

---

## 聲明

本檔案之內容僅供下載人自學或推廣化學教育之非營利目的使用。並請於使用時註明出處。  
[如本頁取材自○○○教授演講內容]。

---



# 永續化學合成(2)

## 永續化學的非傳統反應方法與溶劑

劉廣定

臺大化學系

(ktliu@ntu.edu.tw)



# 永續化學合成

Plechkova and Seddon said: Your work is not green because you choose to call it green and publish it in *Green Chemistry*. Improving a yield, eliminating a toxic reagent, increasing a selectivity, are all admirable, but just a **green attitude**. The term **green chemistry** has to be applied to a total process, not to an single step.

*(Methods and Reagents for Green Chemistry, 2007, p. 110)*

**Thus, reaction conditions, reagents, solvents, catalysts, etc. should all be considered for a sustainable chemical synthesis.**

In addition, a better yield or a higher selectivity at a condition not in line with the principles of green chemistry will not be regarded to have “green attitude,” either.



## Non-conventional preparation methods

**E-factor is the most important especially from the practical point of view, not only for production, but also for R&D**

**Alternative activation methods and alternative reaction media are sought for the purpose of **reducing**:**

- **Cost**
- **Energy**
- **Environmental impact**
- **Materials**
- **Non-renewables**
- **Risk and hazard**
- **Waste**

**Sustainable (Green) chemistry is defined as the practice of chemistry in a manner that maximizes its benefits while eliminating or greatly reducing its adverse impacts.**

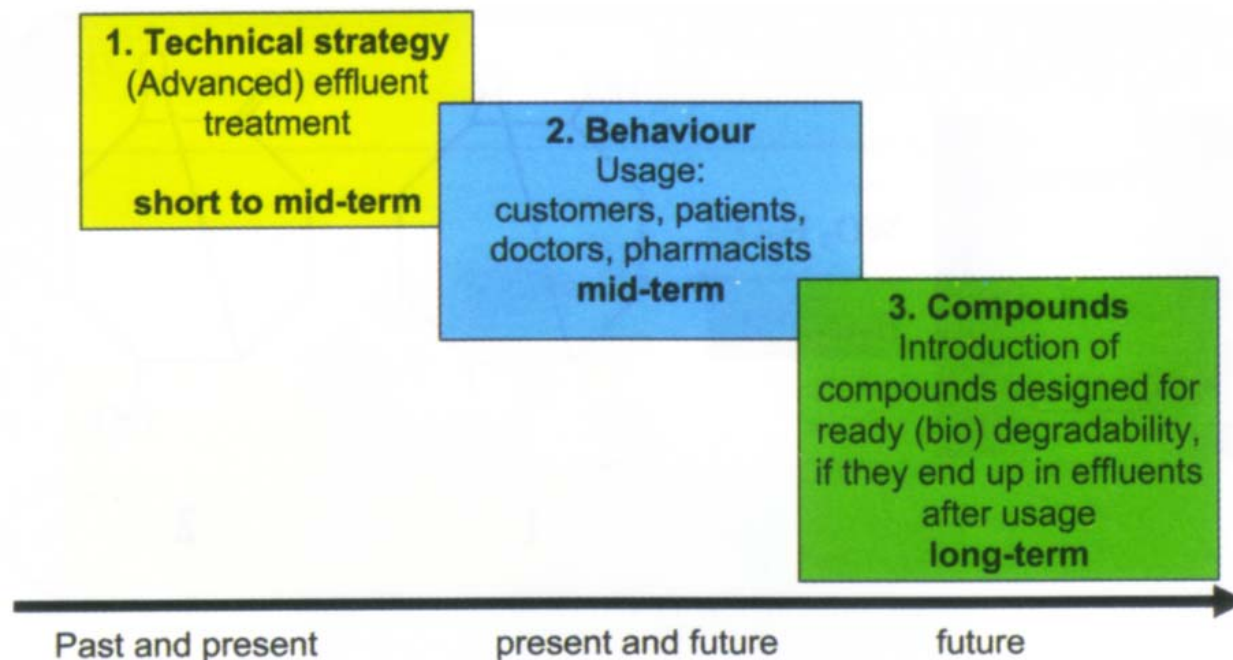


# Sustainable from the very beginning

**Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry**

Klaus Kümmerner *Green Chem.* **2007**, 9(8), 899

Taking into account the full life cycle of chemicals will lead to a different understanding of the full functionality necessary for a chemical. Examples are presented to underline the feasibility and the economic potential of the approach benign by design.





# Methods for chemical activation

## Energy methods

Thermo chemistry  
Photo chemistry  
Electro chemistry  
Piezo chemistry  
Sono chemistry  
Microwave chemistry  
Mechano chemistry

## System requires

Heating  
Chromophore, light source  
Conducting media  
High pressure  
Ultrasound source  
Polar media, microwave source  
Solid, mill-grinding

From sustainability point of view, “greener” technologies with **high energy efficiency** are recommended to use.

Examples are **ball milling**, **microwave** irradiation, and **ultrasound** irradiation. (*Green Chem.*, 2008, 10, 1129-1130, 1131-1141)



# Replacement of volatile organic solvents

**Solvent free** or minimum solvent used

**Solvent alternatives:**

Water

Non-Volatile solvents (fluorous?)

Solvents from renewable resources

Other Benign solvents (ionic liquids, gas-expanded liquids)

Supercritical and near-critical fluid systems

*Green solvents for Chemistry: Perspective and Practice*, by Nelson, Oxford, **2003**

*Green solvents for sustainable organic synthesis* (Sheldon, *Green Chem.* **2005**, 7, 267-278.)

*Green Reaction Media in Organic Synthesis* by Mikami, Blackwell, **2005**

*Alternative Solvents: Shades of Green* (Clark and Tavener, *Org. Proc. Res. Dev.* **2007**, 11, 149-155)

*Solvents from nature* (Horváth, *Green Chem.* **2008**, 10, 1024-1028.)

*Alternative Solvents for Green Chemistry* by Kerton, RSC, **2009**



# Solvent-free Reactions



Reduction	Rearrangement
Oxidation	Elimination
C-C Bond formation	Protection (bond formation)
C-N Bond formation	De-protection (bond-breaking)
C-O Bond formation	Complex formation
C-S Bond formation	Salt formation
C-P Bond formation	Guest-host reaction
C-Halogen Bond formation	Isomerization
N-N Bond formation	Polymerization, etc.

(K. Tanaka, *Solvent-free Organic Synthesis*, Wiley-VCH, 2003.)

F. Toda (Ed), *Top. Curr. Chem. 2005* Vol. 254 (Organic Solid State Reactions)

Z. V. Todres, *Organic Mechanochemistry and its Practical Applications*,  
CRC/Taylor & Francis, 2006.

*Chem. Rev.* 2007, 107, 2503-2545.

*Chem. Soc. Rev.* 2007, 36, 846-855 (metal complexes), 1239-1248 (metal ion catalysed reactions).

Chapter 2 in *Alternative Solvents for Green Chemistry* RCS, 2009



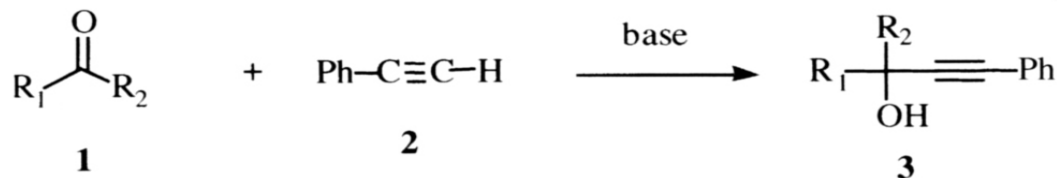


# C-C Bond Formation



**Reaction condition:** solvent-free

**Keywords:** ethynylbenzene, ketone, tertiary alkynol



- a: R<sub>1</sub>=Me; R<sub>2</sub>=Me
- b: R<sub>1</sub>=Me; R<sub>2</sub>=Et
- c: R<sub>1</sub>=Me; R<sub>2</sub>=*n*-Pr
- d: R<sub>1</sub>=Et; R<sub>2</sub>=Et
- e: R<sub>1</sub>=*i*-Pr; R<sub>2</sub>=*i*-Pr
- f: R<sub>1</sub>=Ph; R<sub>2</sub>=Me
- g: R<sub>1</sub>=Ph; R<sub>2</sub>=Et
- h: R<sub>1</sub>=Ph; R<sub>2</sub>=*n*-Pr
- i: R<sub>1</sub>=Ph; R<sub>2</sub>=*i*-Pr
- j: R<sub>1</sub>,R<sub>2</sub>=(CH<sub>2</sub>)<sub>4</sub>-
- k: R<sub>1</sub>,R<sub>2</sub>=(CH<sub>2</sub>)<sub>5</sub>-
- l: R<sub>1</sub>,R<sub>2</sub>=(CH<sub>2</sub>)<sub>6</sub>-

## Experimental procedures:

After acetone **1a** (1.0 g, 17.2 mmol), ethynylbenzene **2** (1.8 g, 17.2 mmol) and potassium *t*-butoxide (1.9 g, 17.2 mmol) were well-mixed with agate mortar and pestle, the mixture was kept at room temperature for 20 min. The reaction product was mixed with 10% aqueous sodium chloride, filtered, washed with water, and dried to give **3a** as colorless crystals (2.6 g, 94% yield).

**References:** H. Miyamoto, S. Yasaka, K. Tanaka, *Bull. Chem. Soc. Jpn.*, **74**, 185 (2001).



## Advantages of using solvent-free conditions

1. There is no reaction media to collect, dispose of, or purify and recycle.
2. On a laboratory's preparative scale, there is often no need for specialized equipment.
3. Extensive and expensive purification procedures such as chromatography can often be avoided due to the formation of sufficiently pure compounds.
4. Greater selectivity is often observed.
5. Reaction times can be rapid, often with increased yields and lower energy usage.
6. Economic considerations are more advantageous, since cost savings can be associated with the lack of solvents requiring disposal or recycling.
7. **Can be applied to solid-solid, solid-liquid, solid-gas, liquid-liquid, and liquid-gas reactions**



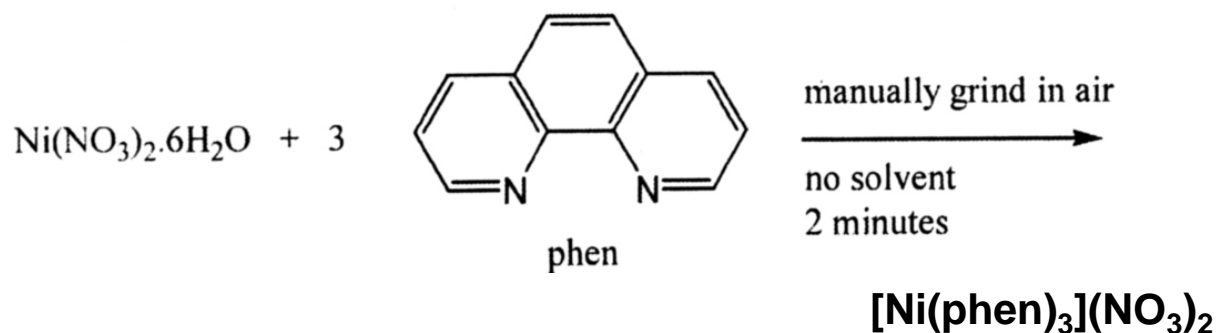
# Solvent-free reactions **without generating hazardous by-product** is a clean technology

For a solid-state reaction to take place, the reactants have to be vigorously mixed by applying external mechanical energy, and may be called **mechanochemistry**. It has been used for inorganic solids, and for inorganic-organic composite materials. Purely organic reactions were not well-developed since about mid 1970s.

## Metal complex formation



Nickel nitrate and phenanthroline

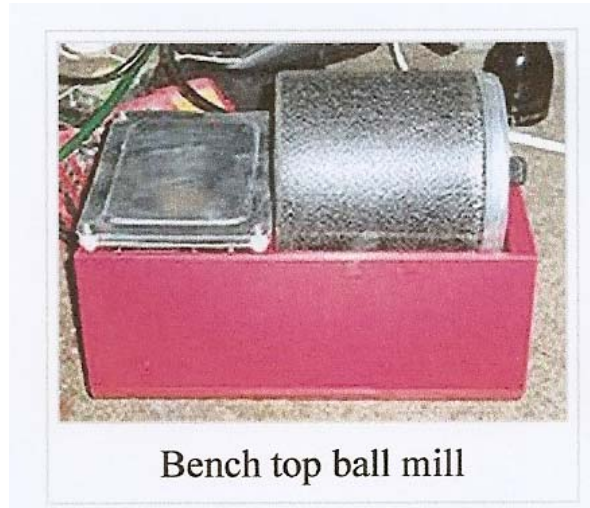
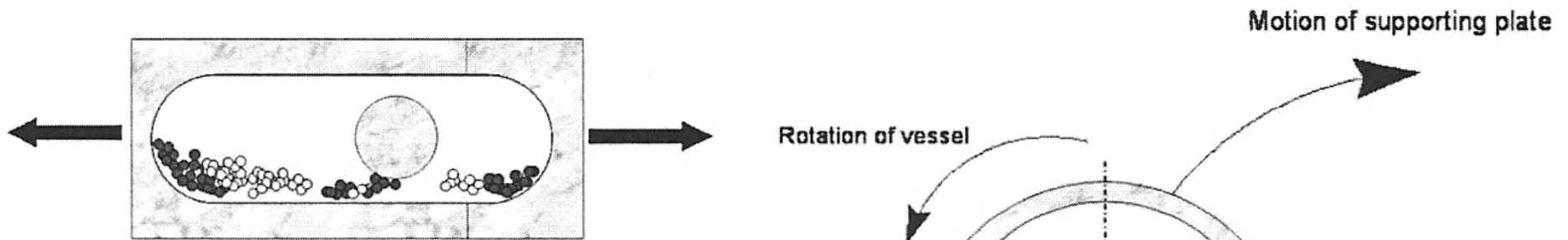




# Commercial ball mills

- a shaker mill (vibration)

a planetary mill (rotation)

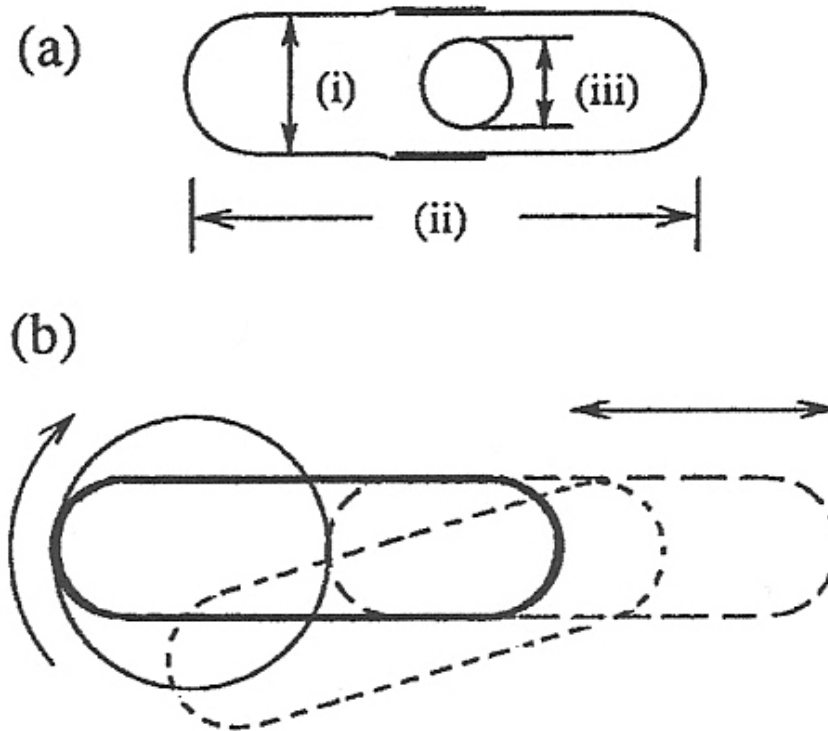


Bench top ball mill



# High speed vibration mill (HSVM)

HSVM at the speed of 3500 rpm was developed by Komatsu and coworkers. A pressure of 10-20000 bar may be generated.

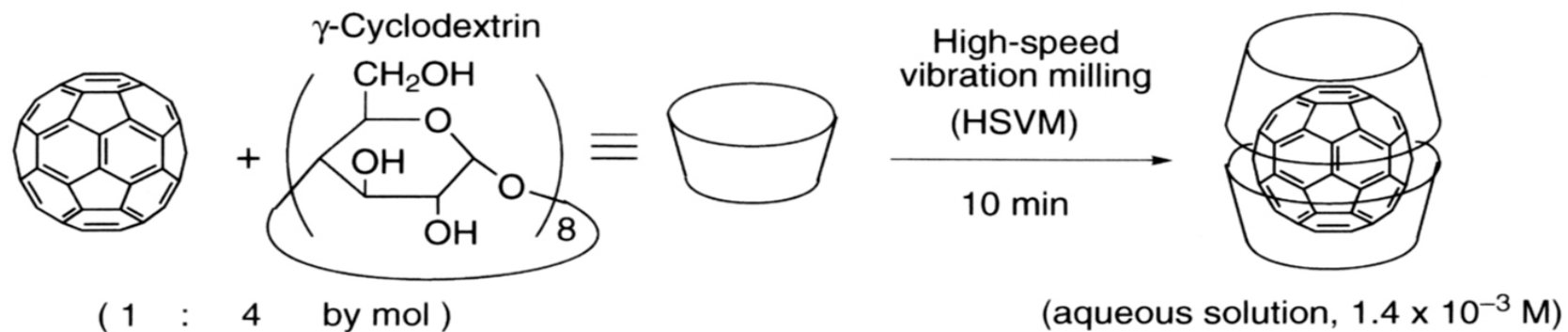


**Figure 13.** (a) A mixing capsule with a milling ball: (i) inner diameter, 9.0 mm; (ii) inner length, 26 mm; (iii) diameter, 6.0 mm. (b) Schematic representation of the movement of the capsule: one end moves around a circle while the other end moves horizontally.

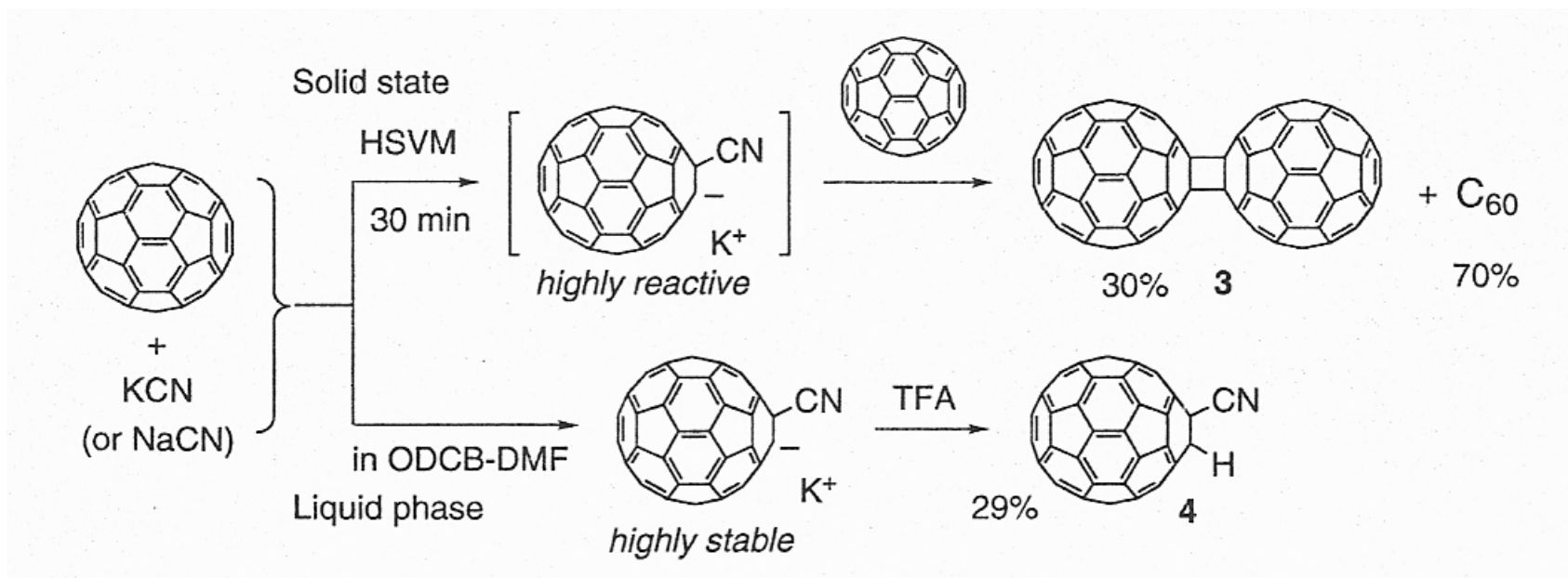




# Guest-Host interaction

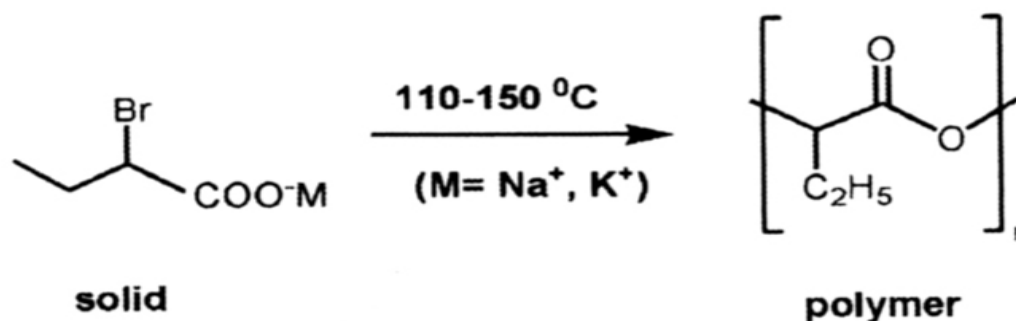


# Dimerization of C-60

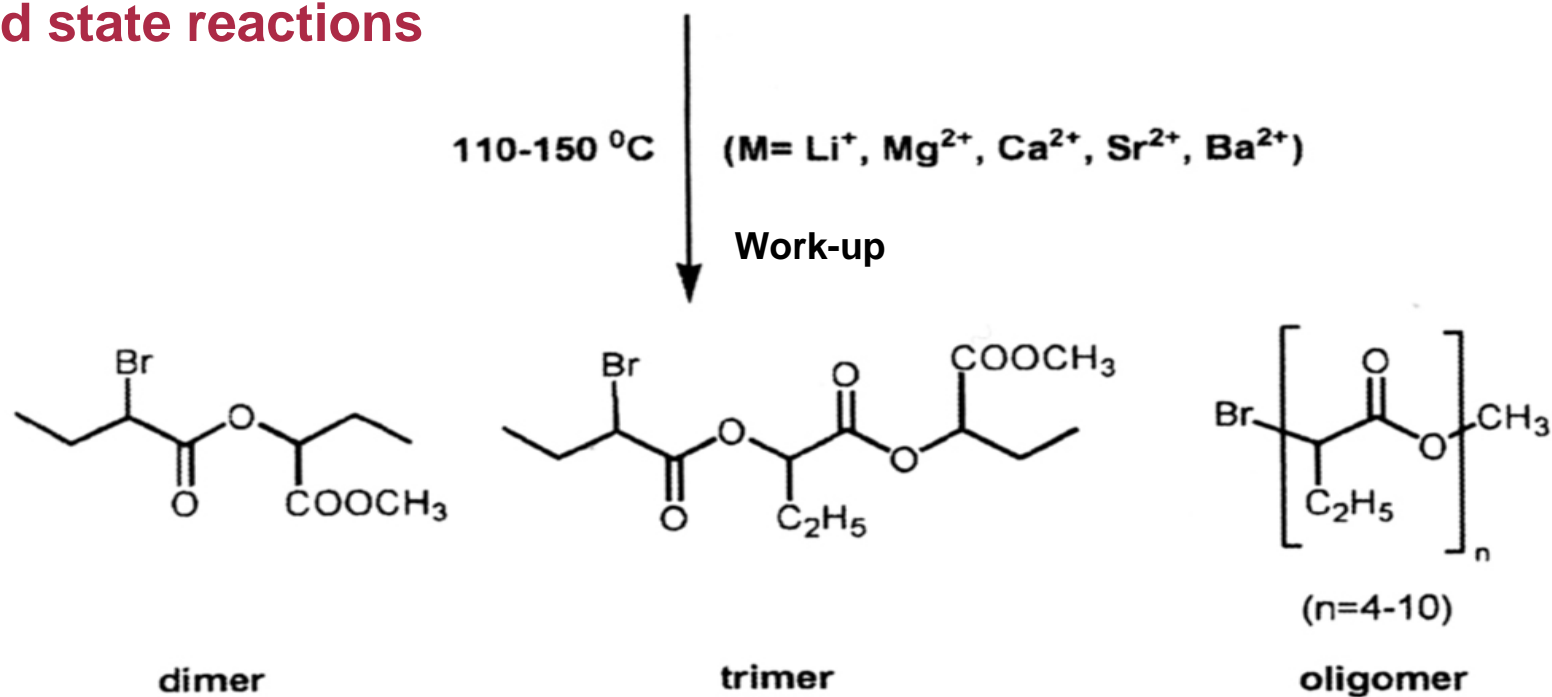




# Mechanically induced polymerization

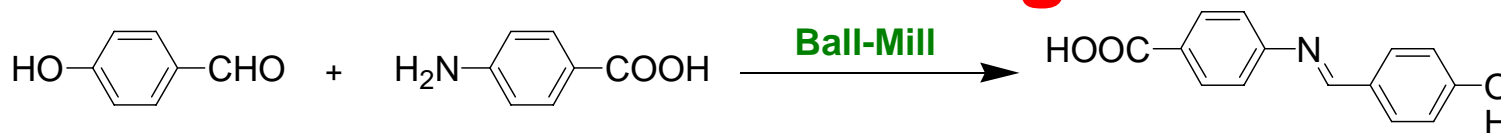


## Solid state reactions



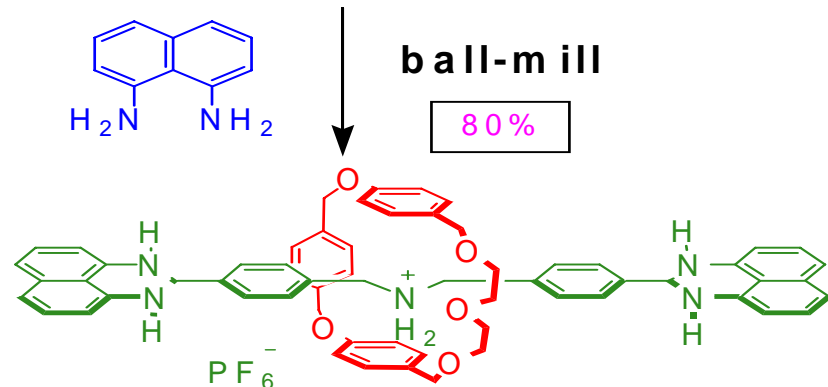
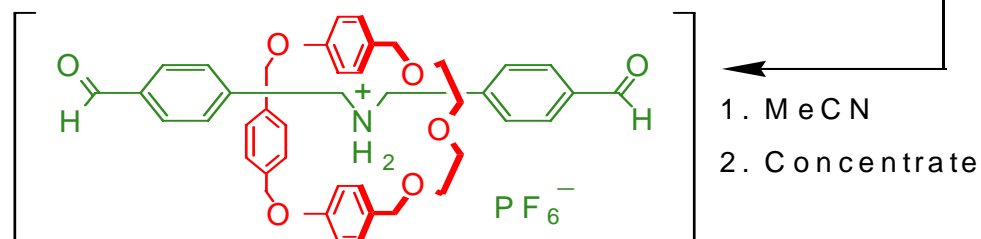
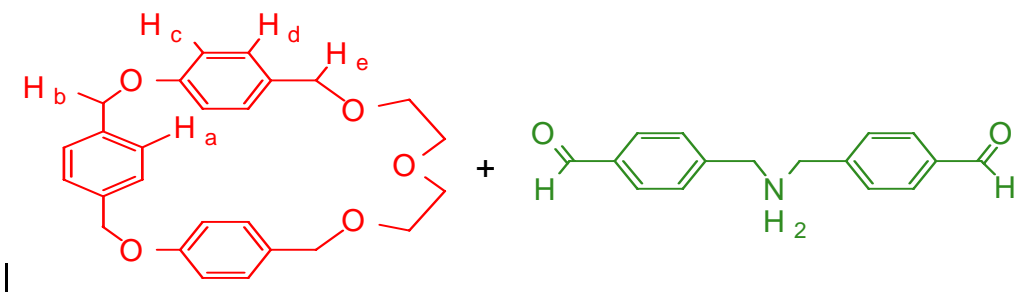


# Solid-to-Solid Ball-Milling Process



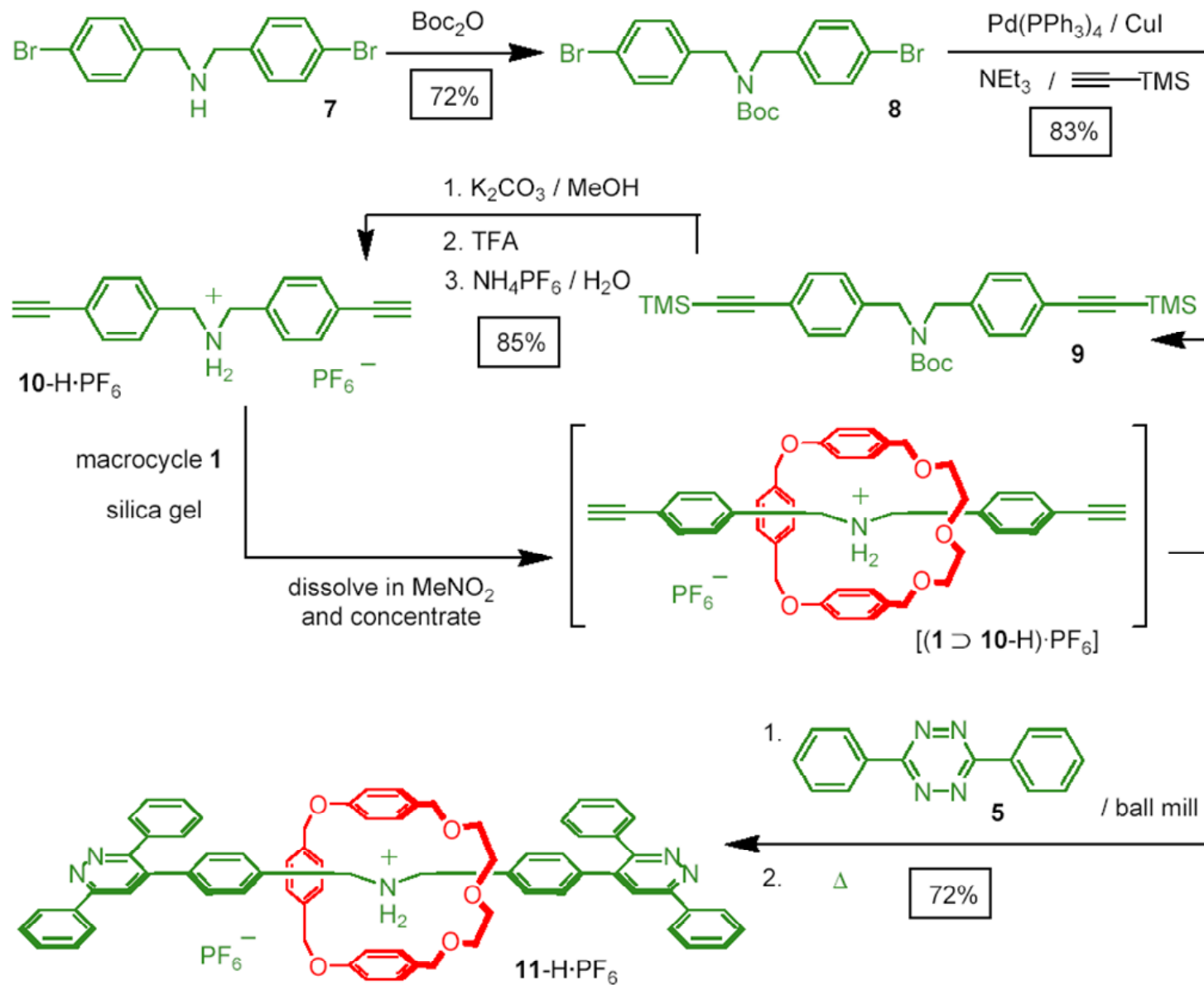
Kaupp, et al. *Chem. Engin. Sci.* 2002, 57, 763

## A [2]-Rotaxane



Chiu, S.-H. et al. *Angew. Chem. Int. Ed.* 2008, 47, 4436-4439





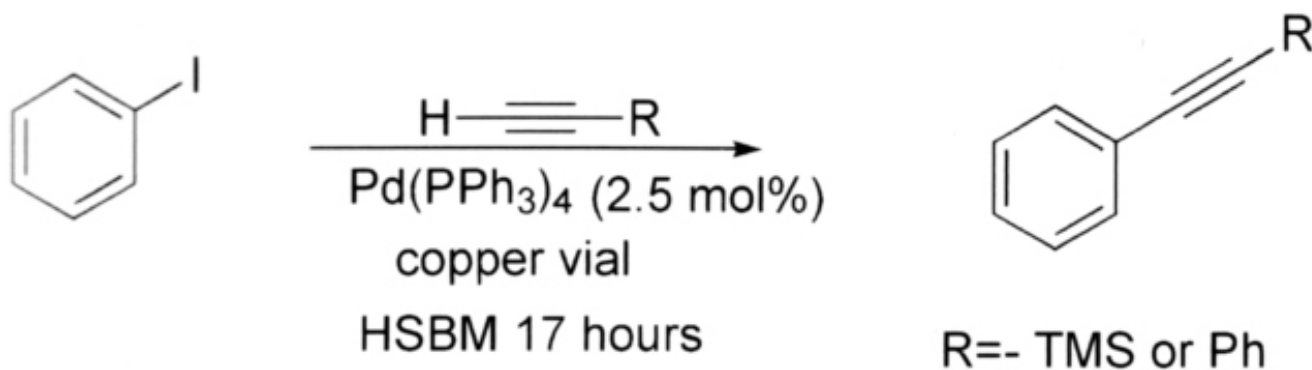
邱勝賢等 *Tetrahedron* 2009, 65, 2824-2829



## Solvent-free Sonogashira coupling reaction *via* high speed ball milling

Dennis A. Fulmer, William C. Shearouse,  
Shareika T. Medonza and James Mack\*

Herein, we report on the solvent-free Sonogashira reaction utilizing high speed ball milling. When the reaction is conducted in a copper vial in lieu of copper iodide, the reaction gives the coupling product in high yields. This demonstrates the first report on the use of the vial and ball material as a catalyst in a ball milled chemical reaction.



93-95% yield, lower if substituted ArI

(*Green Chem.* **2009**, *11*, 1821-1825)

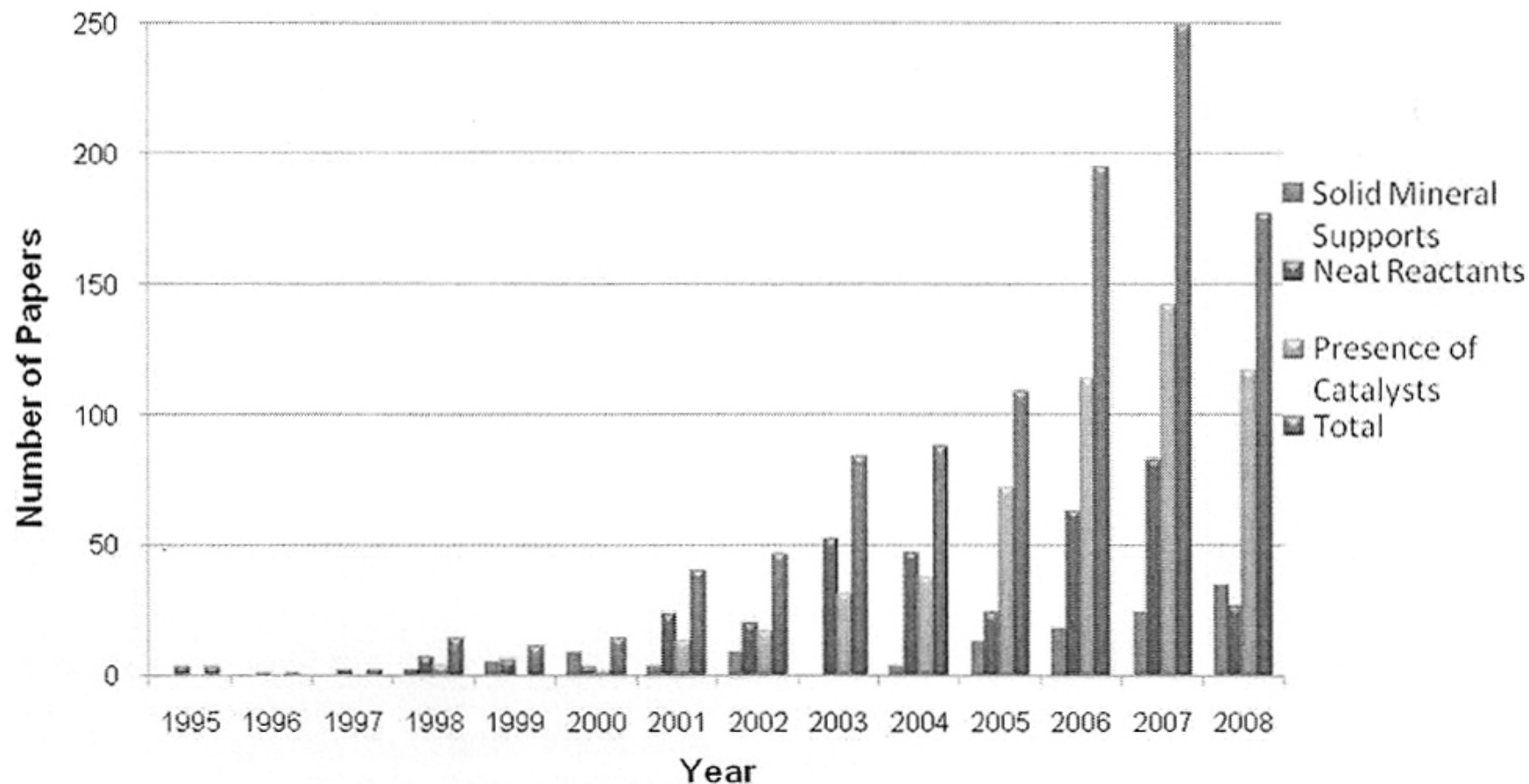


# Solvent-free Heterocyclic Synthesis



M. A. Martins, et al., *Chem. Rev.* **2009**, *109*, 4140-4182

Distribution of papers dealing with synthesis of heterocyclic compounds under solvent-free condition by year



Heating, microwave irradiation, ultrasound irradiation, and grinding



# The Use of Microwave Irradiation

COST Chemistry Action D32, starting in 2004

(Co-opération Européenne dans le Recherche Scientifique et Technique, European Co-operation in the Field of Scientific and Technical Research)

**Four microwave-based working groups** involving collaboration between scientists with different expertise in modern technology:

1. Diversity oriented synthesis under **high efficient microwave conditions**. The objectives are:
  - (a) to apply **solvent-less** condition and **alternative reagents** to known reactions;
  - (b) to perform organic reactions in **aqueous media**;
  - (c) to evaluate multi-component reactions under **microwave and/or micro-reactor** condition to minimize waste and optimize atom-efficiency in comparison with conventional stepwise reaction under traditional conditions;
  - (d) to establish, in a combinatorial approach, novel atom economic **multi-component reactions assisted by microwave and/or micro-reactor** technology to efficiently access pharmaceutical applications.



2. **Microwave** and high-intensity **ultrasound** in the synthesis of fine chemicals.
3. **Ultrasound and microwave-assisted** synthesis of nanometric particles.
4. Development and design of **reactors** for microwave-assisted chemistry in the laboratory and on the pilot scale.

**The objective of COST D32 is to establish a firm EU base in microwave chemistry and to exploit the new opportunities provided by microwave techniques singly or in appropriate combination, for the widest range of applications in modern chemistry.**

#### References:

- A. Loupy (Ed), *Microwaves in Organic Synthesis, 2nd Edition, 2 Vols*, Wiley-VCH, 2006
- C. O. Kappe and A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, 2005
- Microwave dielectric heating in synthetic organic chemistry*, C. O. Kappe, *Chem. Soc. Rev.* 2008, 37, 1127-1139
- C. O. Kappe, *et al.*, *Practical Microwave Synthesis for Organic Chemists*, Wiley-VCH



## Characteristics of microwaves

electromagnetic waves with low energy photon

## Microwave-matter interaction

causes movement of molecules (dipolar rotation)

causes movement of ions (ionic conduction)

will be reflected, transmitted or absorbed

volumetric heating throughout an absorbing material

## Microwave effects

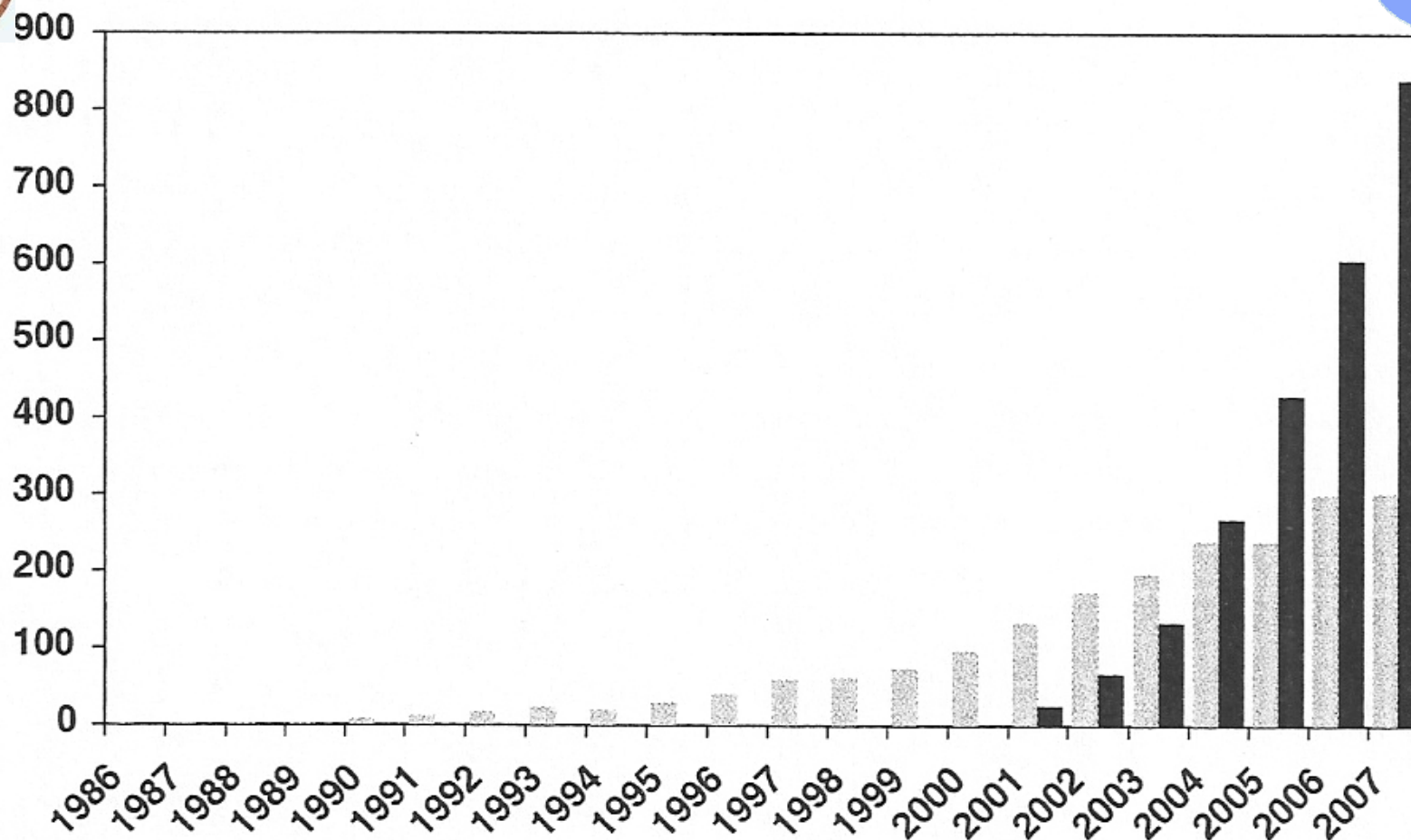
thermal effects – dipolar polarization

superheating in a mw cavity

non-thermal effects – increasing pre-exponential factor  $A$

decreasing activation energy





**Figure 1.1** Publications on microwave-assisted organic synthesis (1986–2007). Gray bars: Number of articles involving MAOS for seven selected synthetic organic chemistry journals (*J. Org. Chem.*, *Org. Lett.*, *Tetrahedron*, *Tetrahedron Lett.*, *Synth. Commun.*, *Synthesis*, *Synlett*). SciFinder Scholar keyword search on

“microwave”). The black bars represent the number of publications (2001–2007) reporting MAOS experiments in dedicated reactors with adequate process control (about 50 journals, full text search: microwave). Only those articles dealing with synthetic organic chemistry were selected. **(Kappe, 2009, p. 4)**



## Loss tangents ( $\tan \delta$ of solvents at 2.45 GHz and 20°C)

Solvent	$\tan \delta$	Solvent	$\tan \delta$
Ethylene glycol	1.350	N,N-dimethylformamide	0.161
Ethanol	0.941	1,2-dichloroethane	0.127
Dimethyl sulfoxide	0.825	Water	0.123
2-propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-butanol	0.571	Acetone	0.054
2-butanol	0.447	Tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	Dichloromethane	0.042
1-methyl-2-pyrrolidone (NMP)	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

(Kappe et al., 2009, p. 15)

Solvents can be classified as high ( $\tan \delta > 0.5$ ), medium ( $\tan \delta 0.1- 0.5$ ) and low ( $\tan \delta < 0.1$ ) microwave absorbing. ( $\tan \delta = \delta'' / \delta'$ )





# Absorption of MW by Vessels

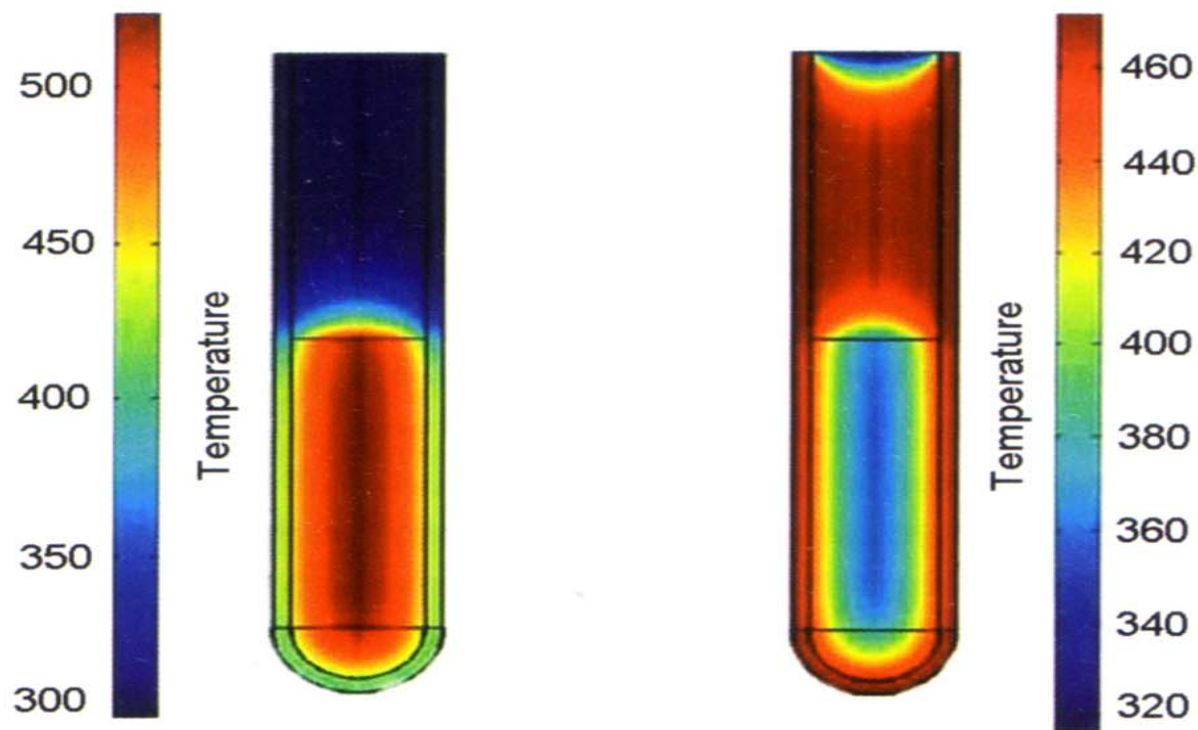
Loss tangents ( $\tan \delta$ ) of low-absorbing materials, 2.45 GHz, 25 °C

Material	$\tan \delta (\times 10^{-4})$	Material	$\tan \delta (\times 10^{-4})$
Quartz	0.6	Plexiglass	57
Ceramic	5.5	Polyester	28
Porcelain	11	Polyethylene	31
Phosphate glass	46	Polystyrene	3.3
Borosilicate glass	10	Teflon	1.5

(Kappe et al., 2009, p. 18)



# Microwave vs conventional thermal heating



**Fig. 2.6** Inverted temperature gradients in microwave versus oil-bath heating [12]. Temperature profiles (finite element modeling) after 1 min as affected by microwave irradiation (left) compared to treatment in an oil bath (right). Microwave irradiation raises the

temperature of the whole volume simultaneously (bulk heating), whereas in the oil-heated tube the reaction mixture in contact with the vessel wall is heated first. Temperature scales in Kelvin. Reproduced with permission from [12].



# Super-heating

Solvent	B.p./ °C)	B.p. MW/°C	Difference
Water	100	105	5
Ethanol	79	103	24
Methanol	65	84	19
Dichloromethane	40	55	15
Tetrahydrofuran	66	81	15
Acetonitrile	81	107	26
Propan-2-ol	82	100	18
Acetone	56	81	25
Ethyl acetate	78	95	17
Dimethylformamide	153	170	17
Diglyme	162	175	13

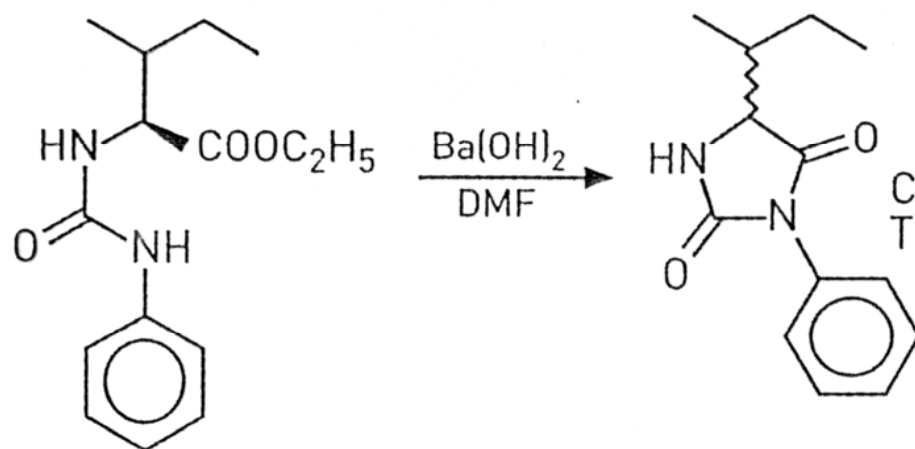


# Examples in pharmaceutical chemistry

## NEW DOORS

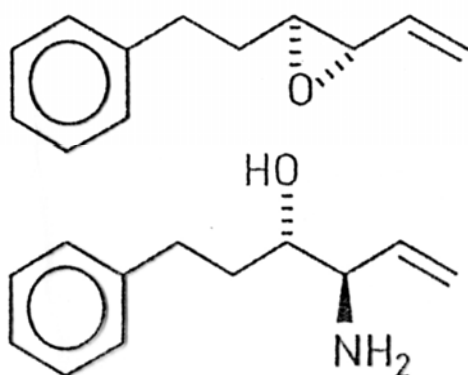
Microwave-based system may contribute to shorter drug development times

### Hydantoin synthesis



Coherent Synthesis: 4 minutes, 90% yield  
Traditional synthesis: 48 hours, 54% yield

### Aminolysis

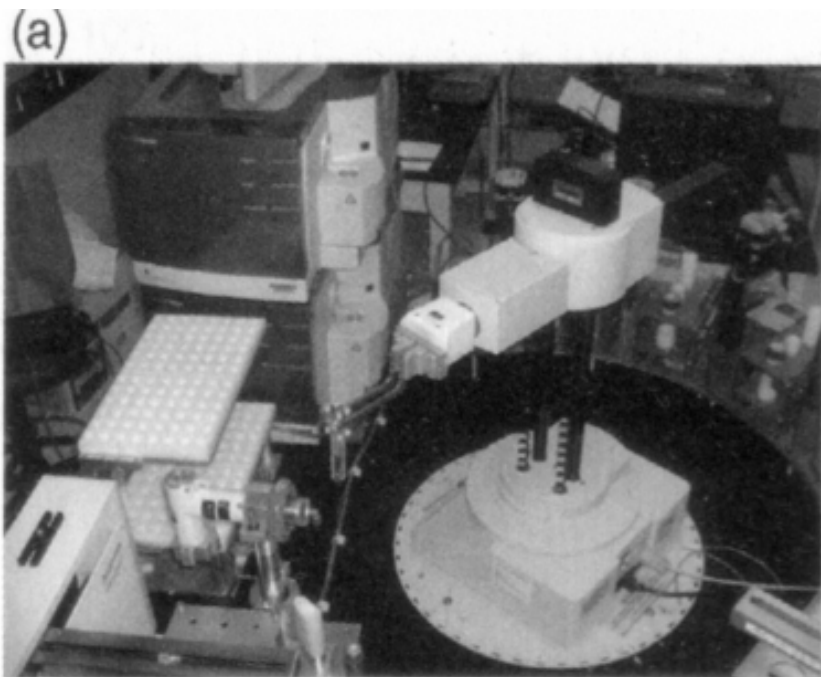


Coherent Synthesis: 7 minutes, 93% yield  
Traditional chemistry: 240 hours, 13% yield

(C&EN, Feb, 11, 2002, pp. 17-18)



# Robotic facility (Abbott Lab) (a) and high throughput factory (Novartis) (b)

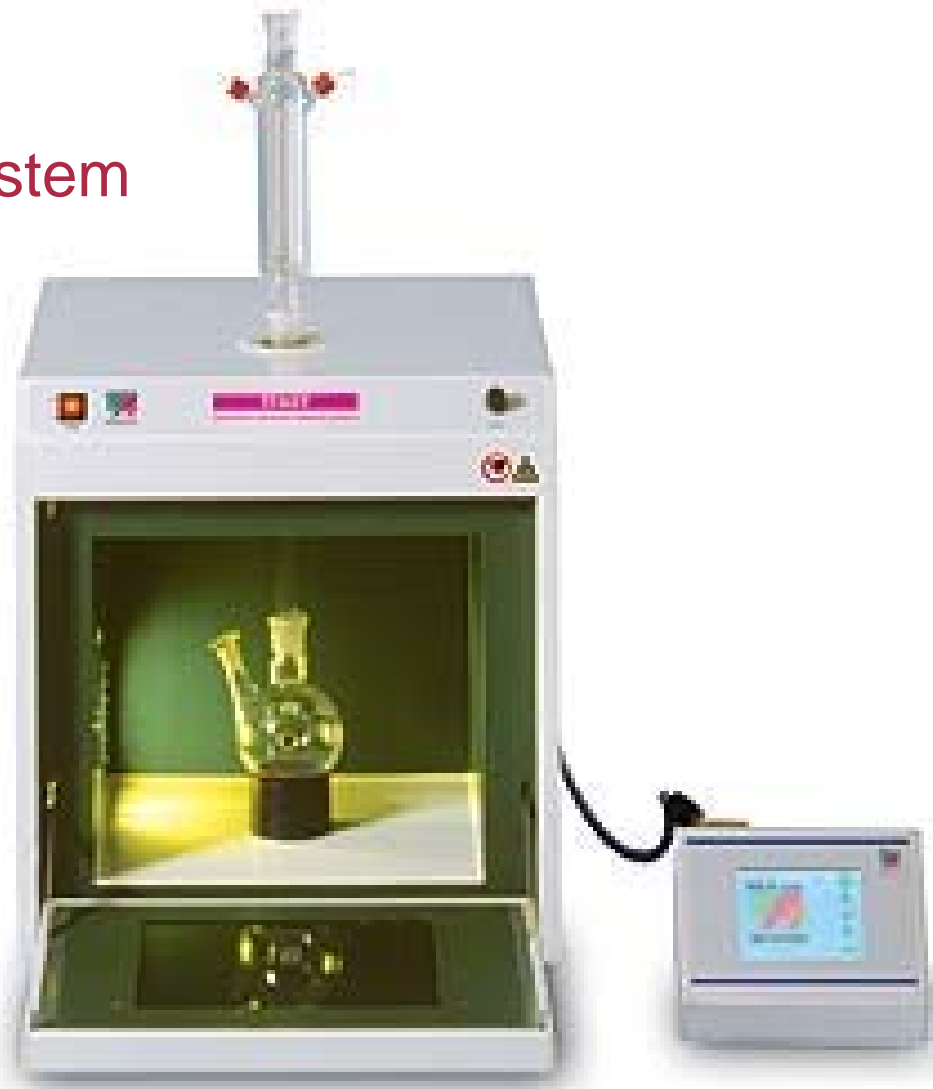


(Kappe, *et al.*, 2009, p. 117)



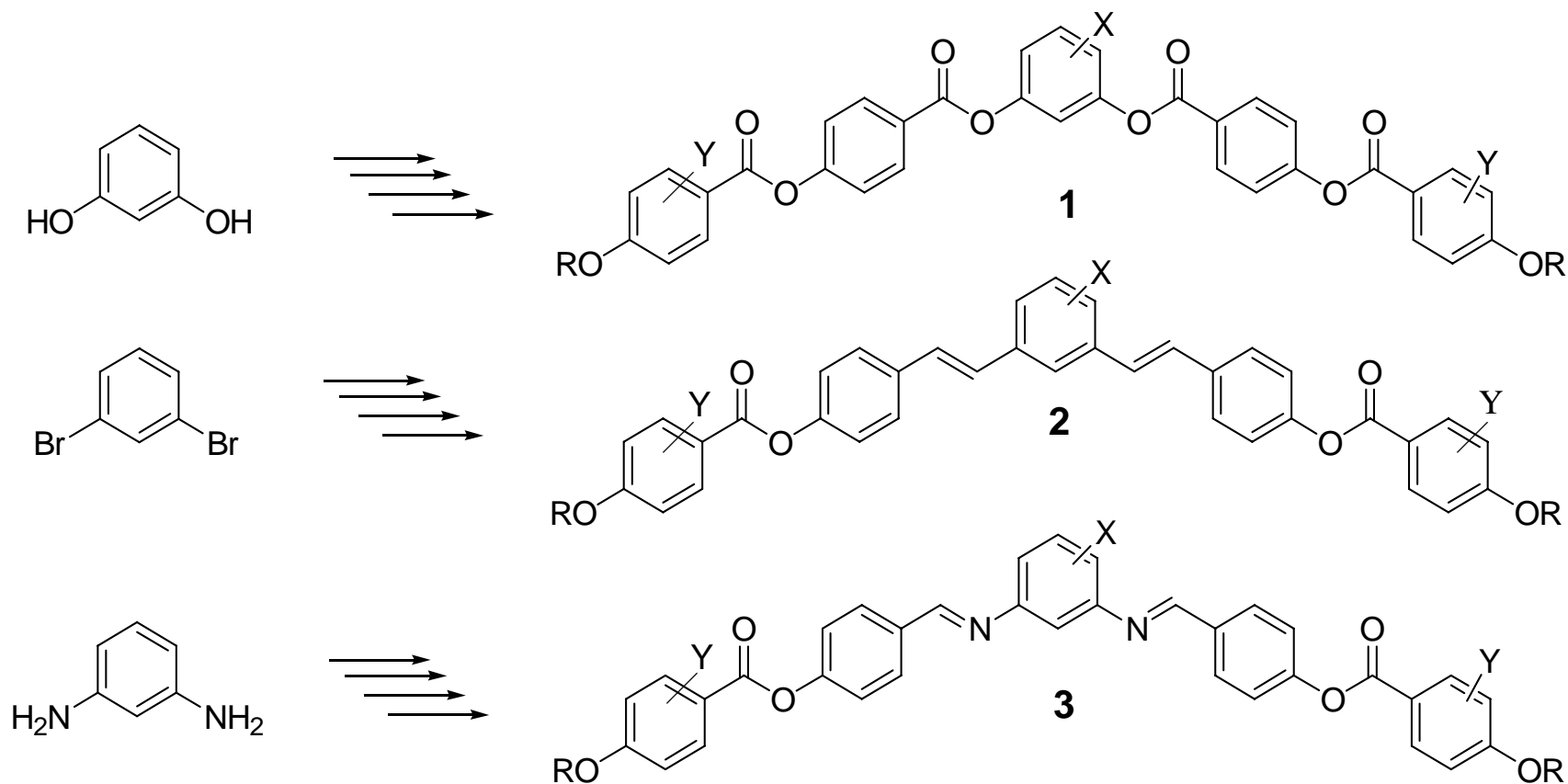
# Laboratory scale preparations

## Milestone START System





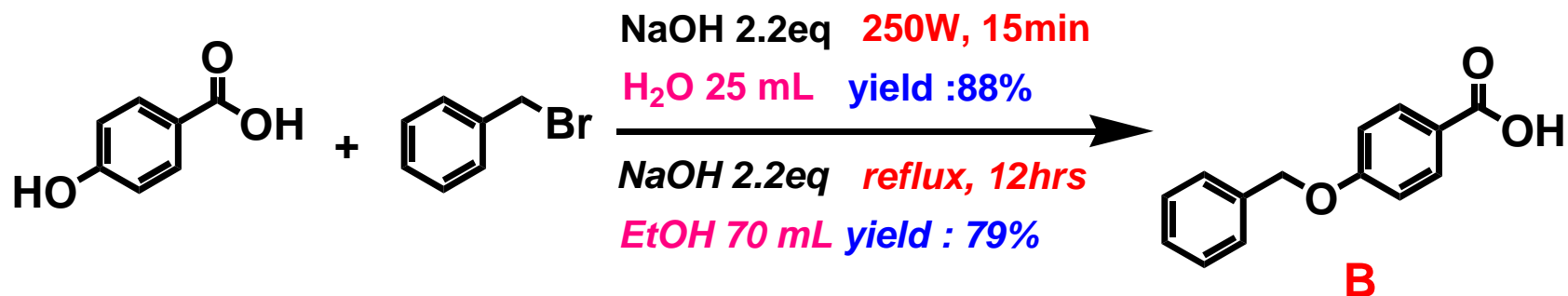
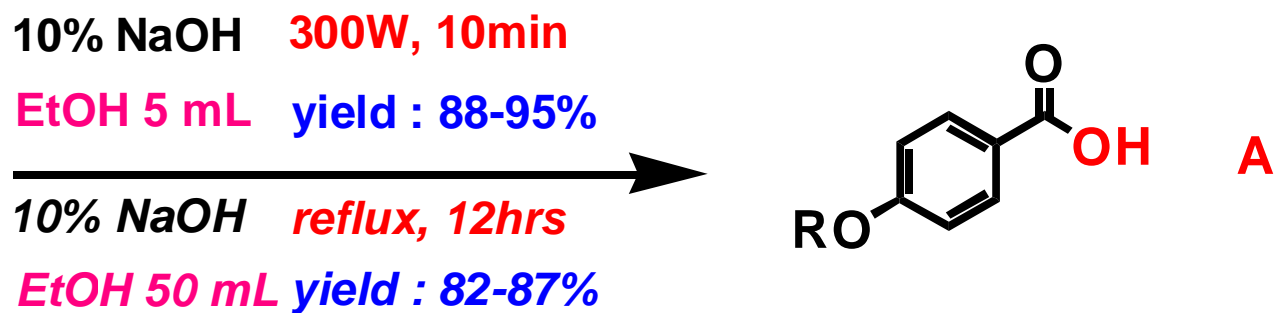
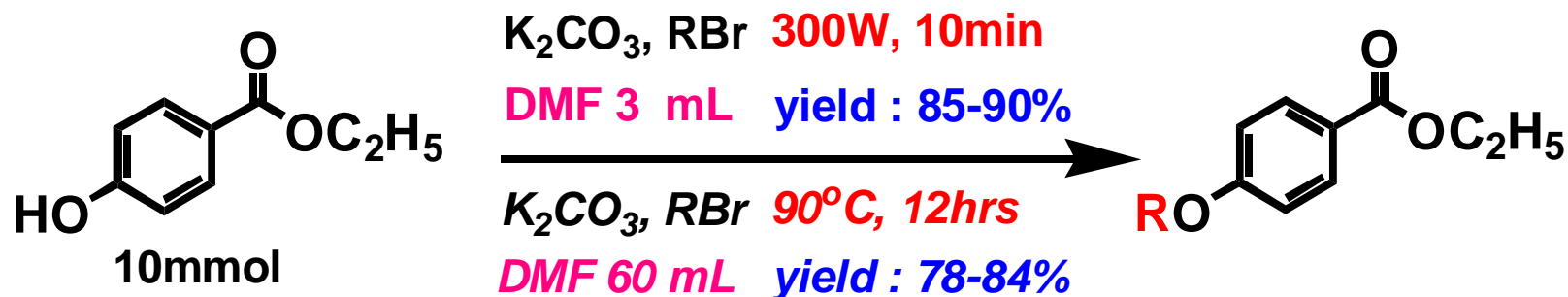
# Microwave-assisted Organic Preparations of banana shape molecules



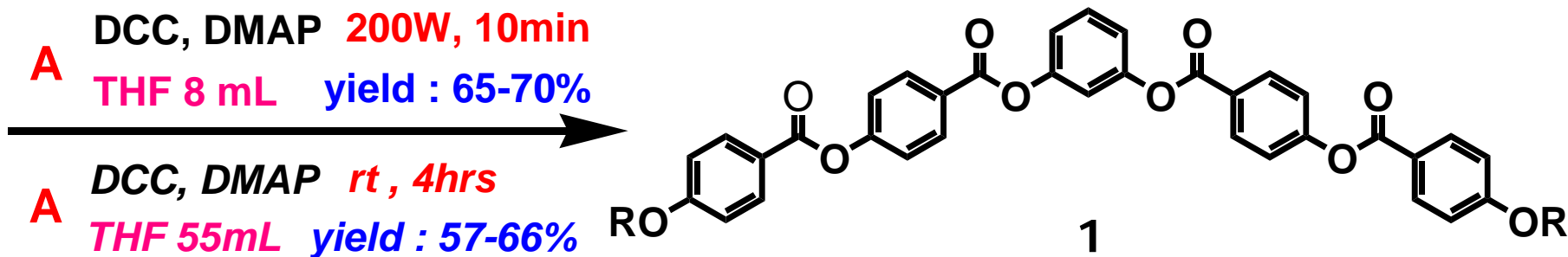
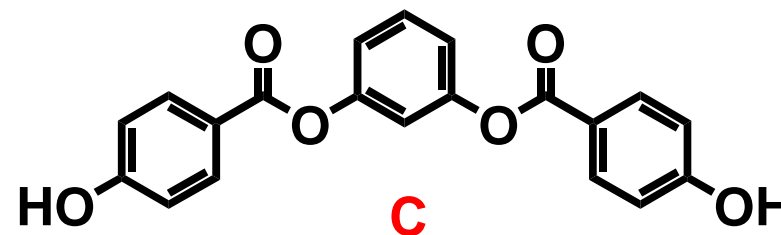
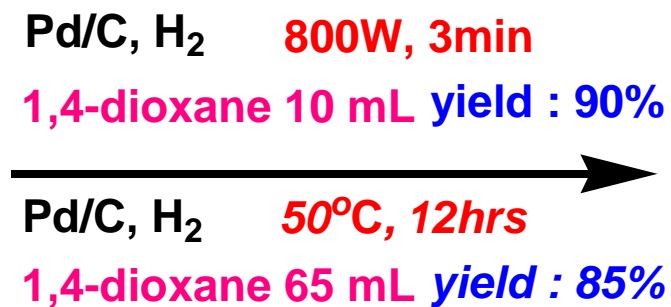
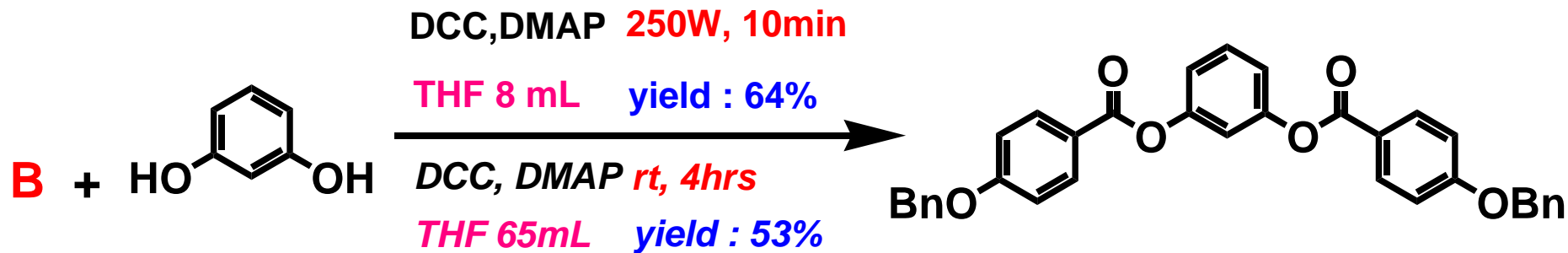
**R = alkyl groups of different chain length**

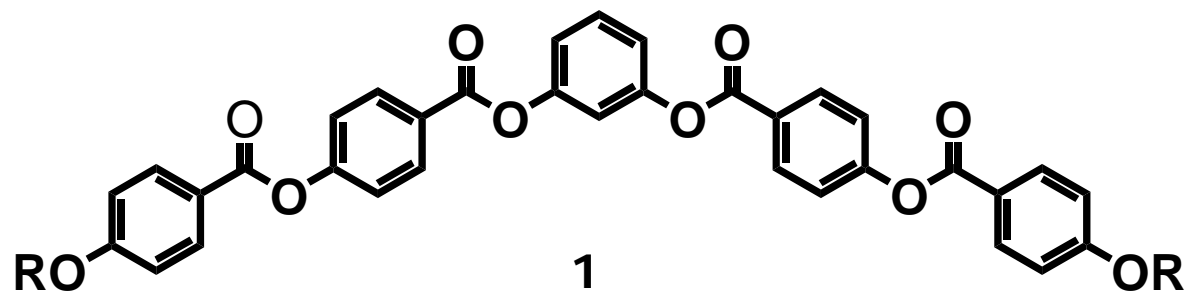
(Liu and coworkers, 2003-2006)







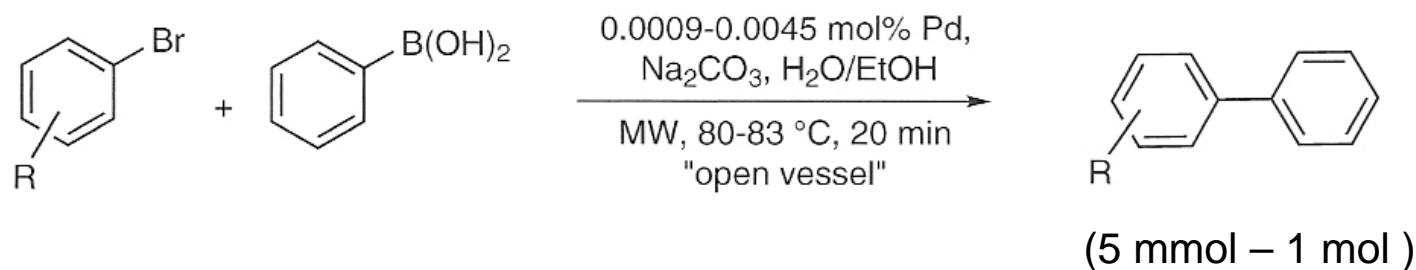




	MW	Traditional
<b>Yield (6 steps from resorcinol)</b>	<b>33-35%</b>	<b>20-23%</b>
<b>Reaction time</b>	<b>58 min</b>	<b>56hrs</b>
<b>Solvent</b>	<b>34 mL</b>	<b>360 mL</b>
<b>Power (kW/hr)</b>	<b>0.85</b>	<b>2.0</b>

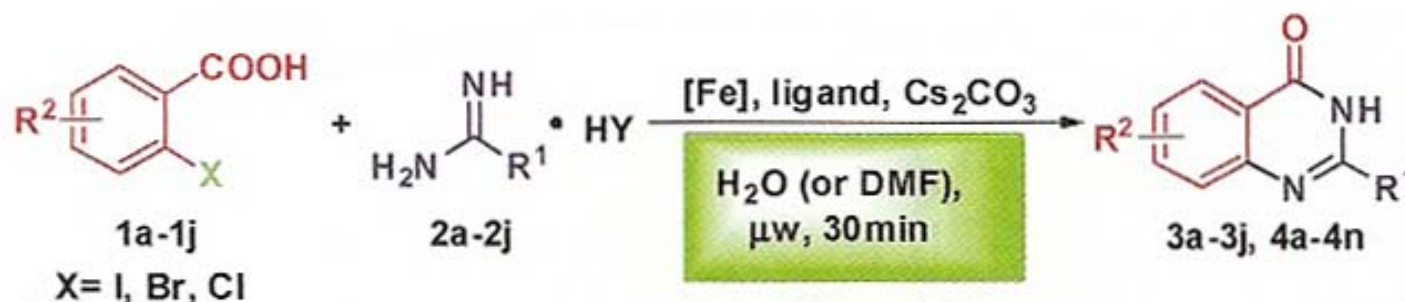


## Suzuki reaction with trace catalyst



Leadbeater, *et al.*, *Org. Process Res. Dev.* **2006**, *10*, 833-837

## Synthesis of quinazolinone derivatives

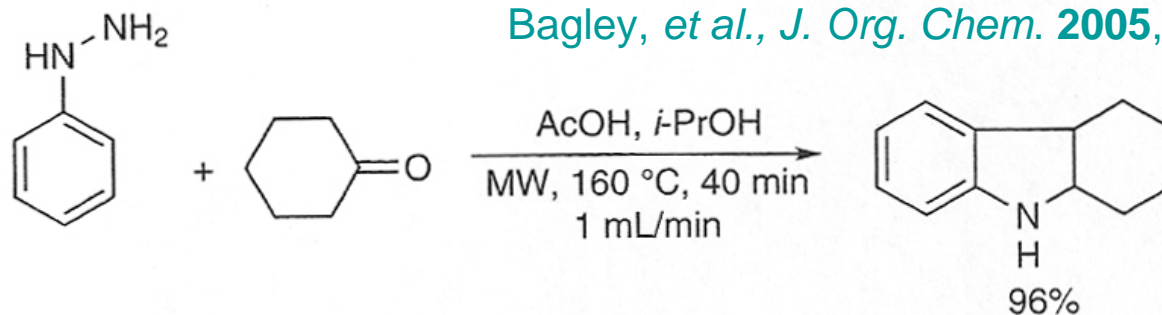


Zhang, *et al.*, *Green Chem.* **2009**, *11*, 1881-1888

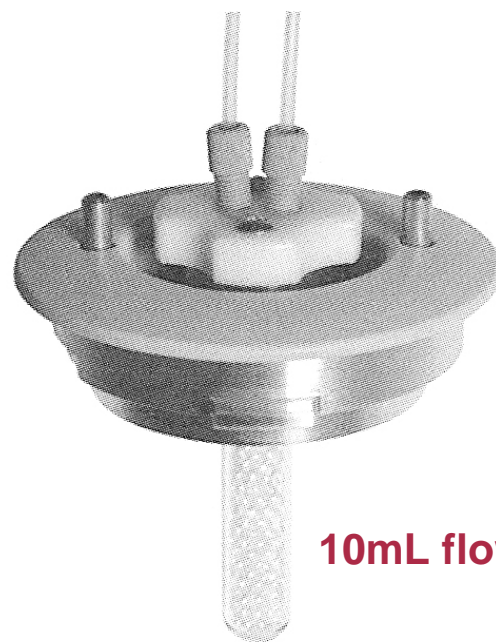


# Fischer Indole synthesis with continuous flow mode to scale-up

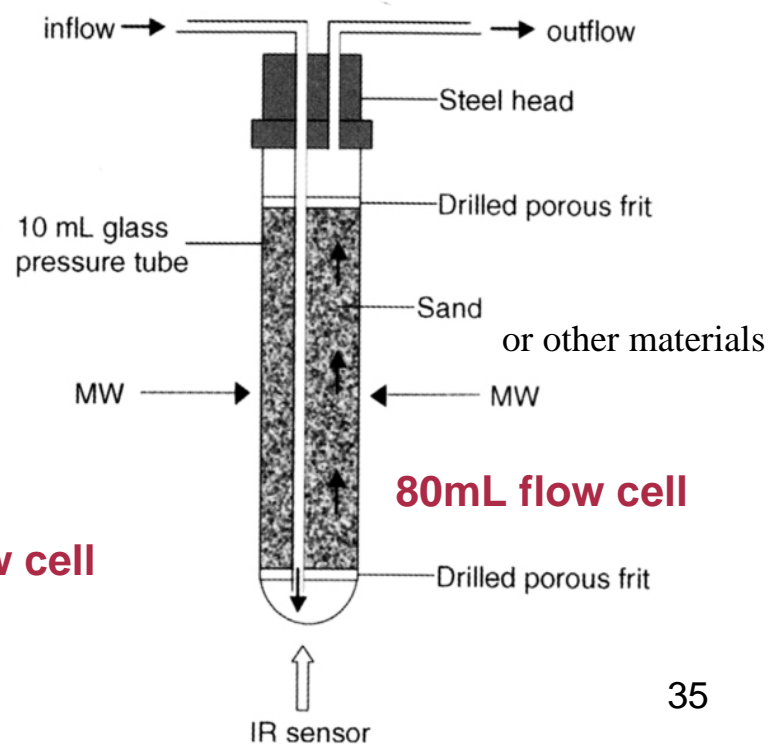
Bagley, *et al.*, *J. Org. Chem.* **2005**, *70*, 7003-7006



CEM Voyager<sub>CF</sub>



10mL flow cell

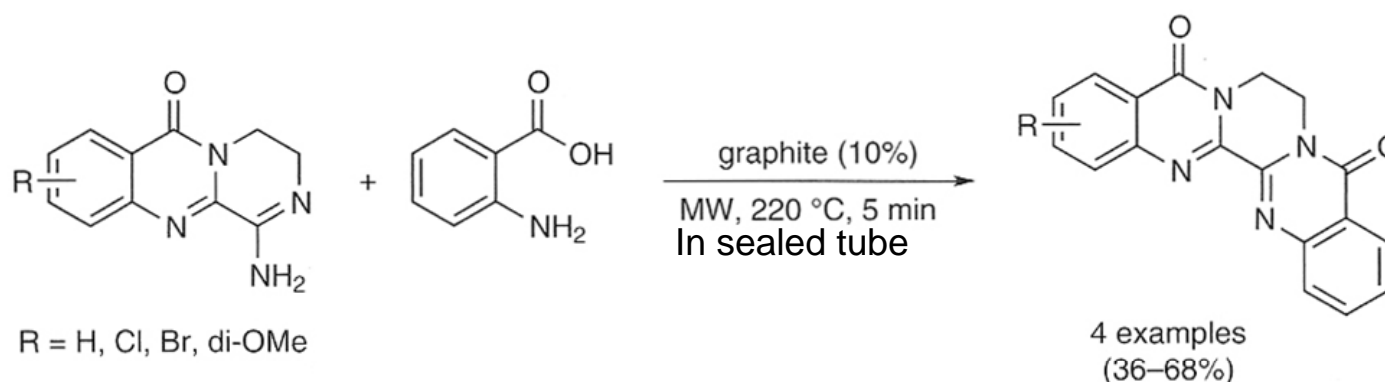




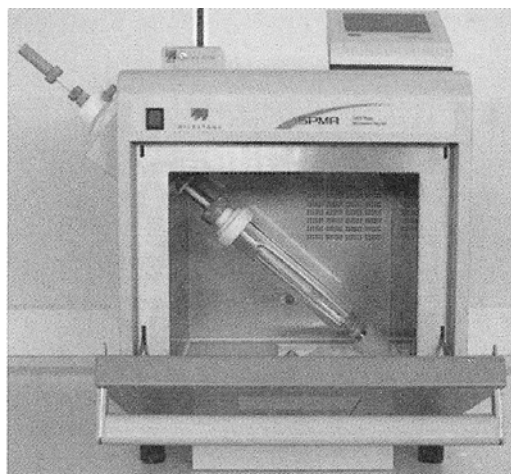
## More examples

### Solventless reaction using graphite as sensitizer

(**caution:** temperature may be very high, the use of quartz reactor is preferred)



de Fatima Pereira, *et al.*, *Tetrahedron Lett.* **2005**, *46*, 3445-3447

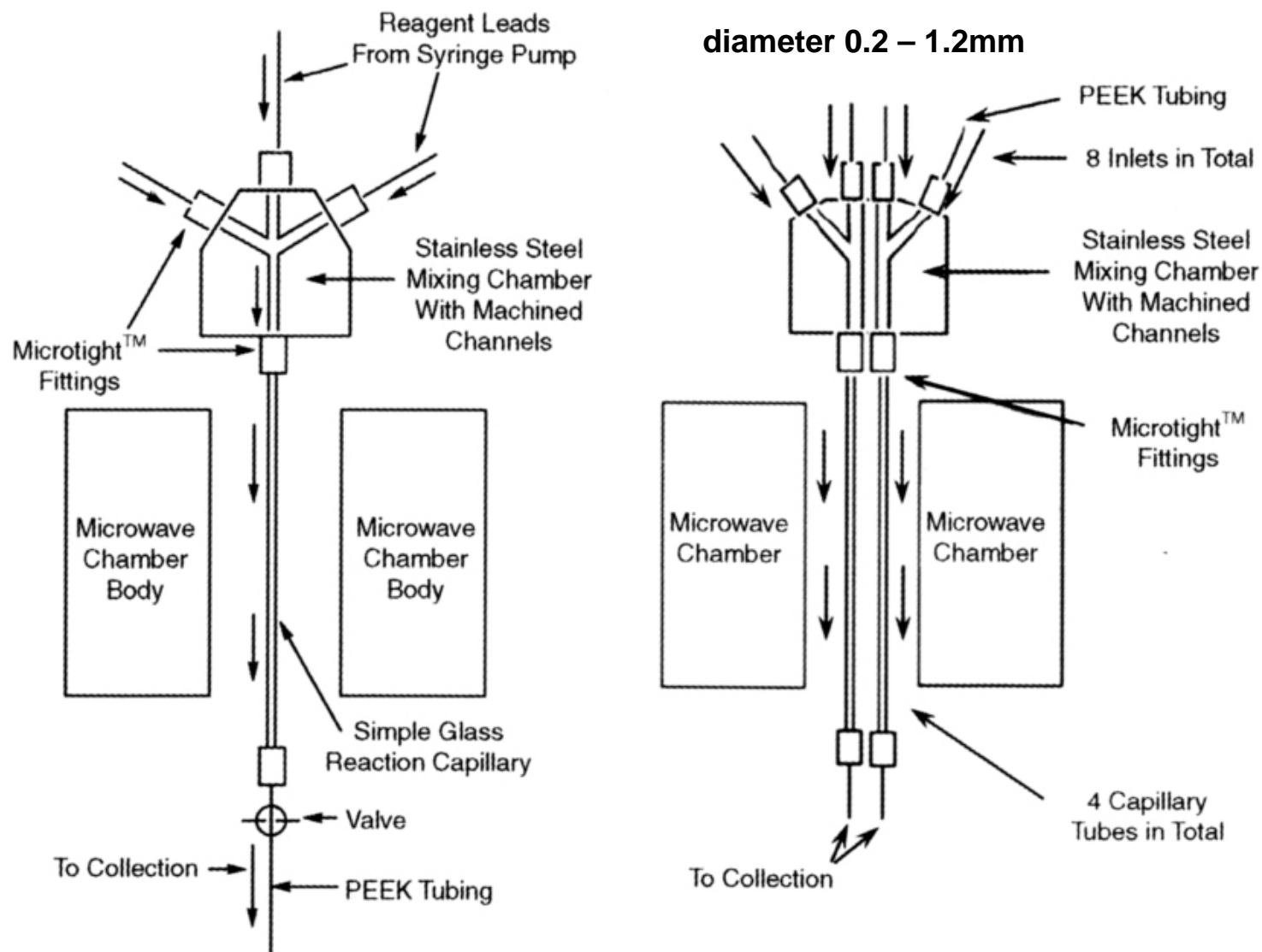


**A device with rotating vessel**  
(Milestone RotoSYNTH)  
Kappe, *et al.*, p. 84



# The use of microreactors

**Suzuki-Miyaura coupling in minutes to give 80-100% yield**



Comer and Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160-8167

37

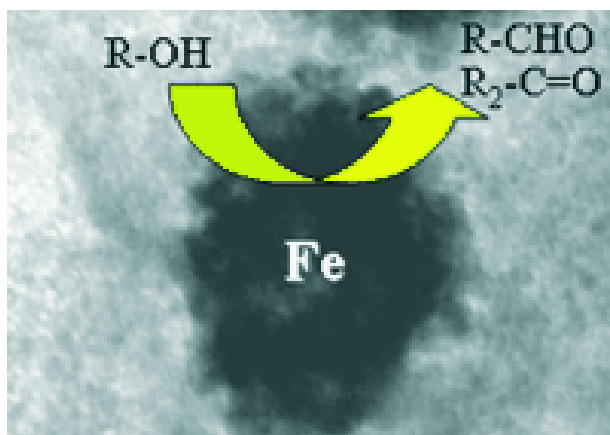
Wirth (Ed), *Microreactors in Organic Synthesis and Catalysts*, Wiley-VCH, **2008**





## Efficient microwave oxidation of alcohols using low-loaded supported metallic iron nanoparticles

Highly active and stable iron nanoparticles have been prepared on a range of supports using a facile and environmentally friendly microwave approach. (Added 0.2 g support to 2 mL EtOH containing 199 mg of  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  and heated in a microwave of 200W for 15 min, 100-120°C, washed with ethanol and then acetone, and dried overnight at 100°C) These inexpensive metallic iron nanoparticles were found to be extremely active and selective in the  $\text{H}_2\text{O}_2$  oxidation of various alcohols (under 200W MW at 70-90°C for 1 hr), achieving excellent turnover numbers (**more than 150**). Fe/MCM-41 (**0.3%, 8.21 nm**) was found to be highly reusable, preserving and even slightly increasing its activity after several uses.



(*ChemSusChem* **2008**, 1, 746-750)



# 鄭重推薦



Advantages of Microwave-assisted preparations:

- Energy saving
- Solvent saving
- Time saving
- Reactivity improved
- Selectivity improved
- Productivity improved

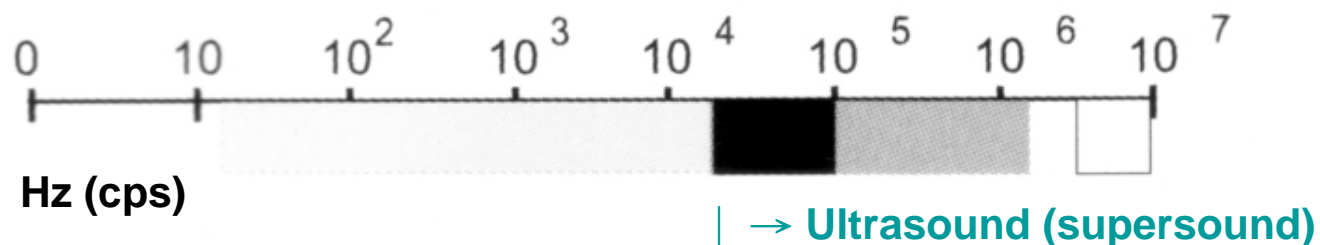
微波反應法便捷, 高效, 節能, 省物. 是一極佳的永續化學製備方法. 建議試用.









# Sonochemistry

## Sound frequencies



Human hearing		20Hz - 20kHz	( Normally, 16Hz to 16kHz)
<u>Conventional power ultrasound</u>		20kHz - 100kHz	<b>high input power</b> (1-1000 W/cm <sup>2</sup> ) <b>(Destructive)</b>
Extended range for sonochemistry		20kHz —2MHz	
Diagnostic ultrasound		5MHz - 10MHz	<b>Low input power</b> ( mW/cm <sup>2</sup> ) <b>(Non-invasive)</b>

Used for cleaning, chemical reactions, plastic welding, etc.

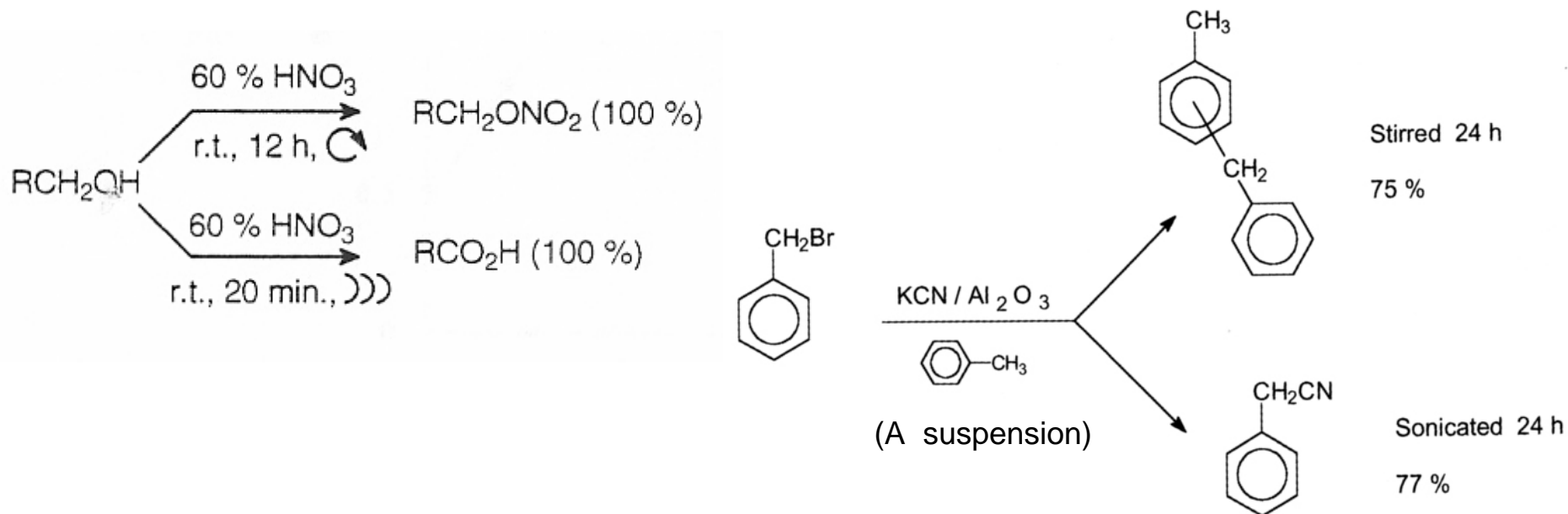
Mason and Lorimer, *Applied Sonochemistry*, Wiley-VCH, 2002

Mason, *Practical Sonochemistry: User's Guide to...*, 2nd Ed, E. Horwood, 2001

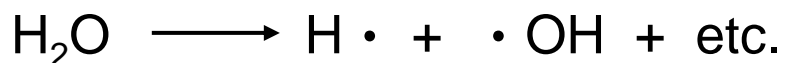


# Sonochemical switching of pathways

For **true** sonochemical reactions (homogeneous or heterogeneous), formation of radical or radical-ion will be favored by ultrasound. But **false** sonochemical reactions (heterogeneous) are influenced by physical and mechanical properties of sonication (ultrasound agitation). Examples are:



Sonochemical decomposition pathway of water into radicals





## Cleaner with timer and heater



**Less expensive, but in some cases it is also less effective.**

## ultrasound horn





# Heterogeneous reactions in a cleaning bath



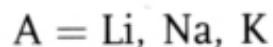
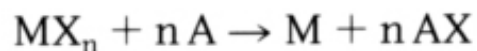
## Formation of Grignard reagents

(Mason and Lorimer, p. 98)

$\text{CH}_3\text{CH}_2\text{CHBrCH}_3 + \text{Mg} \rightarrow \text{CH}_3\text{CH}_2\text{CH}(\text{MgBr})\text{CH}_3$		
Type of diethyl ether used	Method	Induction time
Pure, dried (0.01% water)	Stirred	6–7 min
(0.01% ethanol)	Sonicated	less than 10 s
Reagent grade (0.5% water)	Stirred	2–3 h ( <i>crushed</i> )
(2.0% ethanol)	Sonicated	3–4 min

## Generation of metal powders

(Mason and Lorimer, p. 95)



Method	Time
$\text{CuI}_2 + \text{K}$ reflux in THF	8 h
$\text{CuBr}_2 + \text{Li}$ ultrasonic bath at 25 °C in THF	less than 40 min
$\text{NiCl}_2 + \text{Li}$ (powder) stir at 25 °C	14 h
$\text{NiCl}_2 + \text{Li}$ (powder) stir in ultrasonic bath at 25 °C	less than 40 min

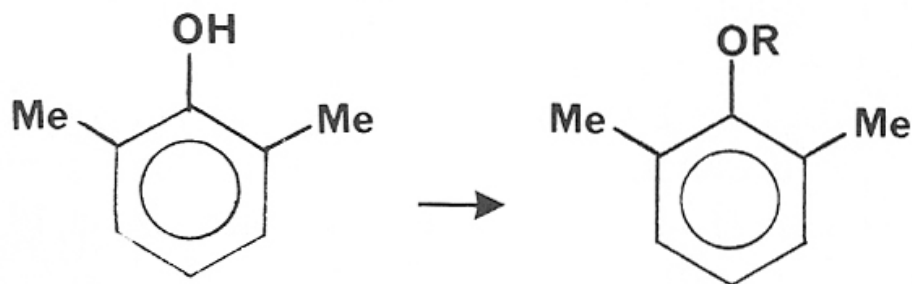


# Reactivity enhanced

## Alkylation of hindered phenols

Halocompound	Yield % (glc) after 1.5 h	
	Sonicated	Normal
Iodomethane	90	45 (60 after 4 h)
1-iodopropane	95	33 (45 after 4 h)
3-bromoprop-1-ene	100	38

With suspension of  $K_2CO_3$  in NMP  
Using an ultrasonic horn



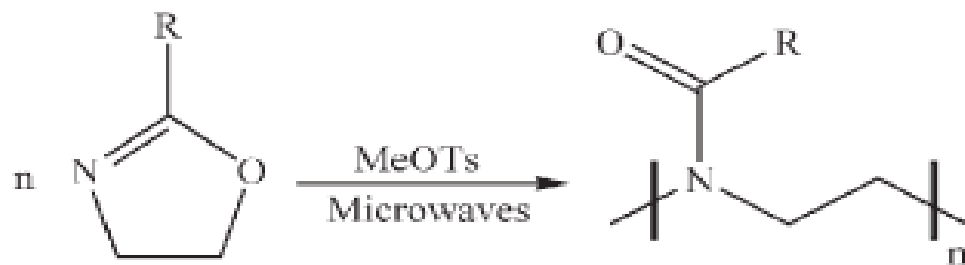


## Promoting emulsion and suspension polymerizations

Ultrasonic waves have also been found to increase the rates of emulsion and suspension polymerisations. For example, we have found a twofold increase in the thermally initiated production of polystyrene by emulsion polymerisation when in the presence of ultrasound (20 kHz). Possible explanations for these increases include:

- (i) the oxidation of impurities (see above),
- (ii) the removal of oxygen (known to inhibit radical reactions) by ultrasonic degassing, and
- (iii) ultrasonic degradation of the polymer to provide more active sites (i.e. autocatalysis).

### Cationic ring-opening polymerization of 2-oxazolines



R = ethyl, nonyl, phenyl, soyalkyl

(*Green Chem.* **2007**, *9*, 304-314)

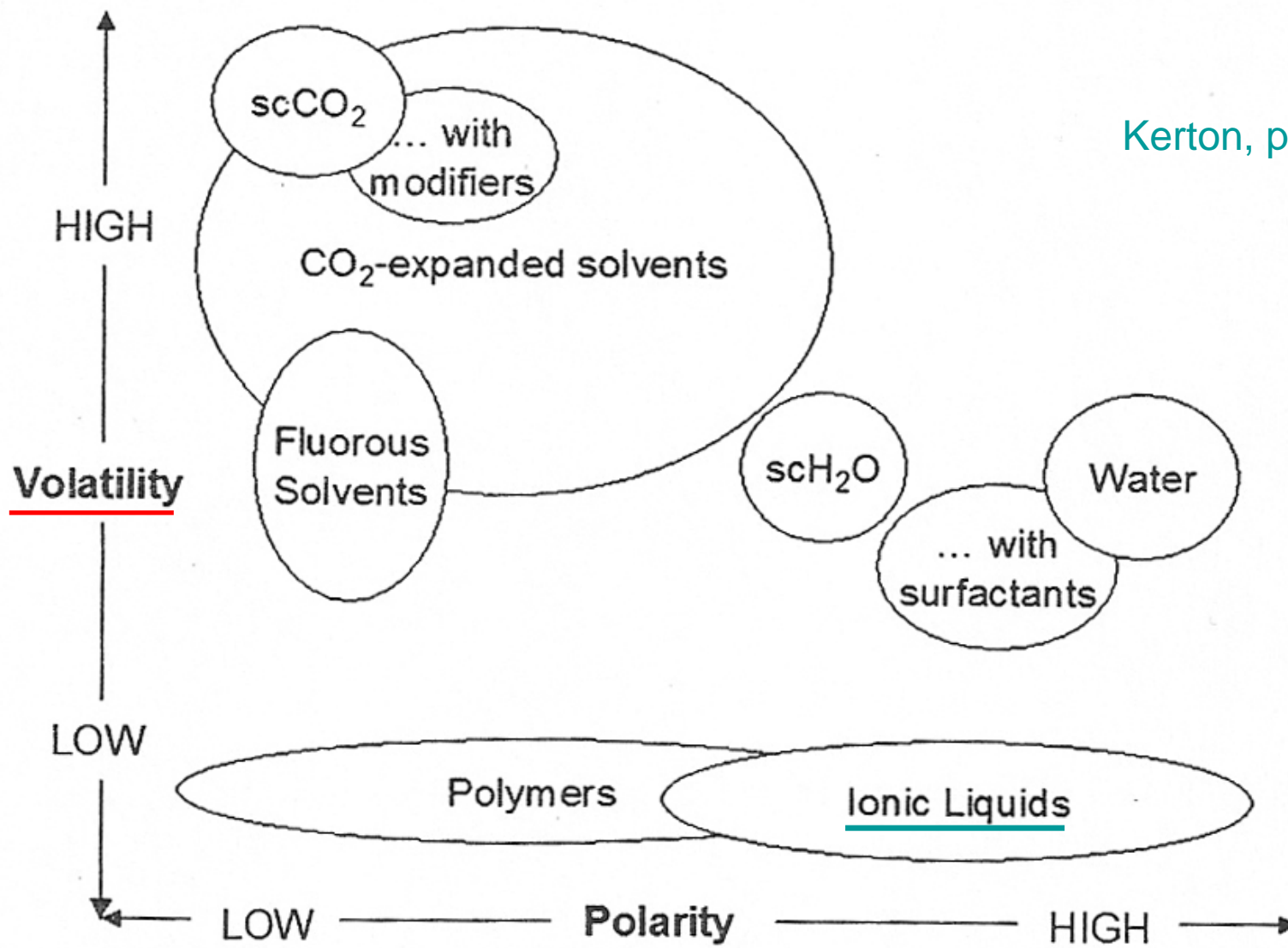




# Alternative solvents

## Polarity and volatility characteristics

Kerton, p. 17







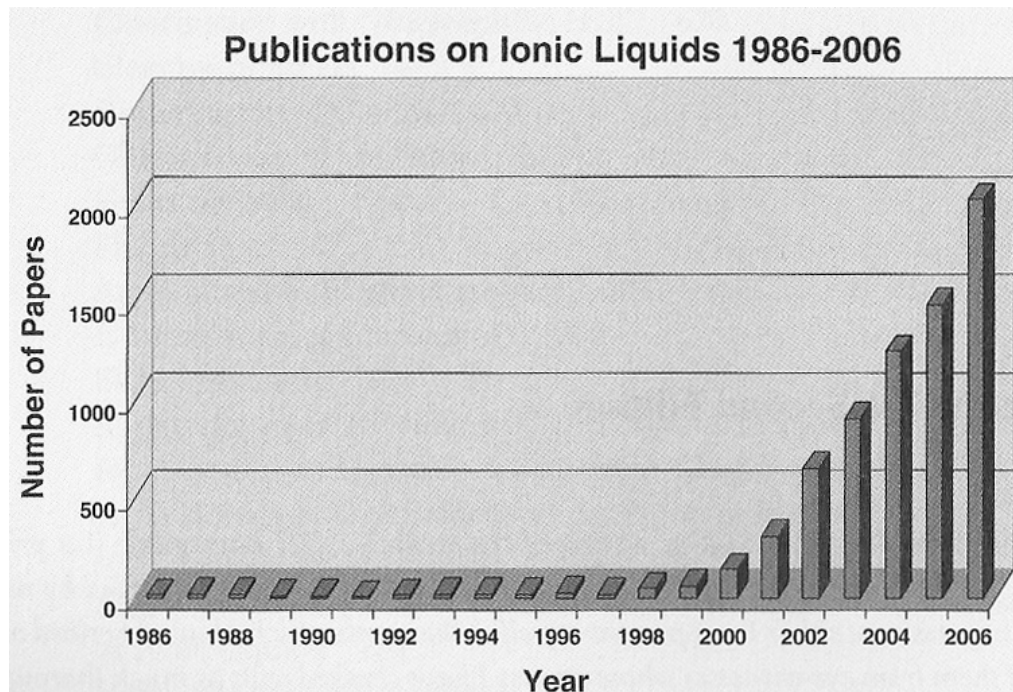
# Ionic liquids in Synthesis

*Ionic Liquids in Organic Synthesis*, Ed. by Malhotra, ACS Symposium Series 950, **2006**

*Ionic Liquids in Synthesis*, 2nd, Completely Revised and Enlarged Edn., 2 Vols, Ed by Wasserscheid and Welton, Wiley-VCH, **2008**

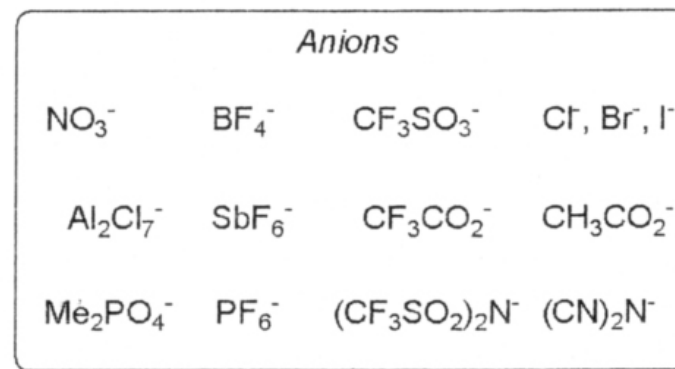
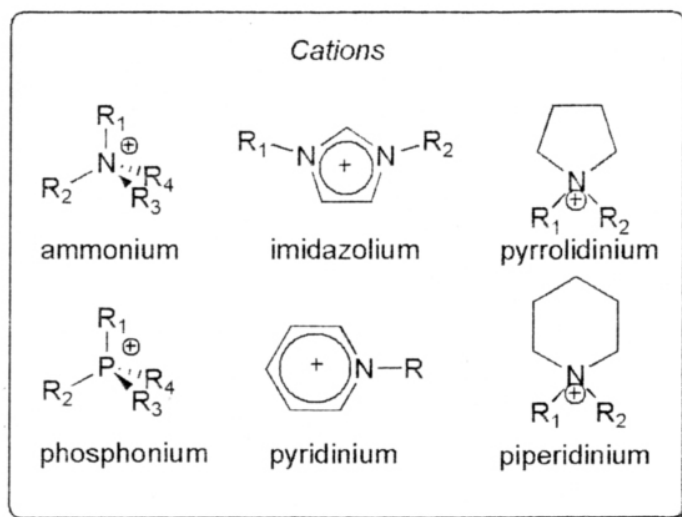
*Alternative Solvents for Green Chemistry*, by Kerton, RSC, Chapter 6, **2009**

Parvulescu and Hardacre, *Chem. Rev.* **2007**, 107, 2615-2665 (**Catalysis in Ionic Liquids**)





# Room temperature ionic liquids



$R = (\text{CH}_2)_n\text{CH}_3, n = 1, 3, 5, \dots$

**Table 6.1** Some physical properties of imidazolium-based ionic liquids.

Cation	Anion	Mp/ $^{\circ}\text{C}$	Thermal stability/ $^{\circ}\text{C}$	Density/ $\text{g cm}^{-3}$	Viscosity/ $\text{cP}$	Conductivity/ $\text{ohm}^{-1} \text{cm}^{-1}$
Emim	$\text{BF}_4^-$	6	412	1.24	37.7	1.4
Bmim	$\text{BF}_4^-$	-81	403	1.12	219	0.173
Bmim	$(\text{CF}_3\text{SO}_2)_2\text{N}^-$	-4	439	1.429	52	0.39
Bmim	$\text{PF}_6^-$	-61	349	1.36	450	0.146
Hmim	$\text{PF}_6^-$	-61	417	1.29	585	-

<sup>a</sup>Emim = 1-ethyl-3-methylimidazolium, Bmim = 1-butyl-3-methylimidazolium, Hmim = 1-hexyl-3-methylimidazolium

(Kerton, p. 119)



# Properties

- Liquid range of 300°C (−96–+200°C)
- Excellent solvents for organic, inorganic, and polymeric materials
- Acidic compositions are superacids ( $pK_a \approx -20$ )
- Some are very water sensitive and must be used in a dry box; others are hydrophobic and air stable
- Thermally stable under conditions up to 200°C
- *Now* — easy to buy and simple to prepare
- *No* measurable vapor pressure at room temperature
- Nonflammable (but some are explosive!)
- Exhibit Brønsted, Lewis, Franklin, and “super” acidity
- *Highly* solvating—therefore low volumes used, thus process intensification
- Catalysts as well as solvents
- Highly selective reactions
- *New chemistry*

**Some are corrosive, and some are harmful**  
**Non-biodegradable**



## Some safety data

	BMIM Cl <sup>a</sup>	EMIM EtOSO <sub>3</sub> <sup>b</sup>	MTEOA MeOSO <sub>3</sub> <sup>c</sup>
Acute oral toxicity	toxic	not harmful	not harmful
Skin irritation	irritant	non-irritant	non-irritant
Eye irritant	irritant	non-irritant	non-irritant
Sensitization	non-sensitizing	non-sensitizing	non-sensitizing
Mutagenicity	non-mutagenic	non-mutagenic	non-mutagenic
Biological degradability	not readily degradable	not readily degradable	readily biodegradable
Toxicity to daphniae	autelytoxic	acutely not harmful	acutely not harmful
Toxicity to fish	acutely not harmful	—	acutely not harmful

<sup>a</sup>BMIM Cl = 1-Butyl-3-methylimidazolium chloride.

<sup>b</sup>EMIM EtOSO<sub>3</sub> = 1-Ethyl-3-methylimidazolium ethylsulfate.

<sup>c</sup>MTEOA MeOSO<sub>3</sub> = Tris-(2-hydroxyethyl)-methylammonium methylsulfate.

*Ionic Liquids in Synthesis (Vol. 2), p. 683*





# Designing Sustainable Ionic Liquids

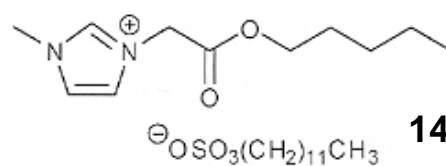
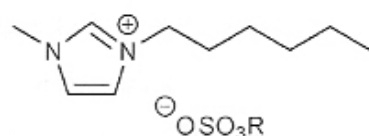
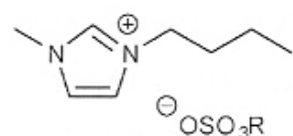


**Ultimate goal: Non-toxic and/or biodegradable**

(Ranke, *et al.*, *Chem. Rev.* **2007**, *107*, 2183-2206

Harjani, *et al.*, *Green Chem.* **2008**, *10*, 436-438; **2009**, *11*, 821-829)

**Table 1** Percentage biodegradation of alkyl sulfates based on [bmim] and [hmim] cations after 28 days as determined by the CO<sub>2</sub> headspace test (ISO 14593)



**12a** R = (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>

**12b** R = (CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>

**12c** R = (CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>

**12d** R = (CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>

**12e** R = (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>

**12f** R = (CH<sub>2</sub>)<sub>11</sub>CH<sub>3</sub>

**13a** R = (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>

**13b** R = (CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>

**13c** R = (CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>

**13d** R = (CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>

**13e** R = (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>

**13f** R = (CH<sub>2</sub>)<sub>11</sub>CH<sub>3</sub>

Entry	No.	Compound <sup>a</sup>	Biodegradation (%)
1	<b>12a</b>	[bmim] [C <sub>6</sub> H <sub>13</sub> OSO <sub>3</sub> ]	34
2	<b>12b</b>	[bmim] [C <sub>7</sub> H <sub>15</sub> OSO <sub>3</sub> ]	36
3	<b>12c</b>	[bmim] [C <sub>8</sub> H <sub>17</sub> OSO <sub>3</sub> ]	40
4	<b>12d</b>	[bmim] [C <sub>9</sub> H <sub>19</sub> OSO <sub>3</sub> ]	47
5	<b>12e</b>	[bmim] [C <sub>10</sub> H <sub>21</sub> OSO <sub>3</sub> ]	54
6	<b>12f</b>	[bmim] [C <sub>12</sub> H <sub>25</sub> OSO <sub>3</sub> ]	58
7	<b>13a</b>	[hmim] [C <sub>6</sub> H <sub>13</sub> OSO <sub>3</sub> ]	30
8	<b>13b</b>	[hmim] [C <sub>7</sub> H <sub>15</sub> OSO <sub>3</sub> ]	33
9	<b>13c</b>	[hmim] [C <sub>8</sub> H <sub>17</sub> OSO <sub>3</sub> ]	38
10	<b>13d</b>	[hmim] [C <sub>9</sub> H <sub>19</sub> OSO <sub>3</sub> ]	36
11	<b>13e</b>	[hmim] [C <sub>10</sub> H <sub>21</sub> OSO <sub>3</sub> ]	44
12	<b>13f</b>	[hmim] [C <sub>12</sub> H <sub>25</sub> OSO <sub>3</sub> ]	49
13	<b>14</b>	['ester'-mim] [C <sub>12</sub> H <sub>25</sub> OSO <sub>3</sub> ]	72

<sup>a</sup> IL concentration = 40 mg L<sup>-1</sup>.

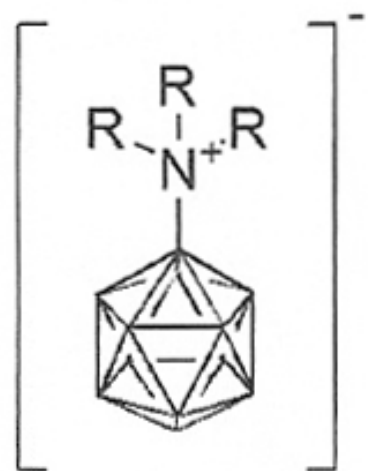


# New ionic liquid with new type of anions

High chemical and physical **stability**, **non-corrosive**, **similar toxicity** to other widely used ILs.

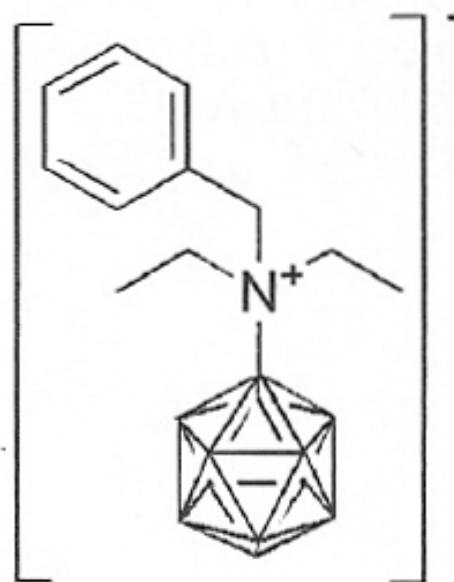
(Schaffran, *et al.*, *Green Chem.* **2009**, *11*,1458-1464)

symmetric substitution



R = CH<sub>3</sub> - C<sub>6</sub>H<sub>13</sub>

asymmetric substitution



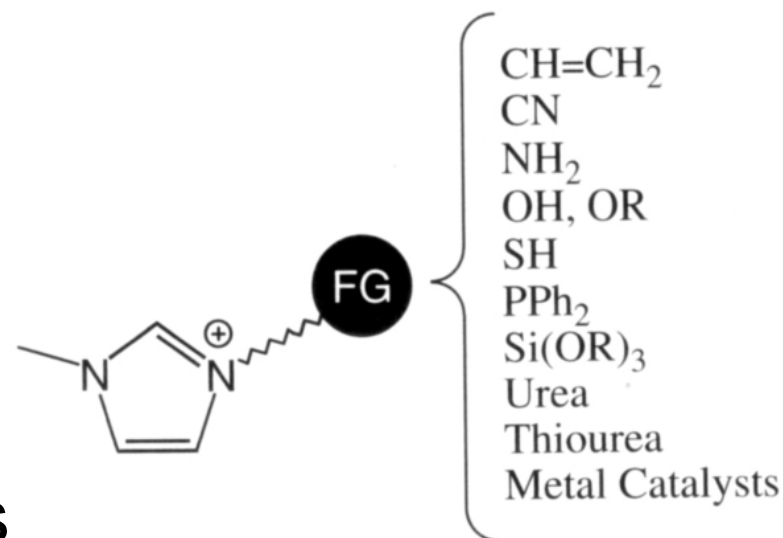
*N,N,N*-trialkylammoniumundecahydrododecaborates (-)



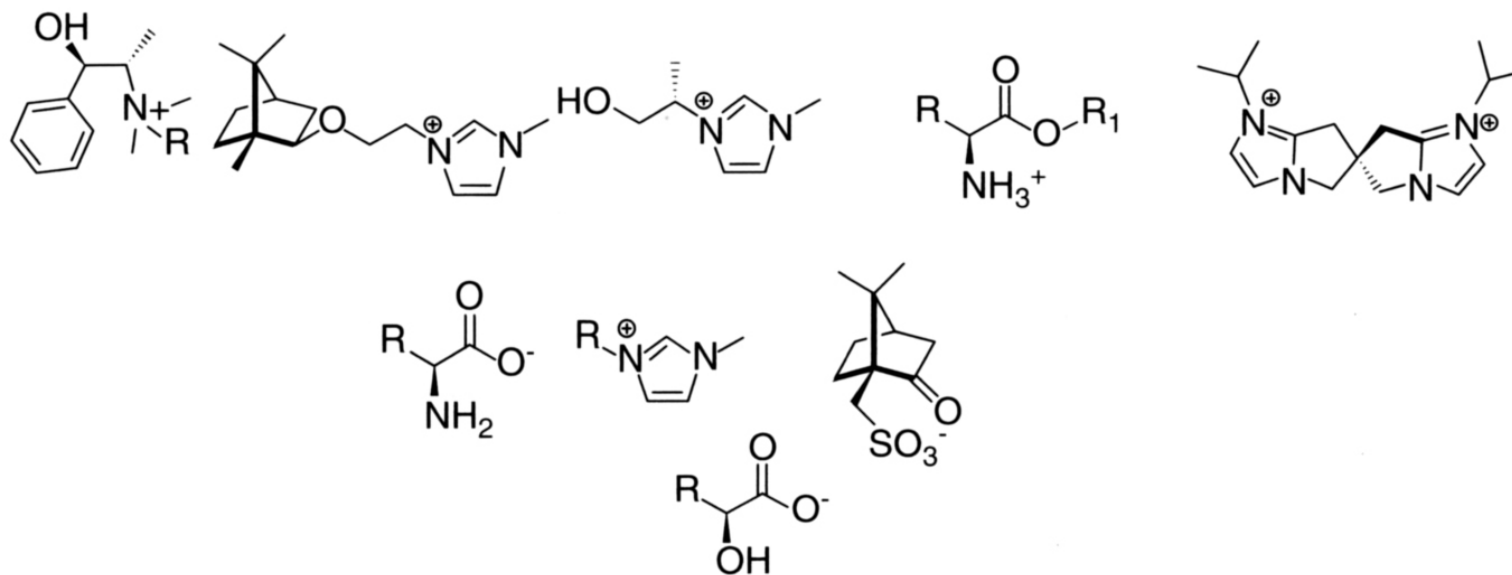
# Task-specific ionic liquids

(Ballini (Ed), *Eco-Friendly Synthesis of Fine Chemicals*, Chapter 4, RSC, 2009)

## Functionalized ionic liquid cations



## Novel chiral ionic liquids







The anions can be prepared in large quantities even with conventional laboratory equipment. Cations can be chosen quite freely, and even potassium, lithium, and unsolvated proton cations

Melting points of *N,N,N*-trialkylammoniumundecahydrododecaborate salts measured in a capillary.

$B_{12}H_{11}NR_3^-$ R =	Melting point [°C]						
	$N(Me)_4$	$N(Bu)_4$	<i>N</i> -hexyl- pyridinium	<i>N</i> -methyl- <i>N'</i> - butyl- imidazolium	K	Li	H
H	>250	188–190					
CH <sub>3</sub>			128–129				
C <sub>2</sub> H <sub>5</sub>	314 (decomp) <sup>[a]</sup>	194 <sup>[a]</sup>	130–132	128–130	370 (decomp) <sup>[b]</sup>		
C <sub>3</sub> H <sub>7</sub>	256–258	172–174	126–128	143–145	>250		
C <sub>4</sub> H <sub>9</sub>	222–225	175–176	40–50	115–116	190 (decomp)		
<i>i</i> -C <sub>5</sub> H <sub>11</sub>		112–114	<25	87–90	128–134		
C <sub>6</sub> H <sub>13</sub>	183–186	75–78	47–50	95–97	65	65	80
C <sub>12</sub> H <sub>25</sub>	60	40–45	<25	25	40		
C <sub>3</sub> H <sub>6</sub> CH=CH <sub>2</sub>		50–60					

(Gabel, *et al*, *Chem. Eur.J.* **2008**, *14*, 1918-1023)



# Applications

Friedel-Crafts reactions

Heck and Suzuki couplings

Oxidation

Reduction

Sulfonation

Nitration

Halogenation

Diazotization

Diels-Alder reaction

Aldol condensation

Formation of Coordination compounds

Formation of inorganic oxides

Oligomerization

Polymerization

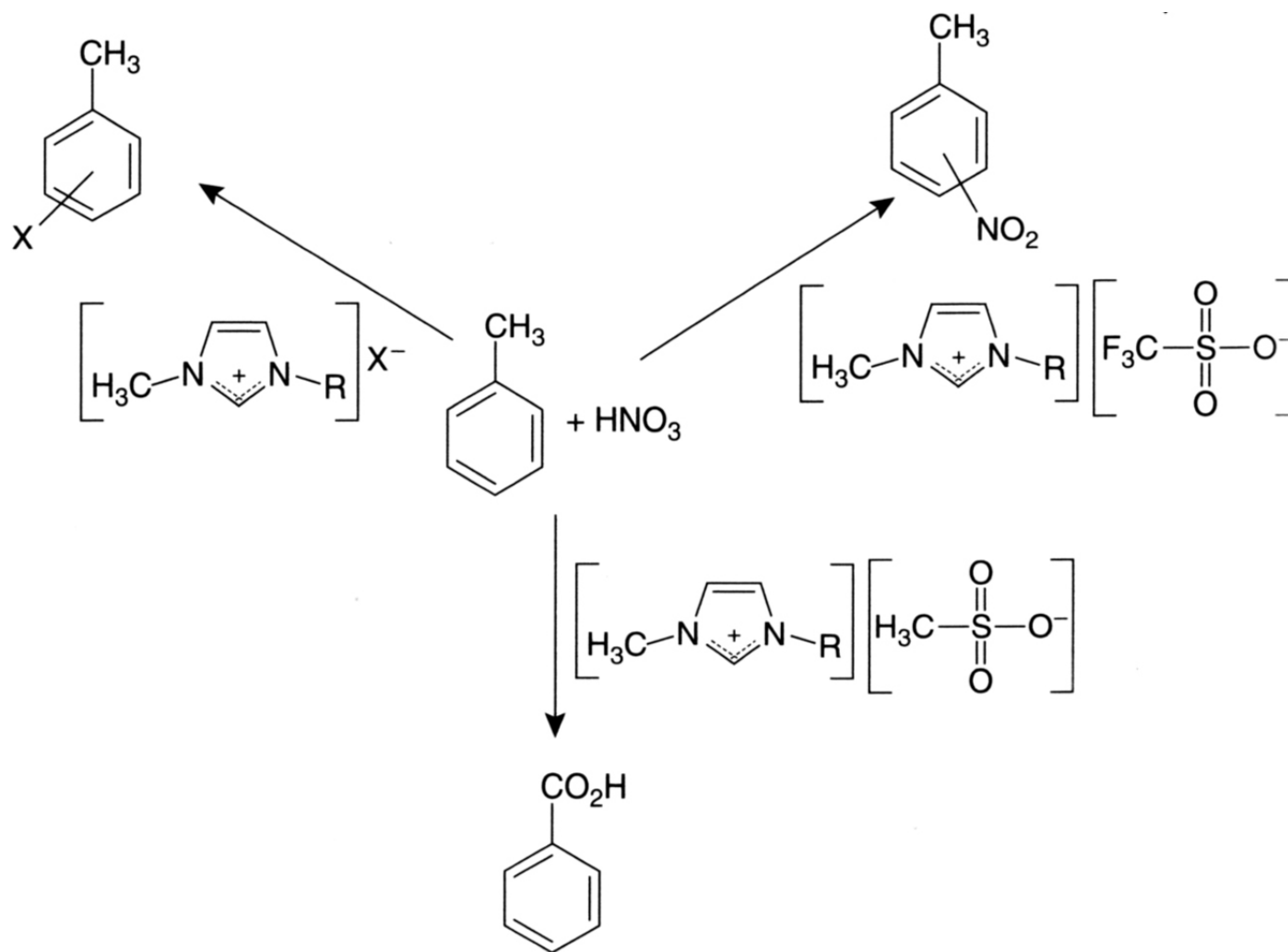
Bio-catalytic reactions

N- and O-alkylations

Chiral hydrogenation

Nanoscale process

and many more

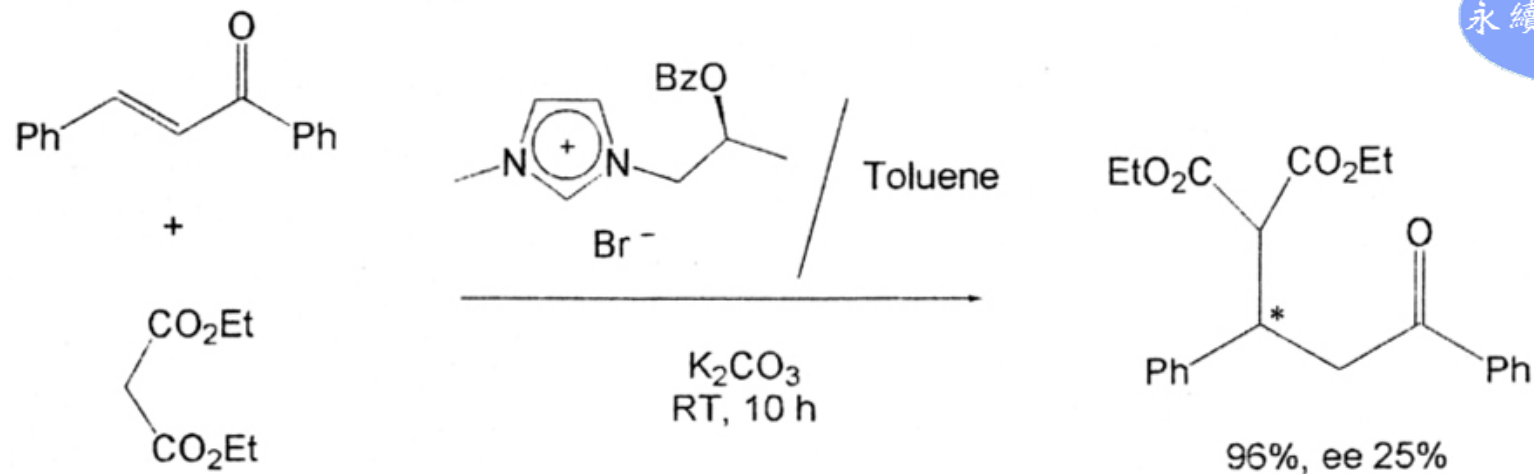


**Figure 5.8** The reactions between toluene and nitric acid in (a) a halide-based ionic liquid, (b) a triflate-based ionic liquid, and (c) a mesylate-based ionic liquid.

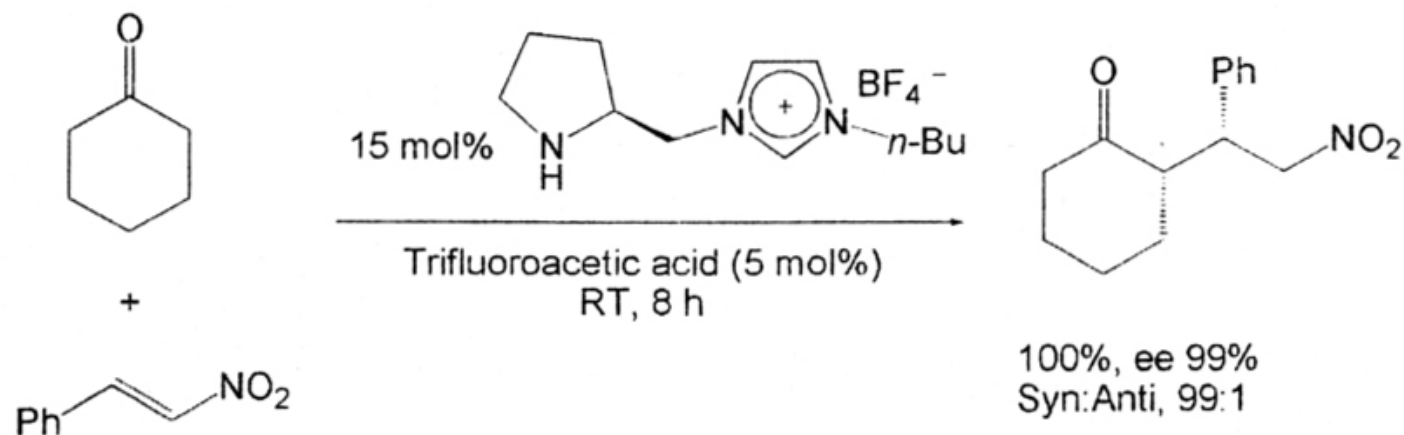
*(Methods and Reagents for Green Chemistry, p. 119, Wiley, 2007)*



a)



b)



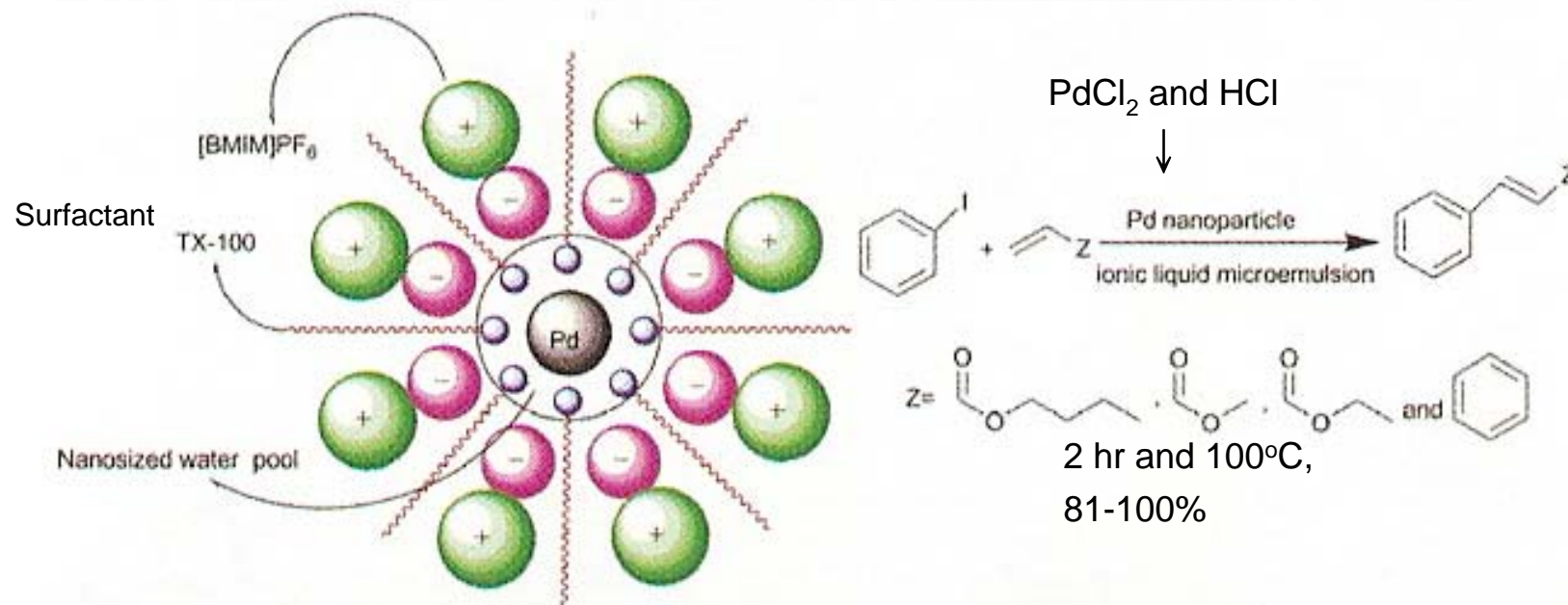
**Figure 6.8** Asymmetric Michael addition reactions using chiral ionic liquids: (a) derived from lactate, (b) derived from proline.



## Pd nanoparticles catalyzed ligand-free Heck reaction in ionic liquid microemulsion

Guoping Zhang, Haihui Zhou,\* Jiaqi Hu, Mei Liu and Yafei Kuang\*

In the H<sub>2</sub>O/TX-100/[BMIM]PF<sub>6</sub> microemulsion, palladium nanoparticles were prepared *in situ* for the first time, and the resultant Pd catalysts exhibited high efficiency for Heck reaction without the aid of phosphine ligands.



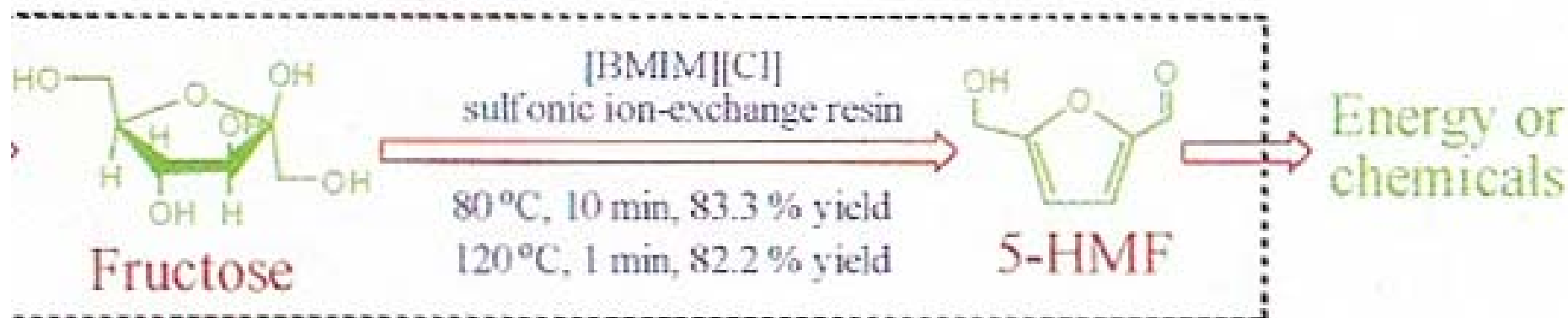
(*Green Chem.* **2009**, *11*, 1428-1432)



## Efficient process for conversion of fructose to 5-hydroxymethylfurfural with ionic liquids

Xinhua Qi,\* Masaru Watanabe, Taku M. Aida and Richard L. Smith, Jr.\*

Efficient conversion of fructose to 5-HMF with sulfonic acid ion-exchange resin as catalyst in [BMIM][Cl] was realized. The ionic liquid and the catalyst could be recycled and the catalyst exhibited constant activity over 7 cycles of evaluation.



(*Green Chem.* **2009**, *11*, 1327-1331 )





# Large scale preparations using IL

Company	Process	IL is acting as:	Scale
BASF	acid scavenging	auxiliary	commercial
	extractive distillation	extractant	pilot
	chlorination	solvent	commercial
IFP	olefin dimerization	solvent	pilot
Degussa	hydrosilylation	solvent	pilot
	compatibilizer	performance additive	commercial
Arkema	fluorination	solvent	pilot
Chevron Phillips	olefin oligomerization	catalyst	pilot
Scionix	electroplating (Cr)	electrolyte	pilot
Eli Lilly	cleavage of ether	catalyst/reagent	pilot
Air Products	storage of gases	liquid support	pilot
Iolitec/Wandres	cleaning fluid	performance additive	commercial
Linde	gas compression	liquid piston	pilot

*Ionic Liquids in Synthesis (Vol. 2), p. 665*





敬請不吝指教

劉廣定  
臺大化學系  
(ktliu@ntu.edu.tw)