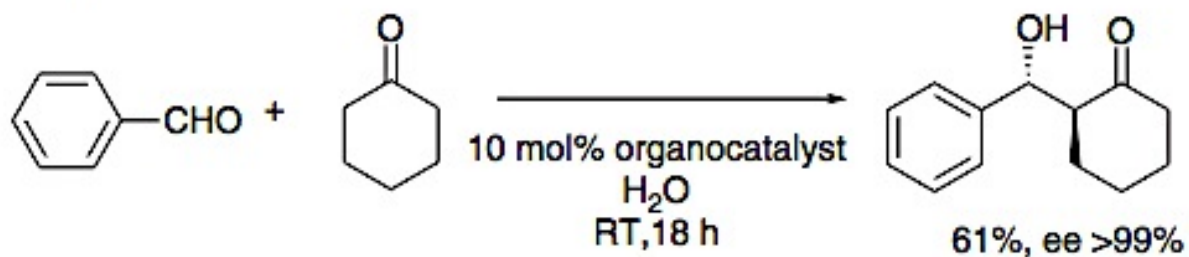
## Baylis-Hillman Reaction



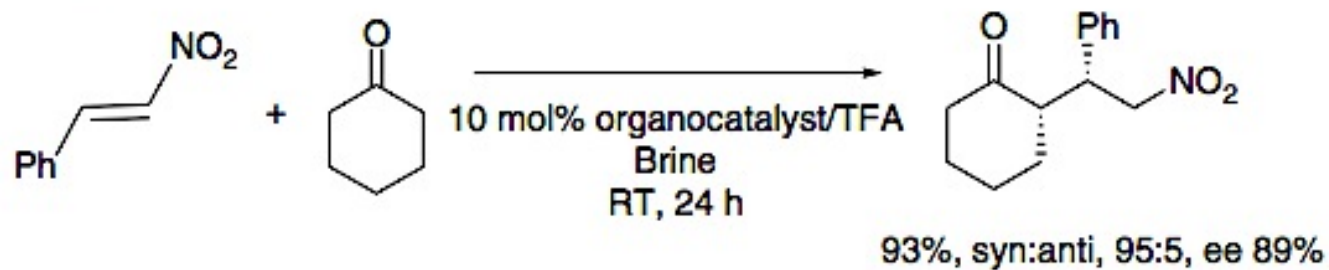
# Chemical Synthesis



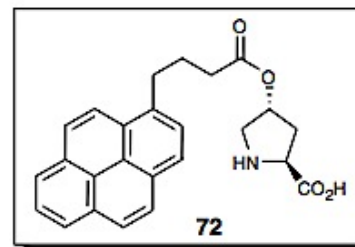
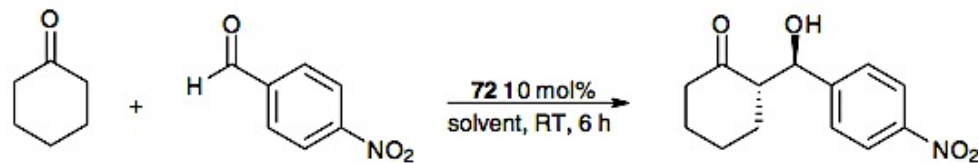
## Asymmetric Aldol Reaction



## Asymmetric Michael Addition



# Chemical Synthesis



Solvent	Conv. (%)	anti/syn	ee (%)
Toluene	47	69/31	96
Chloroform	60	69/31	94
Dimethyl sulfoxide	99	75/25	93
Neat	48	59/41	87
Water	99	95/5	98
Tap water	99	92/8	96

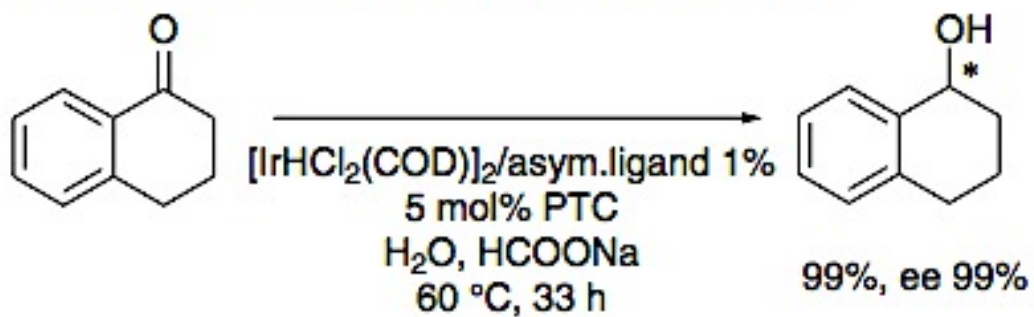
**Scheme 10.40** Influence of the solvent on the reaction of cyclohexanone and 4-nitrobenzaldehyde.



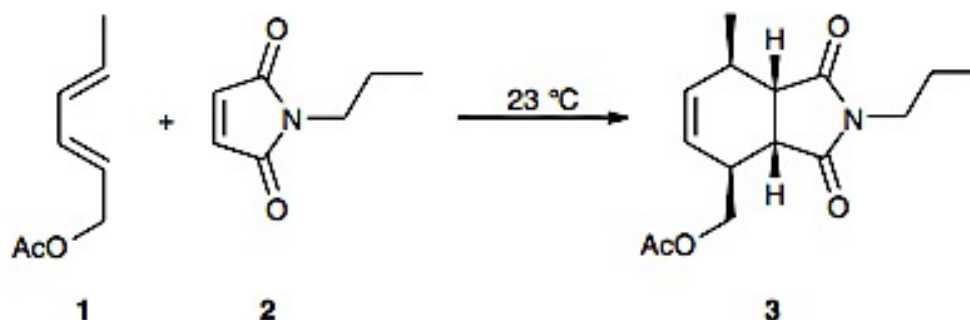
# Chemical Synthesis



## Catalytic Asymmetric Transfer Hydrogenation



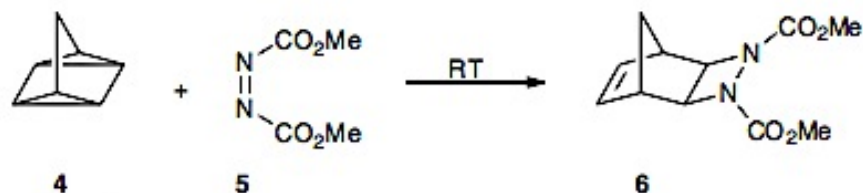
# Chemical Synthesis



Solvent	Time to completion (h)	Yield (%)
Toluene	144	79
Acetonitrile	>144	43
Methanol	48	82
Neat	10	82
Water	8	81

**Scheme 10.1** "On water" accelerated Diels–Alder reaction.

# Chemical Synthesis

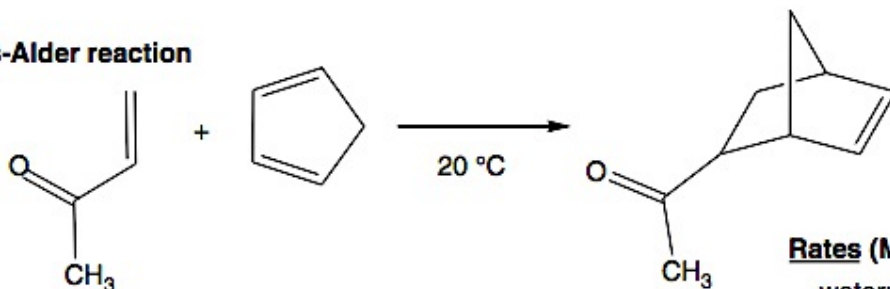


Solvent	Time to completion
Toluene	>120 h
Ethyl acetate	>120 h
Acetonitrile	84 h
Dichloromethane	72 h
Dimethyl sulfoxide	36 h
Methanol	18 h
Neat	48 h
Perfluorohexane	36 h
D <sub>2</sub> O	45 min
Water	10 min

# Chemical Synthesis



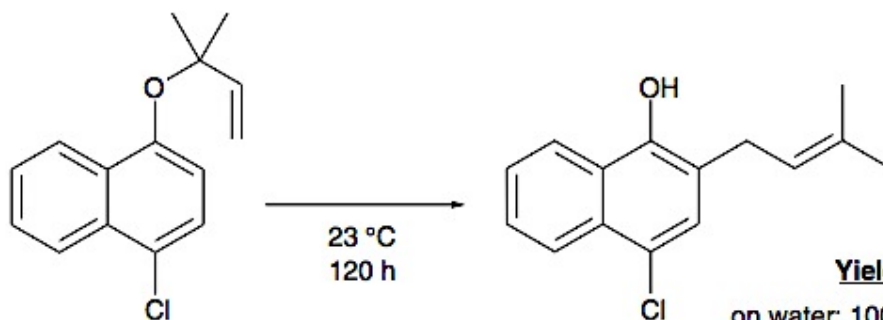
## (a) Diels-Alder reaction



### Rates (M<sup>-1</sup>s<sup>-1</sup>)

water:	4400
LiCl (4.86M):	10800
β-cyclodextrin (10mM):	10900
MeOH:	75.5
isooctane:	5.94

## (b) Claisen rearrangement

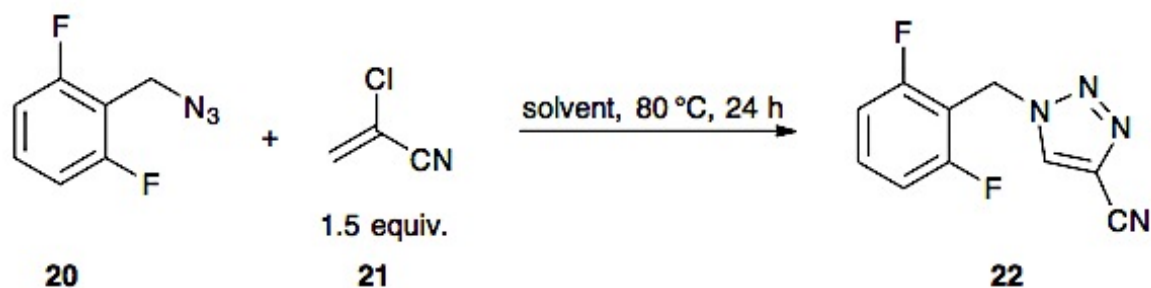


### Yields

on water:	100%
CH <sub>3</sub> CN:	27%
neat:	73%



# Chemical Synthesis



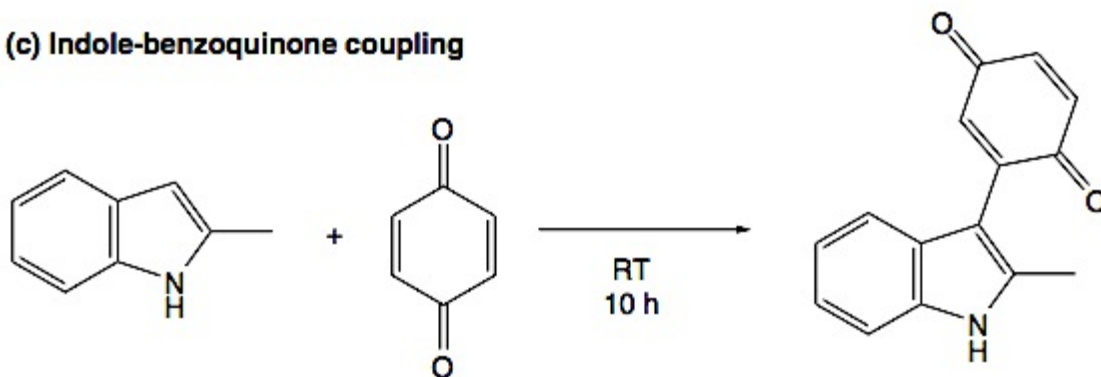
Solvent	Yield (%)
<i>n</i> -Heptane	46
Toluene	51
Dimethylformamide	78
Ethanol	40
Neat	72
Water	98

**Scheme 10.6** Solvent effect for the synthesis of 2,6-difluorobenzyl-4-cyano-1,2,3-triazole.

# Chemical Synthesis



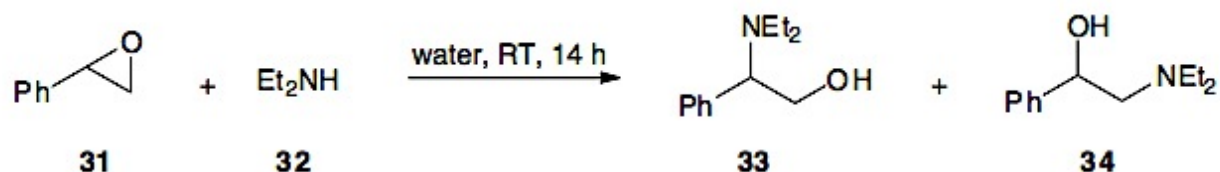
(c) Indole-benzoquinone coupling



**Yields**

on water: 82%  
EtOH: 38%  
CH<sub>3</sub>CN: 0%  
neat: 20%

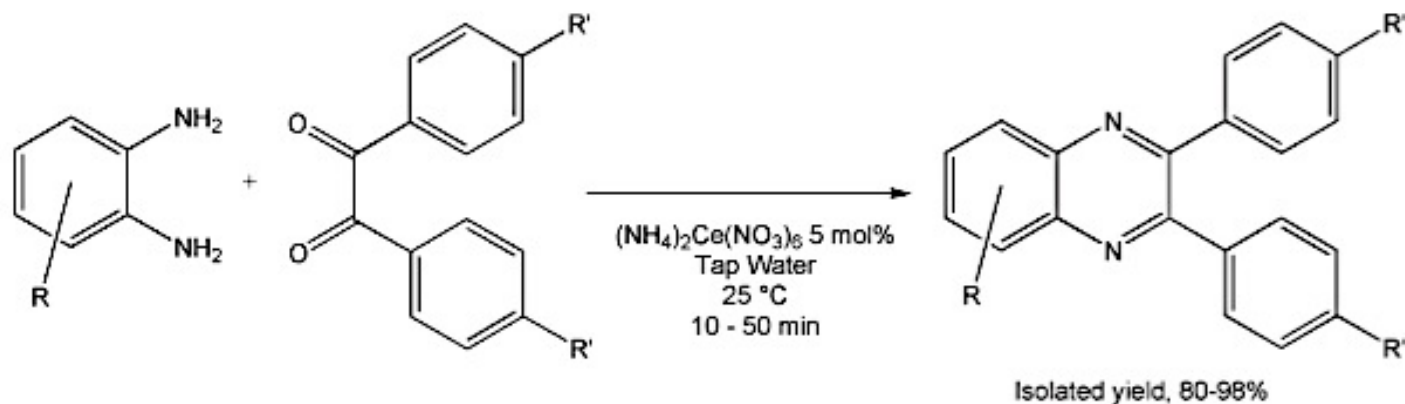
# Chemical Synthesis



Solvent	Yield (%)	Regioselectivity
		33:34
Water	92	24:76
Ethanol	50	45:55
Neat	0	—
Dichloromethane	0	—
Acetonitrile	0	—
Diethyl ether	0	—
Toluene	0	—
Hexane	0	—

**Scheme 10.11** Effect of solvent on the opening of styrene oxide with diethylamine.

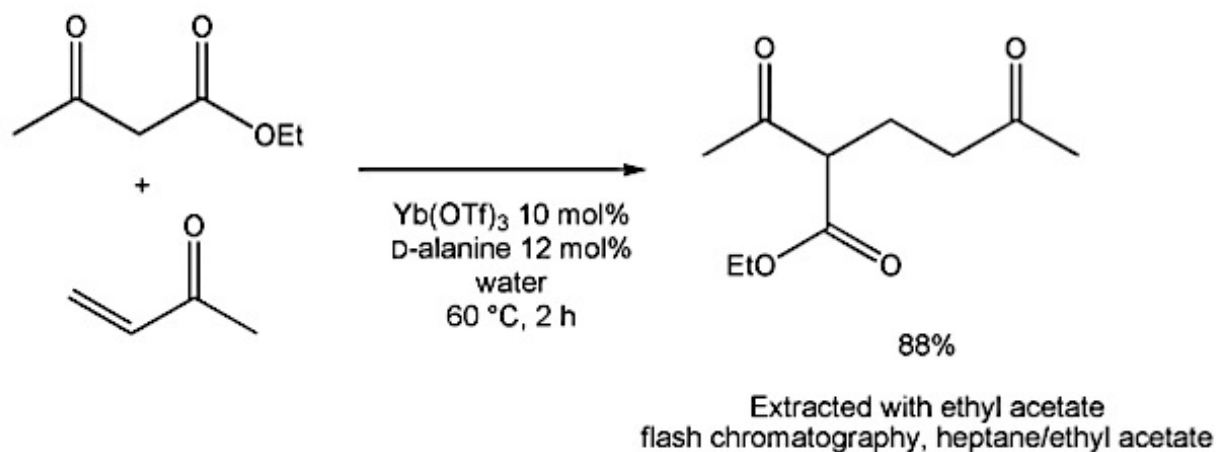
# Chemical Synthesis



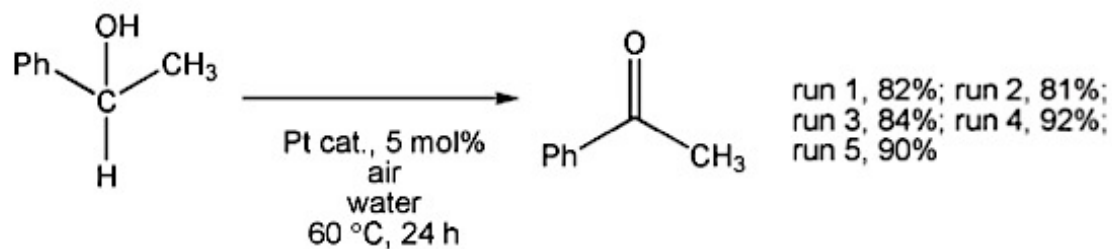
**Figure 3.7** Synthesis of quinoxalines in tap water.



# Chemical Synthesis

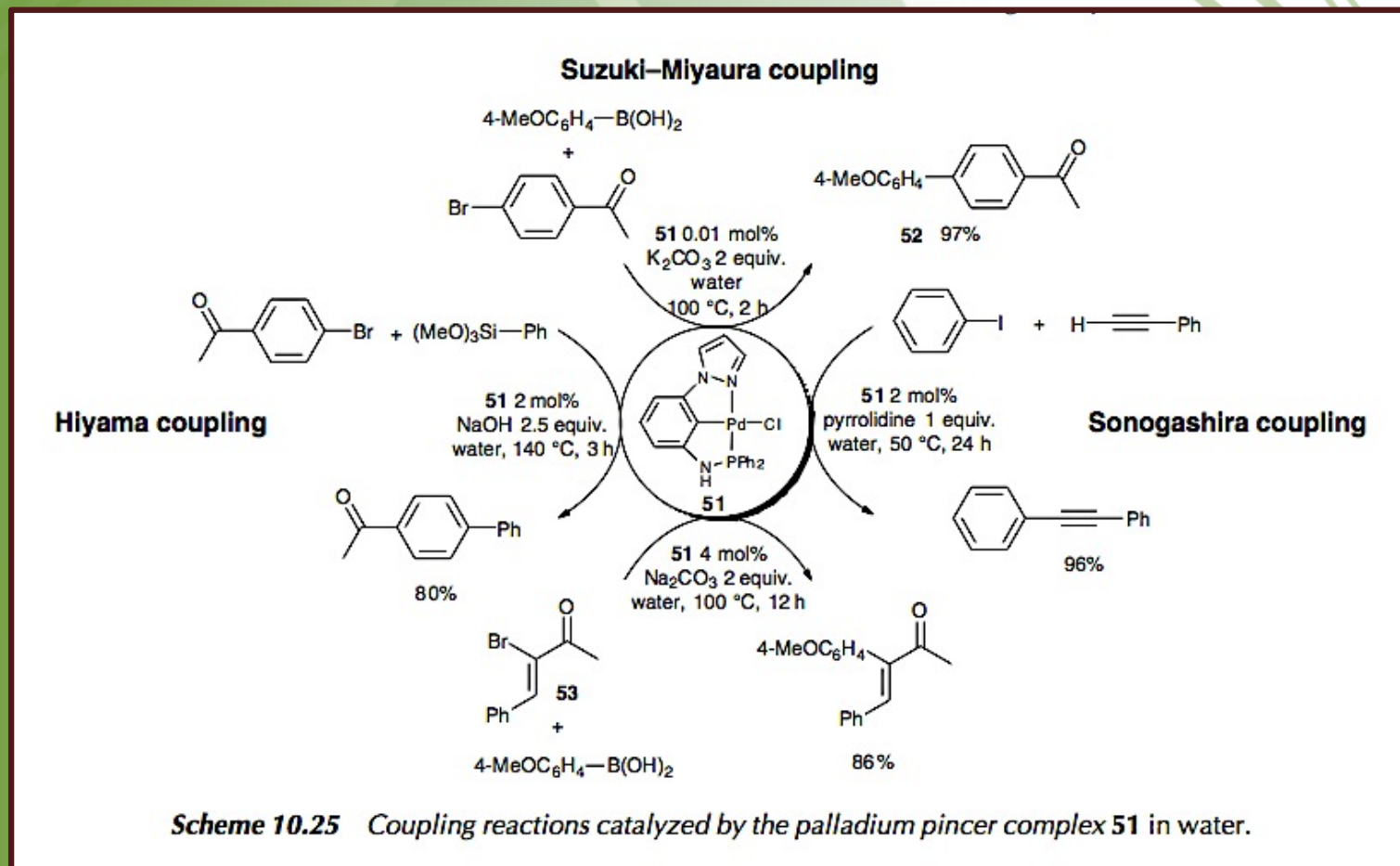


**Figure 3.8** Lewis acid catalysed Michael addition.

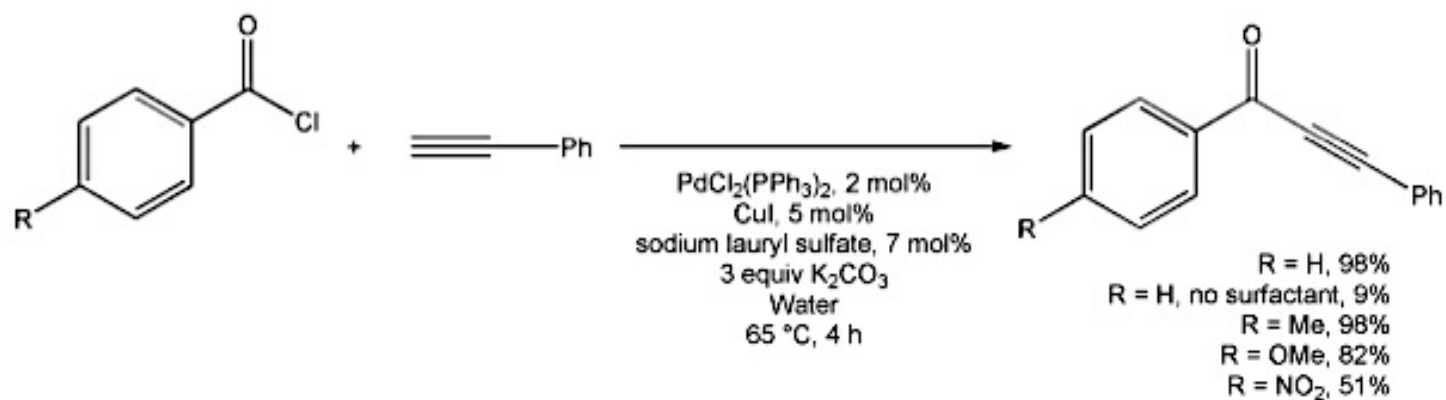


**Figure 3.9** Aerobic oxidation of alcohols using a nanoplatinum catalyst.

# Chemical Synthesis

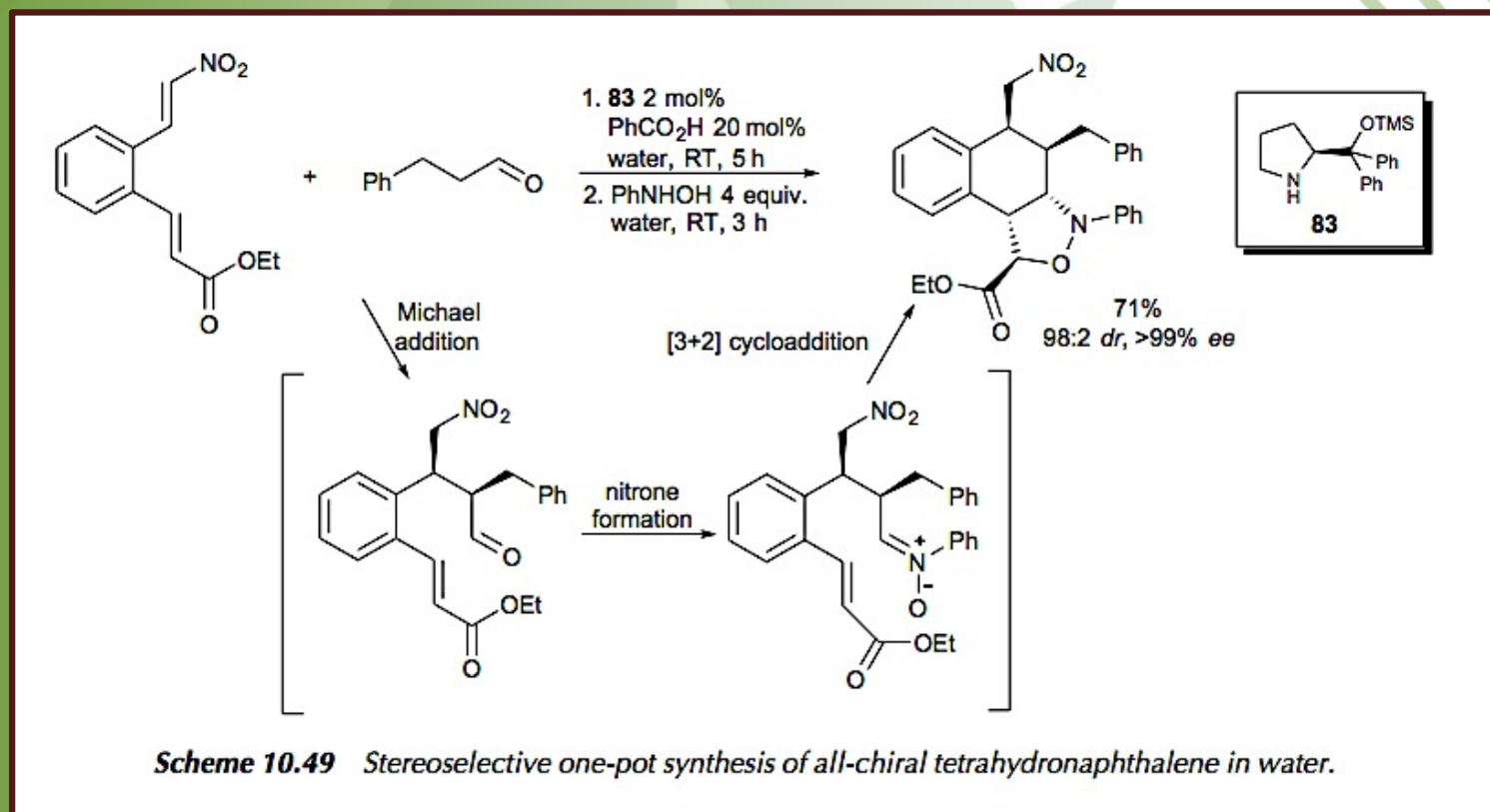


# Chemical Synthesis



**Figure 3.10** Synthesis of ynones through the coupling of terminal alkynes and acid chlorides in water.

# Chemical Synthesis



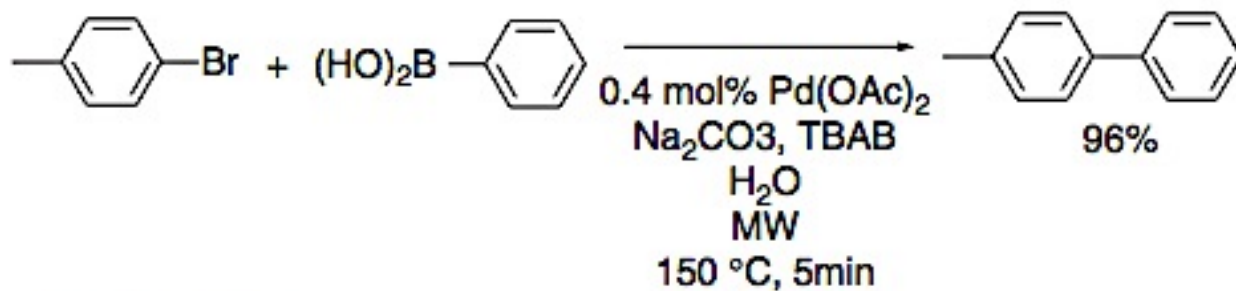


# Chemical Synthesis

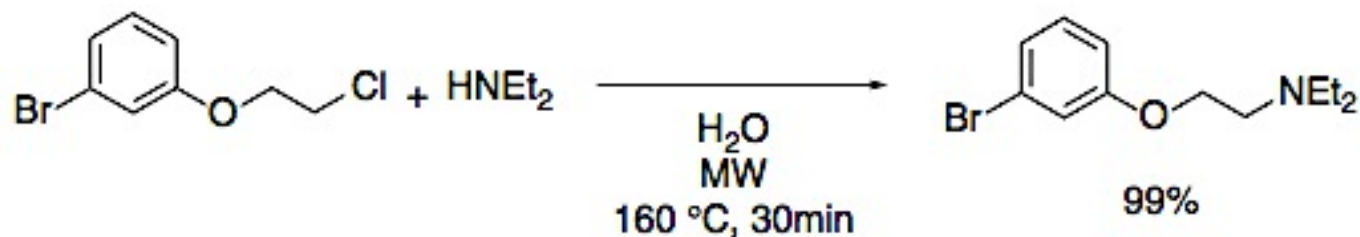


## Microwave Assisted Reaction

### Suzuki Cross-coupling Reaction



### N-Alkylation

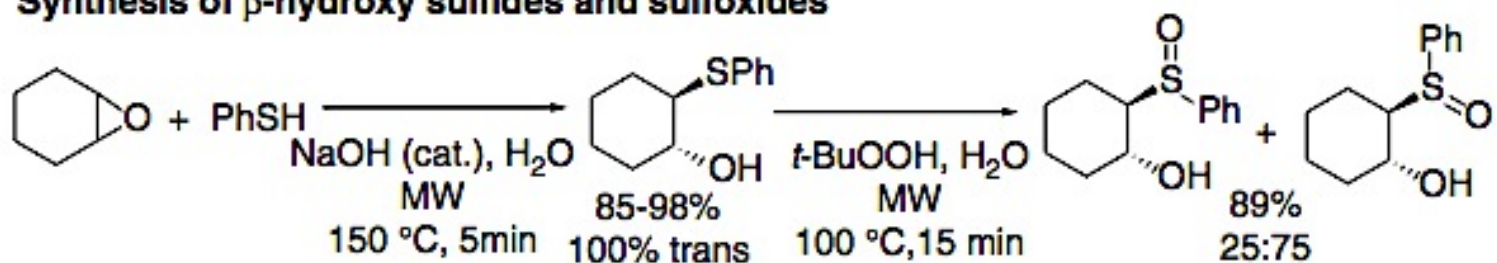


# Chemical Synthesis

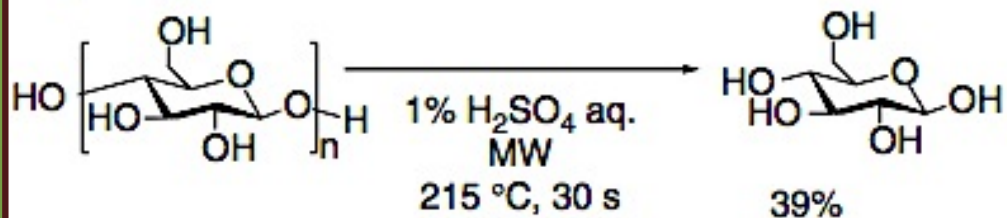


## Microwave Assisted Reaction

### Synthesis of $\beta$ -hydroxy sulfides and sulfoxides



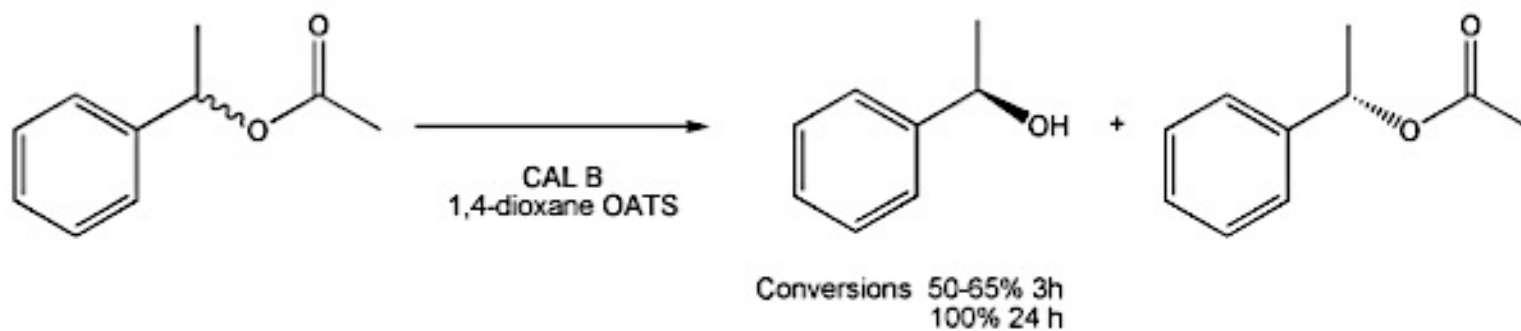
### Hydrolysis of Cellulose



# Chemical Synthesis



## Organic Aqueous Tunable Solvents (OATS)

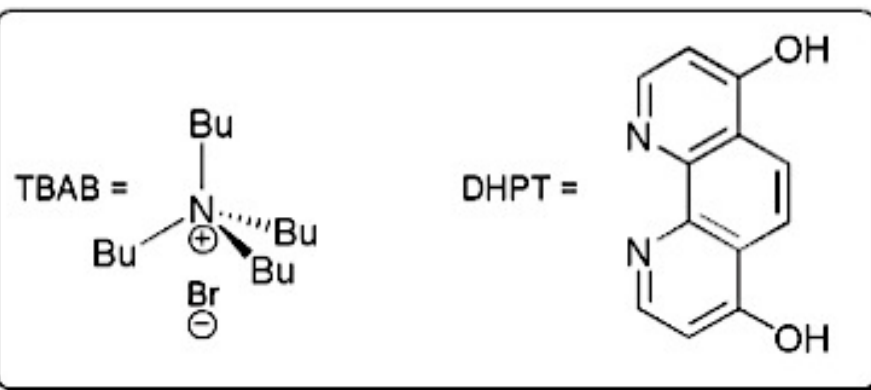
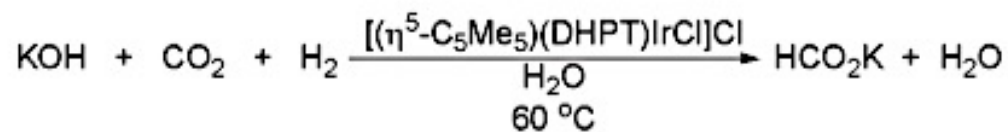
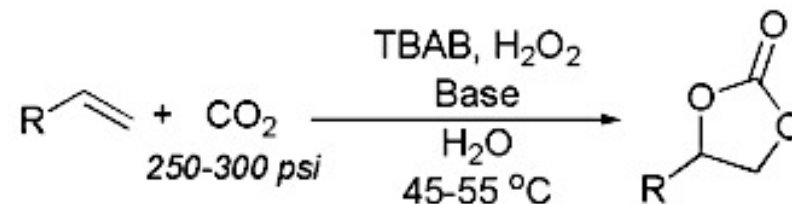


**Figure 3.12** Biocatalysis using organic–aqueous tunable solvents (OATS).

# Chemical Synthesis

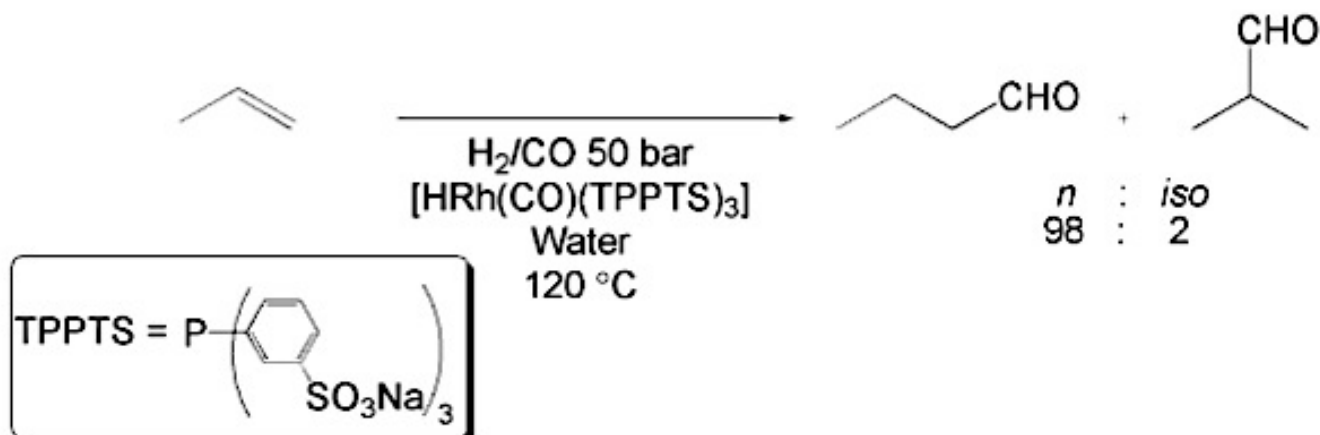


$$[\text{H}^+] = \frac{K_1[\text{H}_2\text{CO}_3]}{a(\text{HCO}_3^-)}$$





# Industrial Application



**Figure 11.2** Aqueous biphasic Ruhrchemie-Rhône-Poulenc hydroformylation process.

**Table 11.1** Summary of environmental benefits of the aqueous biphasic Ruhrchemie-Rhône-Poulenc hydroformylation process.<sup>3</sup>

1. Use of water in place of toxic solvents
2. Close to zero emissions
3. Mild reaction conditions that lead to significant energy conservation
4. High selectivity towards desired linear aldehyde isomer
5. Very low loss of precious-metal catalyst