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。[如本頁取材自〇〇〇教授演講內容]。

永續化學合成(3)

非傳統反應方法與溶劑

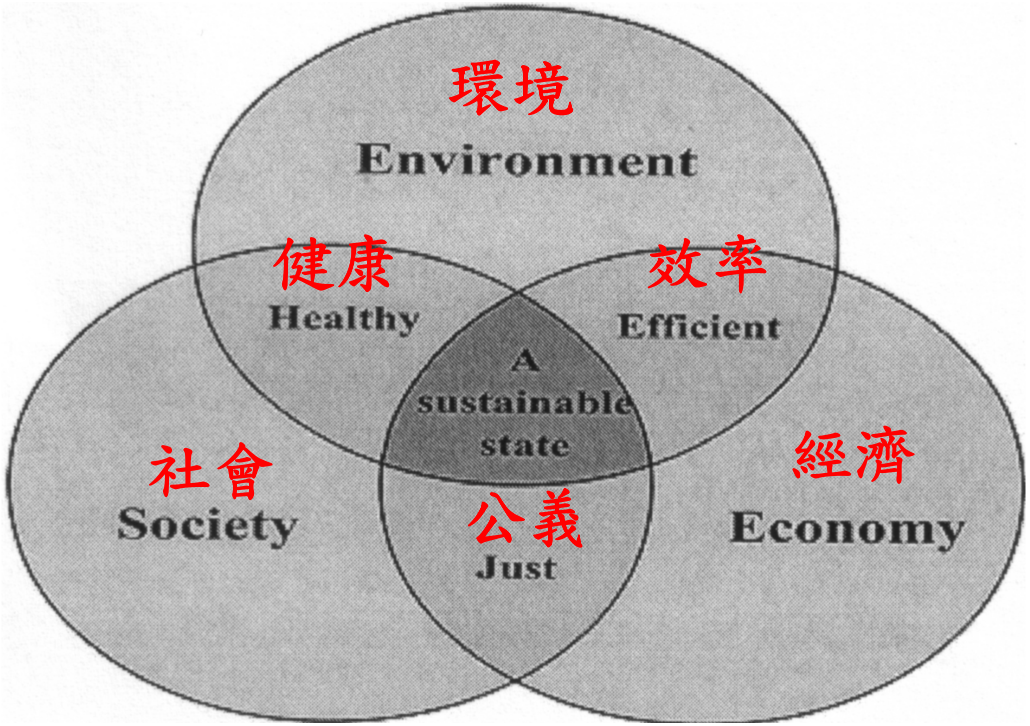
劉廣定

(ktliu@ntu.edu.tw)

December 2, 2011

永續發展
Sustainable development

1993年聯合國成立永續發展委員會, 宣導加強認識自然, 保護環境之觀念外, 並採積極的態度以創新之發明與設計來促成世界進步，俾使環境、經濟和社會資源得以同時持續發展。**保護與發展相輔相成**，世界將可成為「**永續之土**」(A sustainable state)。



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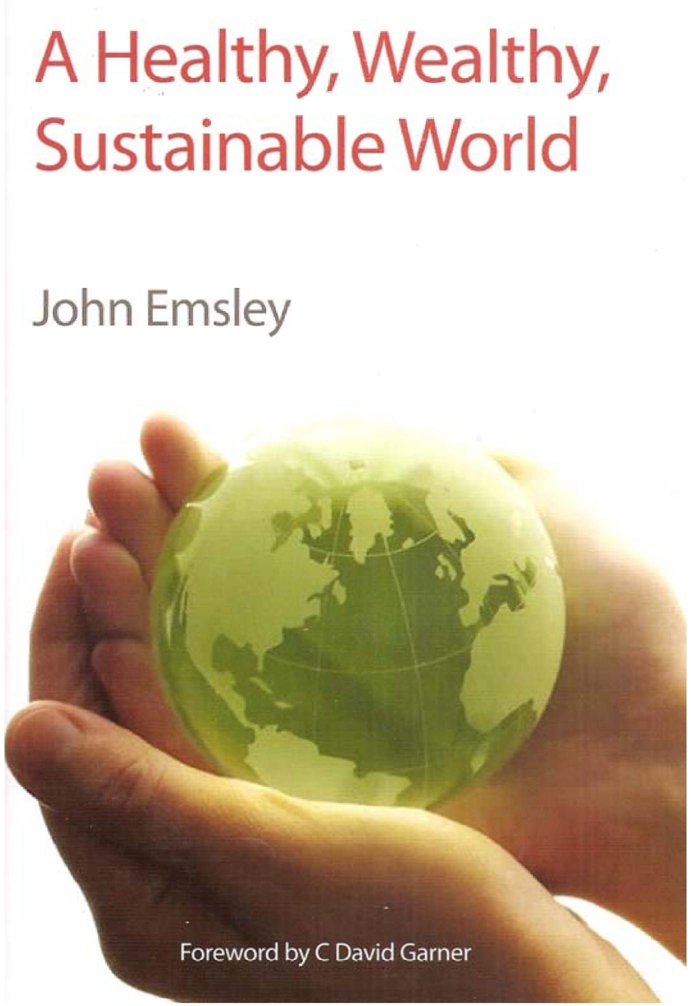
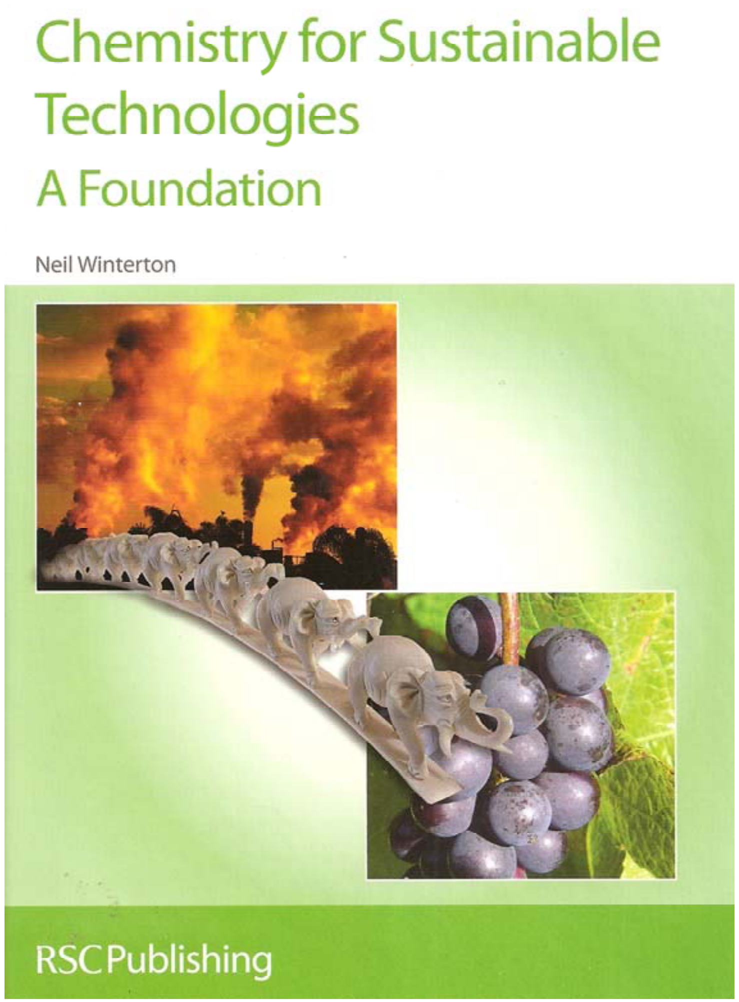
永續世界的難題(人口增長, 能源供應, 氣候異變, 資源枯竭, 糧食貯備, 環境汙染)多方面涉及化學





RSC 2011 Publications

合成化學工作者如何應對?

- 「節能、減碳」與「環境保護」是不夠的
- 當前的目標應是「節能、減廢、增效、維安」
- 合成和製備的反應若能提高產率、增加選擇性、簡化操作、使用無危險性試劑、減少廢棄物、或…，也是不夠的。

反應方法、條件、試劑、溶劑、觸媒等都能盡量配合永續化學十二原則與次原則*才是永續化學合成 (sustainable chemical synthesis)

* Winterton, *Green Chem.* **2001**, *3*, G73-5

Characteristics for ideal chemical synthesis

- Simplicity
- Safety, environmentally benign processes
- High yield and selectivity, material efficiency
- Low E-factor, less wastes
- Energy efficiency
- Use of renewable and recyclable reagents
- Use of renewable and recyclable solvents

etc.

永續化學合成

Sustainable chemistry is the design, manufacture, and use of environmentally benign chemical products and processes to prevent pollution, produce less waste, and reduce environmental and human risks. (OECD, 1999)

採用非傳統反應活化方法，溶劑，反應物…以求減少(**reduce**)

- **Cost**
- **Energy**
- **Environmental impact**
- **Hazards**
- **Materials**
- **Non-renewables**
- **Risk**
- **Waste**

永續化學之合成反應

不要到「收成」階段才考慮「永續」，從實驗室的「研究」開始即須注重。

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

Klaus Kümmerer *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 promoting reactions

Energy methods	System requires
Thermo chemistry	Heating
Photo chemistry	Chromophore, light source
Electro chemistry	Conducting media
Piezo chemistry	High pressure
Sono chemistry	Ultrasound source
Microwave chemistry	Polar media, microwave source
Mechano chemistry	Solid, mill-grinding

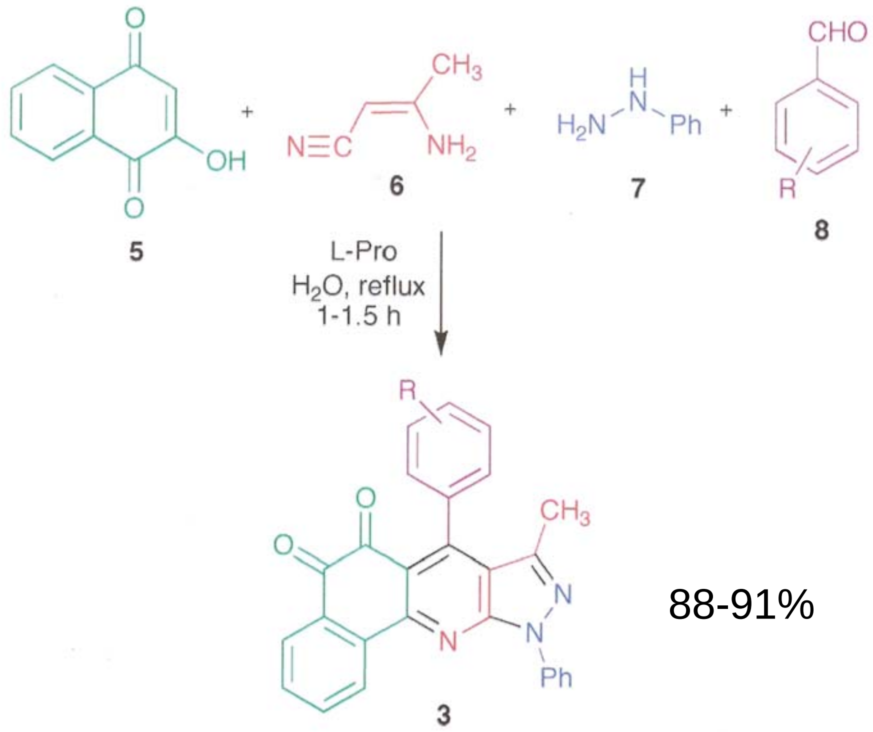
Energy efficiency (the 6th principle) and other factors, such as feasibility, should be considered.

A critical assessment of the greenness and energy efficiency of microwave-assisted organic synthesis (Moseley and Kappe, *Green Chem*. **2011**, *13*, 794-806)

Microwave chemistry can be more energy efficient compared with conventional heating methods, but not always.

More effective methodologies

- **Design multi-component reactions (MCR)**



Green Chem. **2011**, *13*, 3248-3254

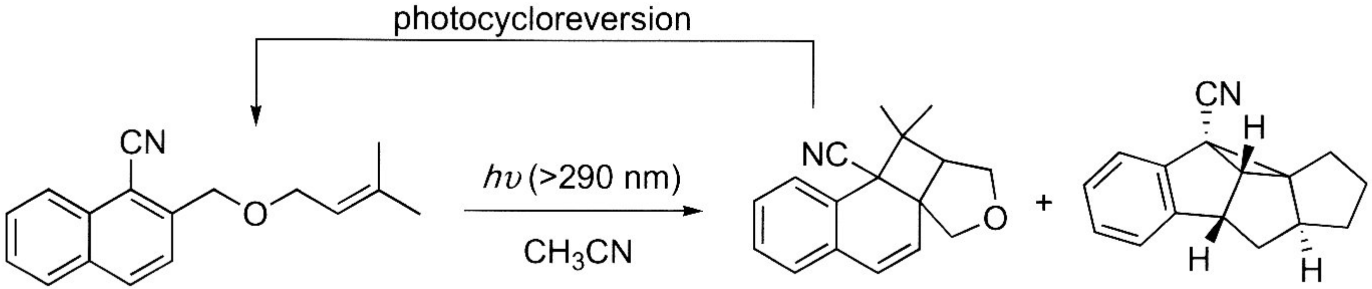
88-91%

A recent review:

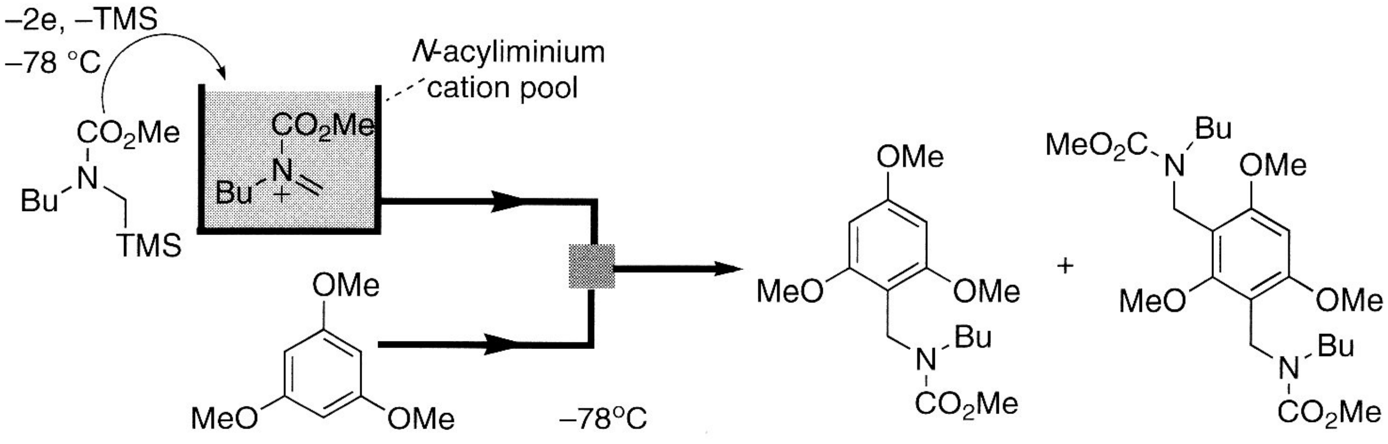
Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis

Chem. Soc. Rev. **2011**, *40*, 1347-1357

- **Microreactors, Continuous flow, flash synthesis**



Batch (180 min)	56%	17%
Microflow (3.4 min)	55%	7%



Microflow	92%	4%
Batch	37%	32%

Microreactors in Organic Synthesis and Catalysts (2008), p. 72, p. 79

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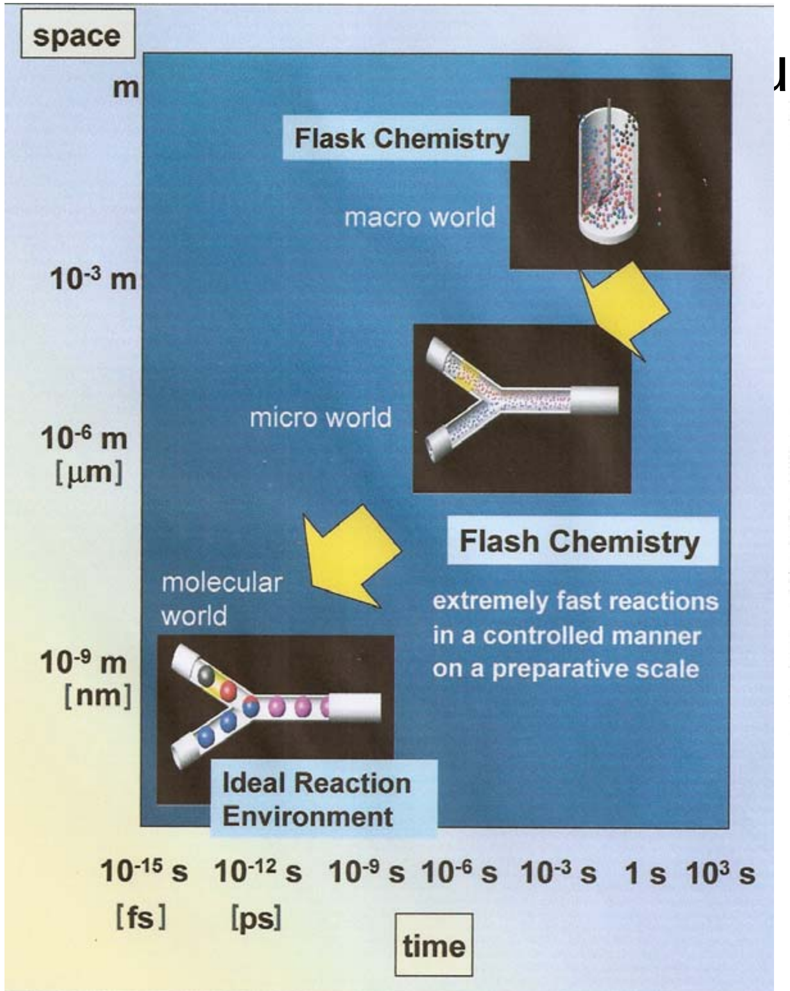
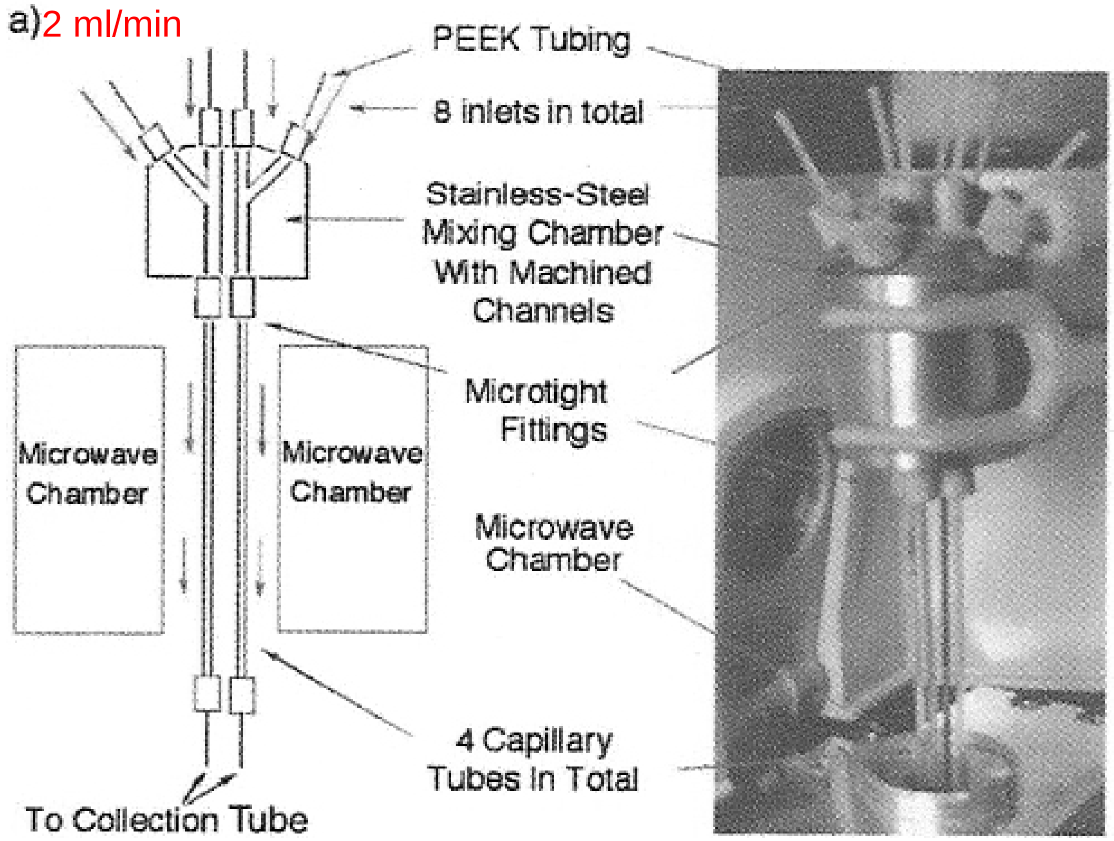
Microreactors

Time- and space- saving

an 8-channel reactor





tubing (d/1.150 mm)

Chem. Eur. J. **2008**, *14, 7450-7459*

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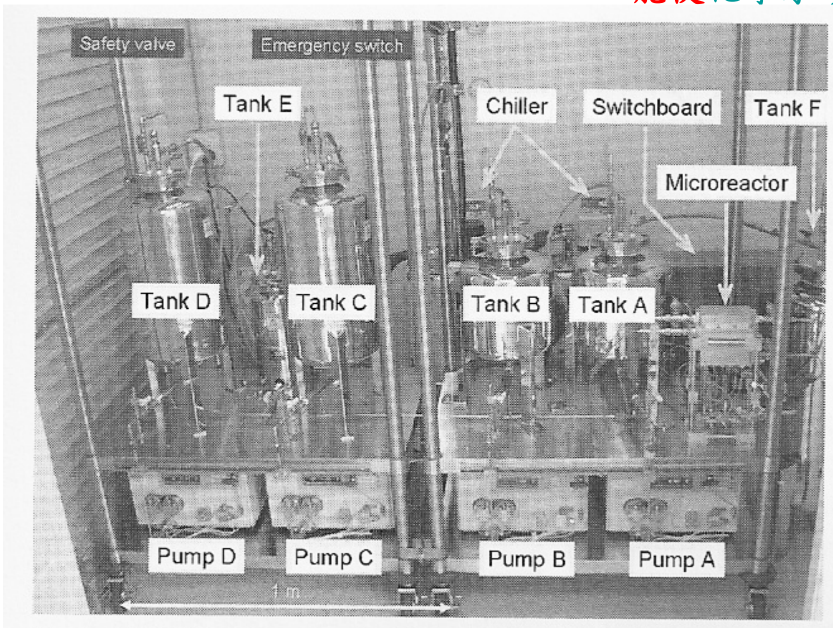
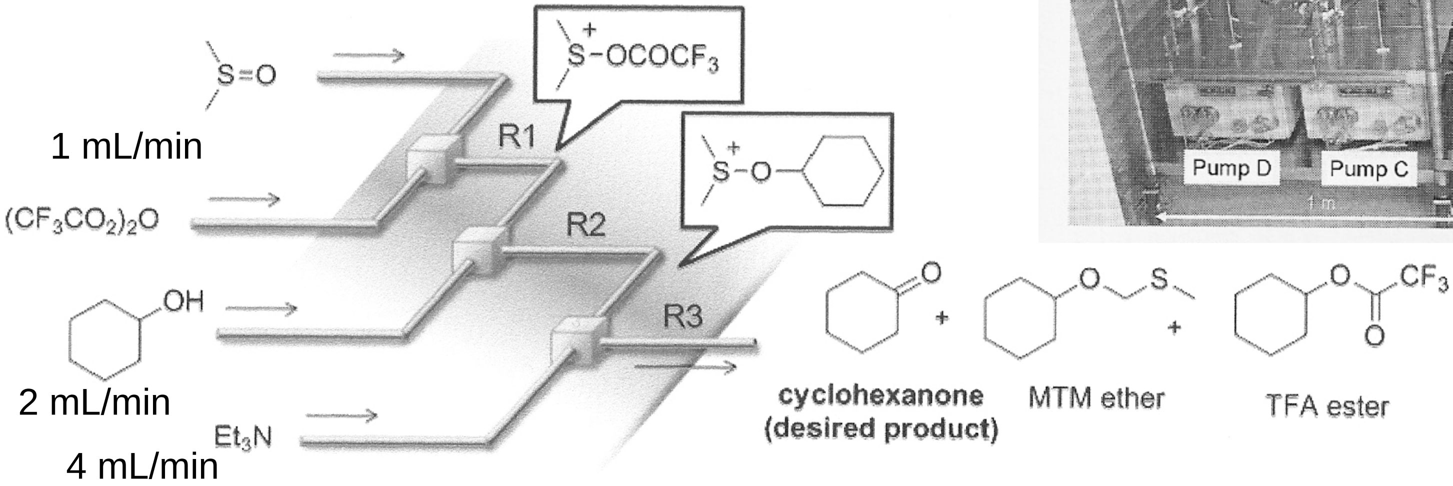
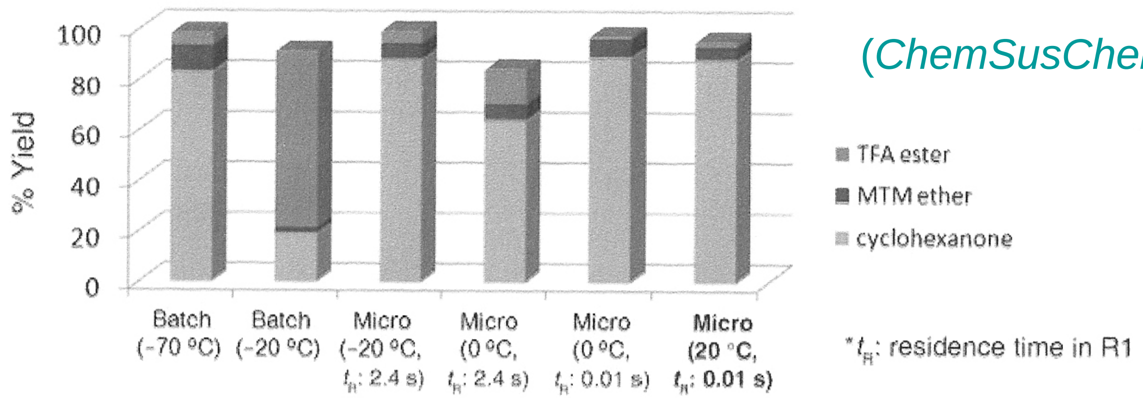
Swern-Moffat oxidation





(*ChemSusChem* **2011**, *4*, 331-340)



Corning Advanced-Flow Reactor, May, 2009

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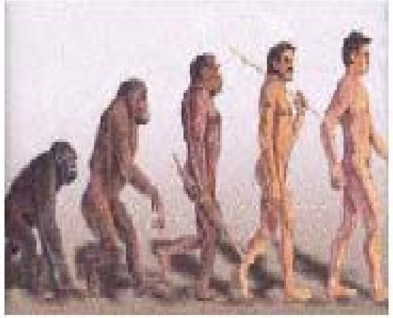
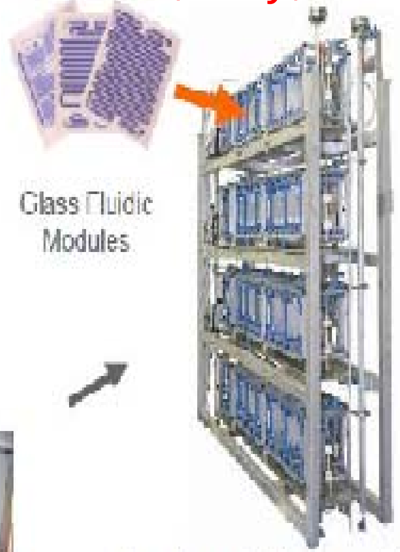
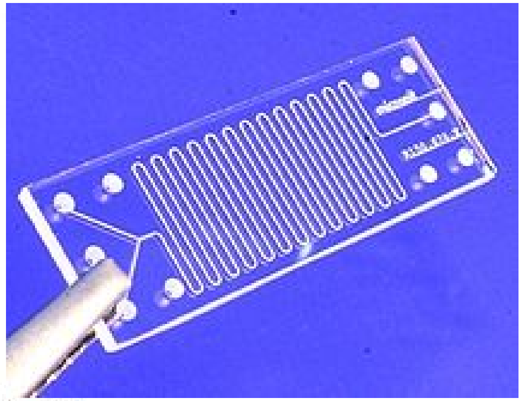




Channel with 150 x 150 μm (Wikipedia)



Georgia Tech to Use Corning Advanced-Flow Reactor in Synthesis Research since April, 2010

Ceramic reactor, announced June, 2011

Recent reviews:

Cross-coupling in flow (*Chem. Soc. Rev*., **2011**, *40*, 5010–5029)

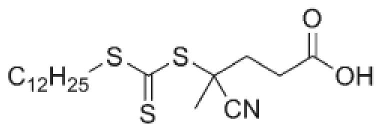
Green and Sustainable Chemical Synthesis using Flow Microreactors (*ChemSusChem* **2011**, *4,* 331-340)

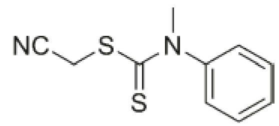
A Versatile Lab to Pilot Scale Continuous Reaction System for Supercritical Fluid Processing (*Org. Process Res Dev*. **2011**, *15*, 1275-1280)

Continuous flow reactors: a perspective (*Green Chem.* **2011**, DO1:19.1039/clgc16022b) **, and many more**

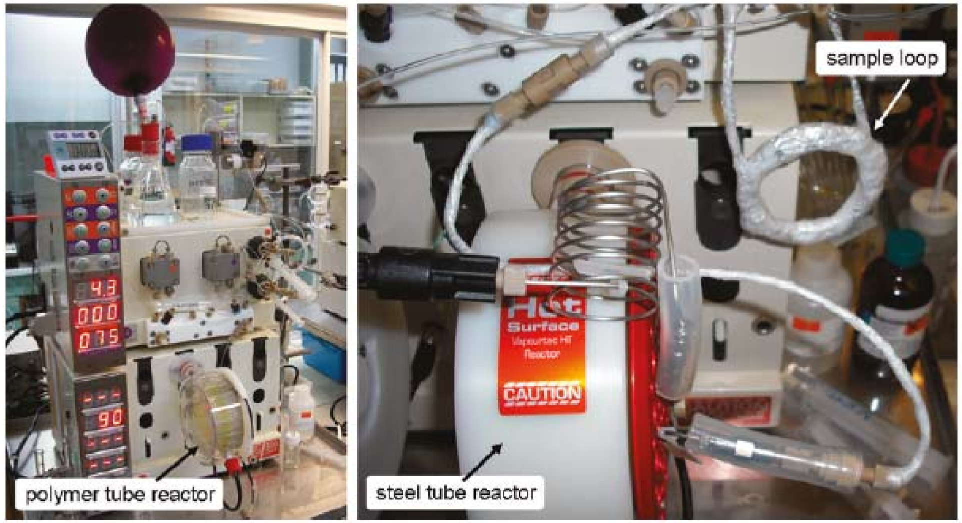
Controlled RAFT Polymerization in a Continuous Flow Microreactor

Controlled radical polymerization using the reversible addition-fragmentation chain transfer approach (RAFT) was successfully conducted under continuous flow processing conditions, provided that steel tubing was used to prevent quenching of the radical process by oxygen. A series of different monomers, including acrylamides, acrylates, and vinyl acetate, were polymerizedto high conversions (between 80 and 100%) at temperatures between 70 and 100 C using various initiators, solvents, and RAFTagents.



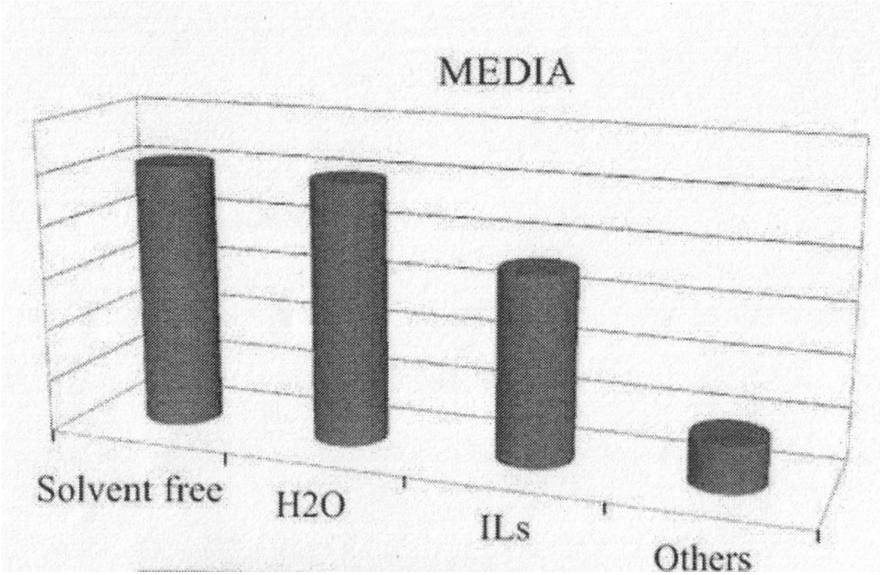


- The methodology provides a facile, alternative scale-up route to conventional batch polymerization.



Org. Process Res Dev. **2011**, *15*, 593-601

• Solvent-free/solid state reactions



2008 論文相對數量分析
(*Green Chem. Lett. Rev.* **2010,** *3*, 105-113)

Can be applied to solid-solid, solid-liquid, solid-gas, liquid-liquid, and liquid-gas reactions

Recent literatures:
Solid-state dynamic combinatorial chemistry; mechanosynthesis (*Chem. Sci.* **2011,** *2*, *696-700***)**
Ball milling in organic synthesis (*Chem. Soc. Rev*. **2011**, *40*, 2317-2329)
Three-component solvent-free synthesis of highly substituted tetrahydroimidazo[1,2-a]pyridines (*RSC Adv*. **2011**, *1*, 596-601)
Electrochemical allylation of aldehydes in a solvent-free cavity cell with a graphite powder cathode (*Green Chem*. **2011**,*13*, 1118-1120)
and many more

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

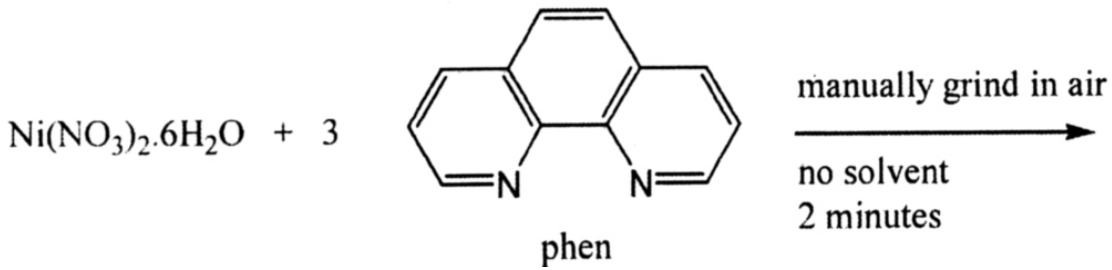
IUPAC definations

Mechano-chemical reaction: a chemical reaction that is induced by the direct absorption of mechanical energy.

Mechanochemistry: breakage of covalent bonds, ionic bonds or lattice as well as crystal packing on mechanical stress.

Metal complex formation

Nickel nitrate and phenanthroline



$[Ni(phen)_3](NO_3)_2$

Chem. Soc. Rev. **2007**, *36*, 846

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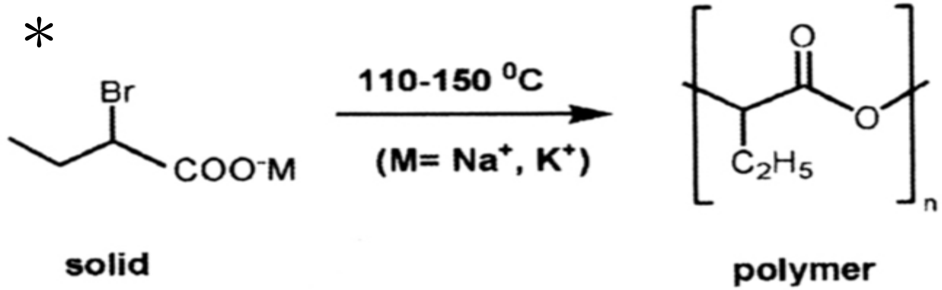
Solvent-free polymerization

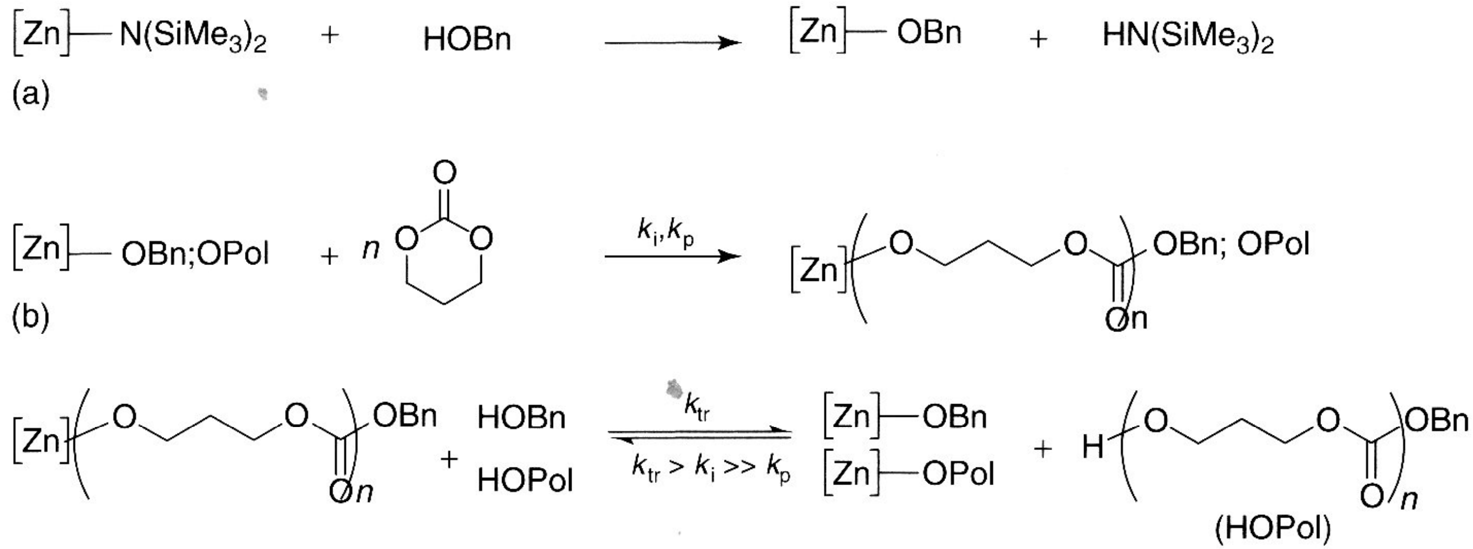
*

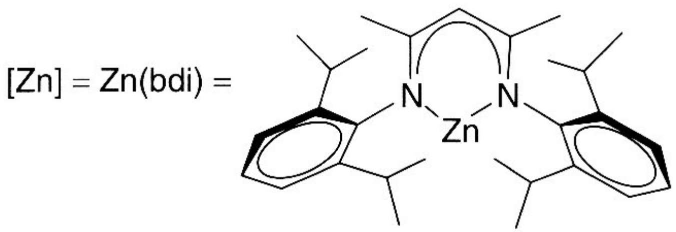


No polymerization if M = other cations

Chem. Soc. Rev. **2007,** *36*, 1239-1248

*



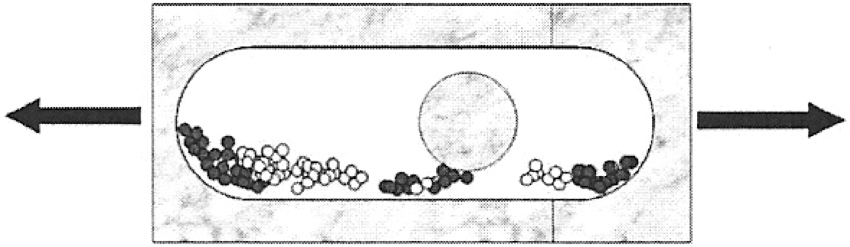


(c)

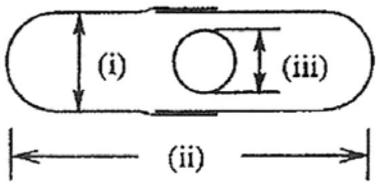
Chem. Eur. J. **2008**, *14*, 8772

Mixing in Mechanochemistry

Method of mixing might be manual grinding, using a ball mill or a pan mill.



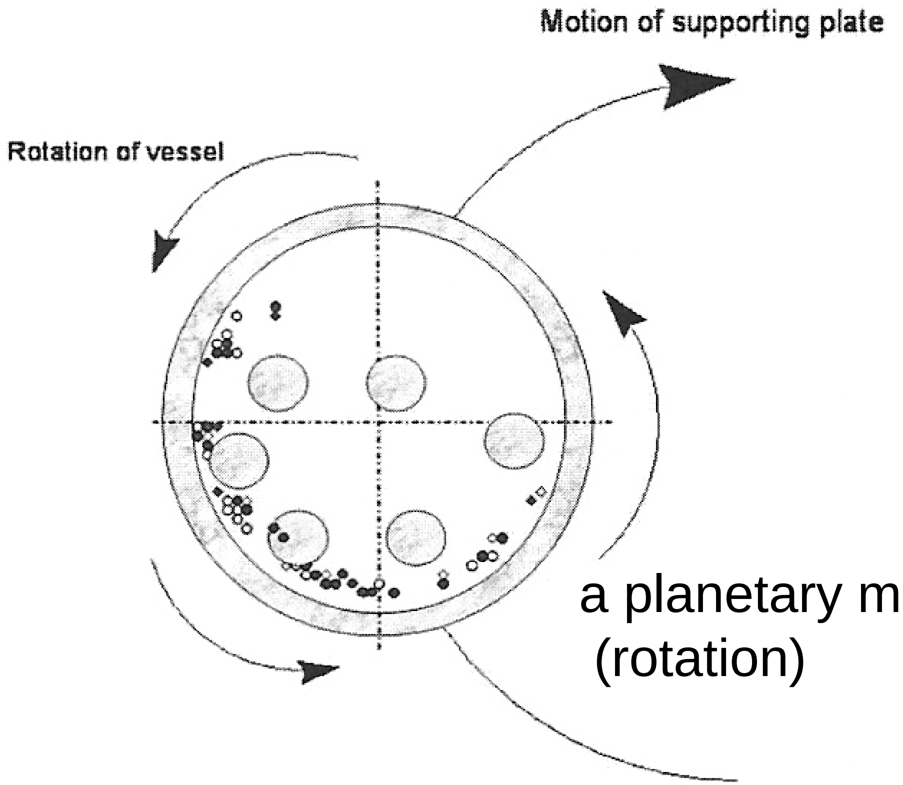
a shaker mill (vibration)



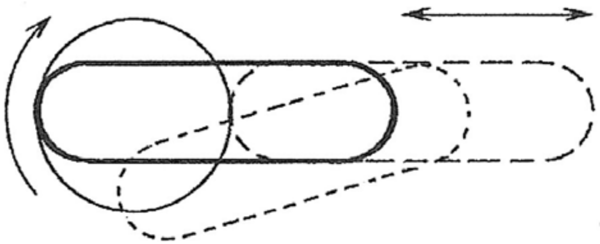
(i) 9 mm

(ii) 26 mm

(iii) 6 mm



a planetary mill
(rotation)



HSVM (High speed vibration mill) at the speed of 3500 rpm by Komatsu et al.

A pressure of 10-20000 bar may be generated.

- <u>Diversity of ball milling instruments:</u>

- ➢ planetary ball mills (1)

- ➢ mixer mills (2)

- ➢ vibration mills (3)

1

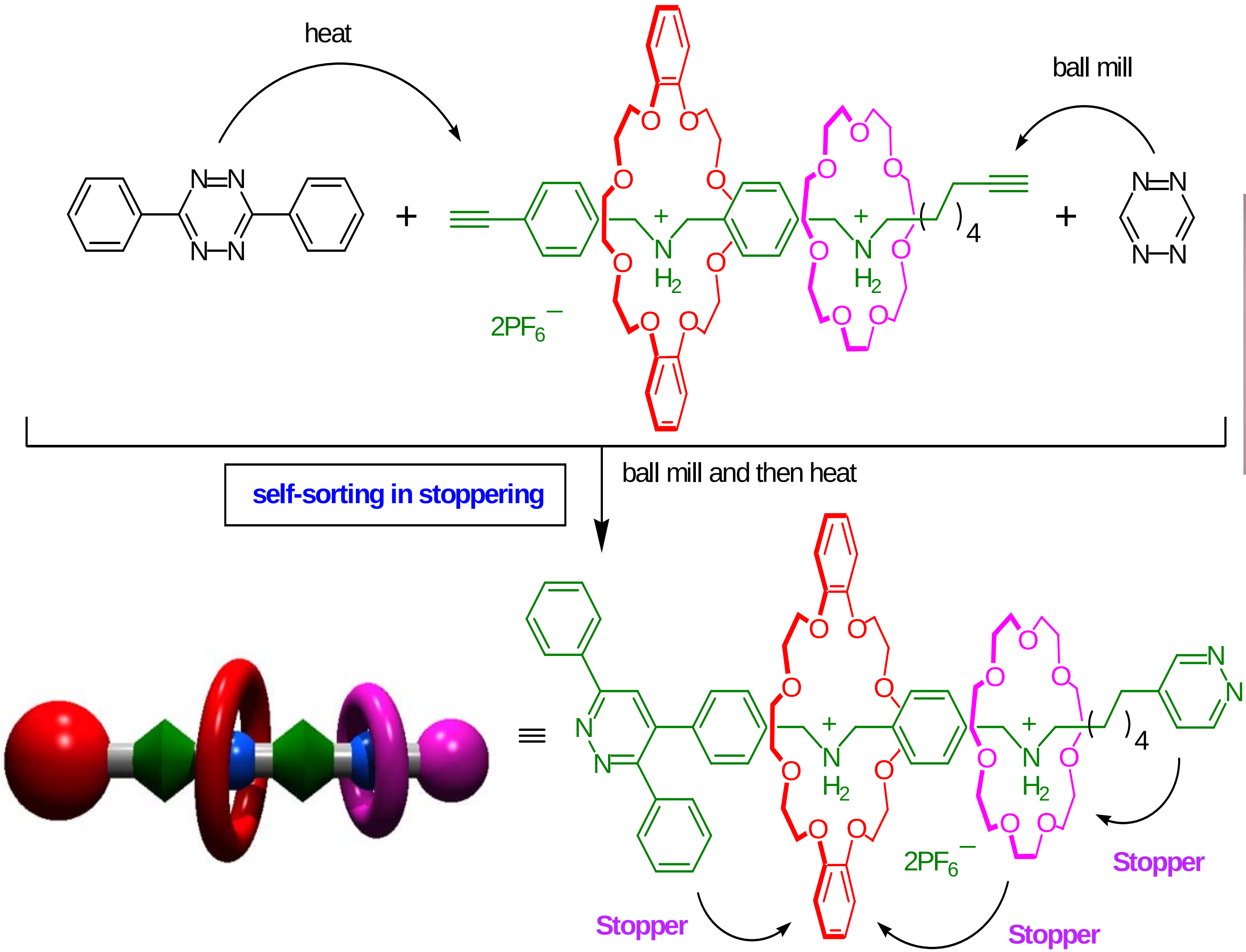
2

3

- (1) http://www.fritsch.de/de/probenaufbereitung/produkte/mahlen/plar
- (2) http://en.wikipedia.org/wiki/File:8000M_Mixer_Mill_%28open%29_
- (3) http://www.chemie.de/content/images/articles/retsch-milling-4.jpg.

(Courtesy of Professor Ondruschka, **2011**)

Hetero[3]rotaxane under solvent-free condition



簡單型儀器

(Chiu, S.-H., *et al. Org. Lett.* **2011**, *13*, 4660-4663)

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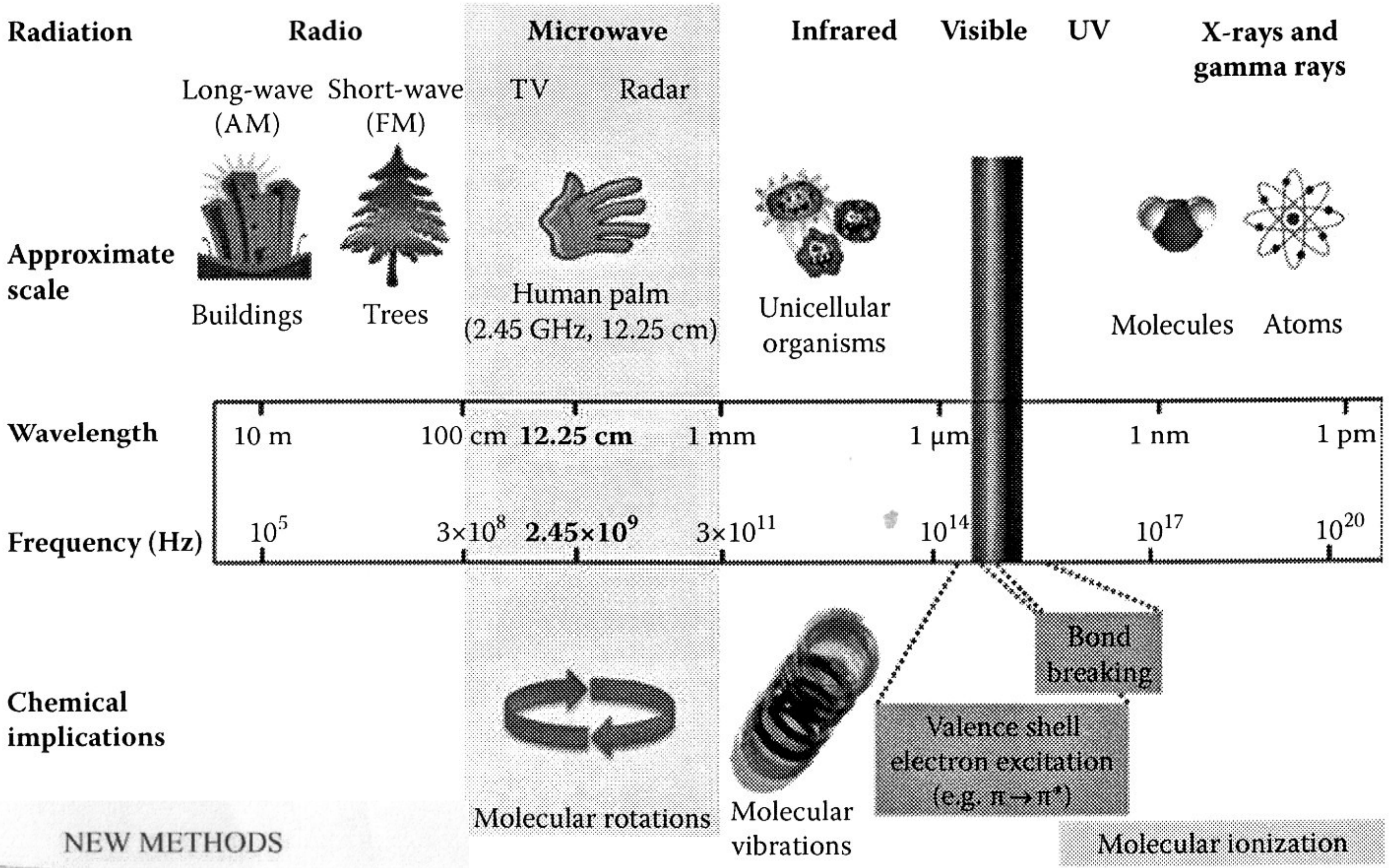
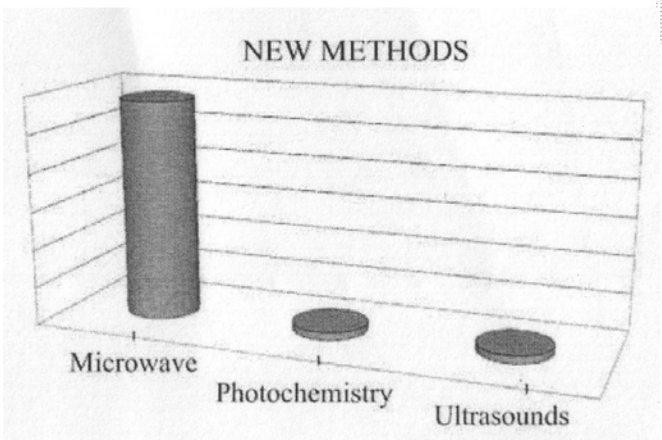
Microwave Irradiation





2008 論文相對數量分析

(*Green Chem. Lett. Rev.* **2010,** *3***,** 105-113)

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COST Chemistry Action D32

(COST = 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.
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. (starting in 2004)

Cann (Ed), *Microwave Heating as a Tool for Sustainable Chemistry*, 2011,CRC

Reviews:

Microwave-Assisted Synthesis of Ag Nanostructures (*Accounts*, **2011**, *44*, 469-478)

Variable Microwave Effects in Synthesis, the Role of Heterogeneity (*Org. Process Res. Dev*. **2011**, *15*, 140-147)

Scale-Up of Microwave-Assisted Reactions in a Multimode Bench-Top Reactor (*Org. Process Res. Dev*. **2011**, *15*, 841-854)

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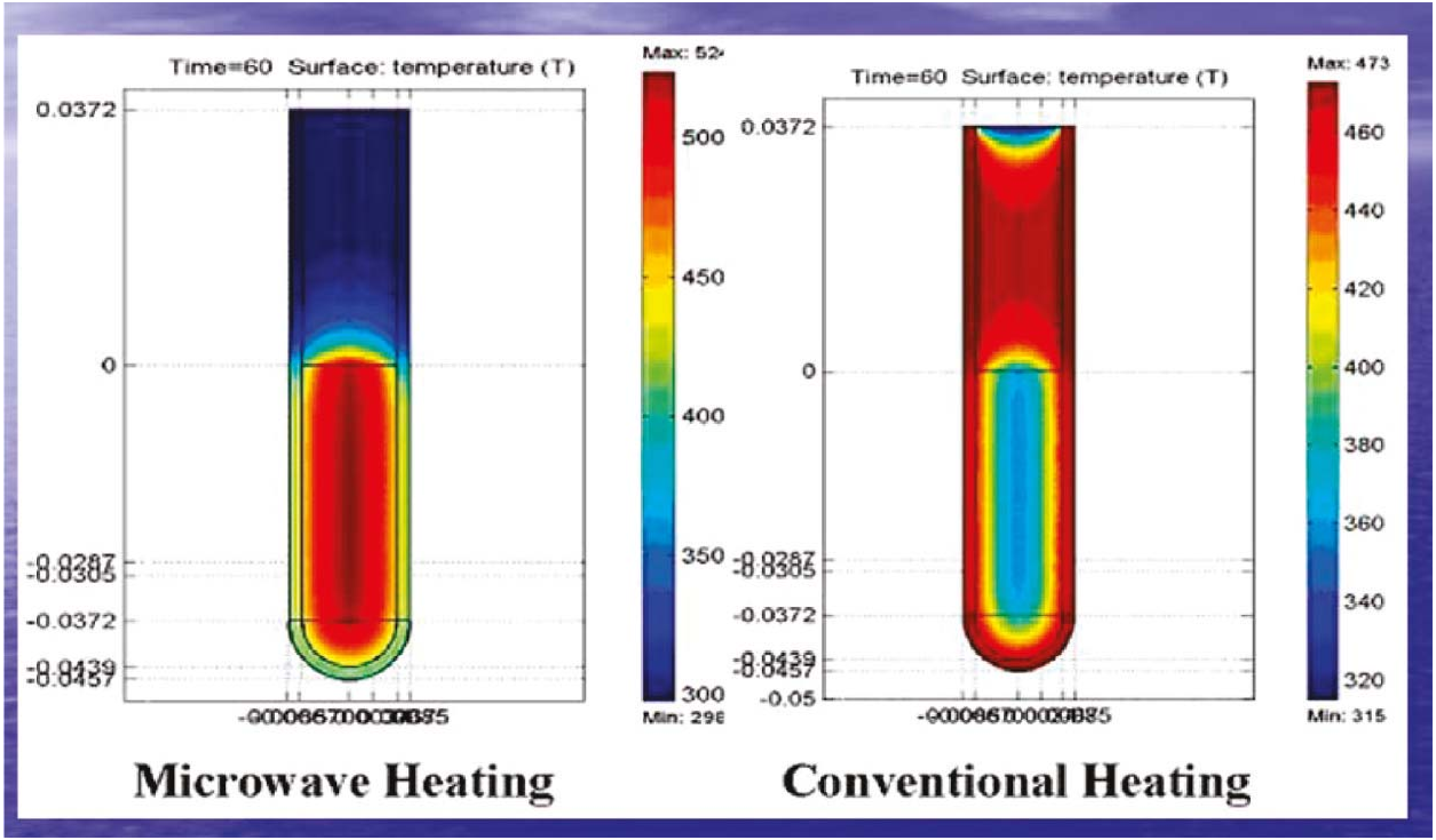
Heating after 60 s



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Super-heating and Loss tangents

Solvent	B.p./ °C)	B.p. MW/°C	Difference	tan δ
Water	100	105	5	0.123
Ethanol	79	103	24	0.941
Methanol	65	84	19	0.659
Dichloromethane	40	55	15	0.042
Tetrahydrofuran	66	81	15	0.047
Acetonitrile	81	107	26	0.062
Propan-2-ol	82	100	18	0.799
Acetone	56	81	25	0.054
Ethyl acetate	78	95	17	0.059
Dimethylformamide	153	170	17	0.161

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

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.*, ***Practical Microwave Synthesis for Organic Chemists*, **Wiley-VCH**, 2009** p. 18)

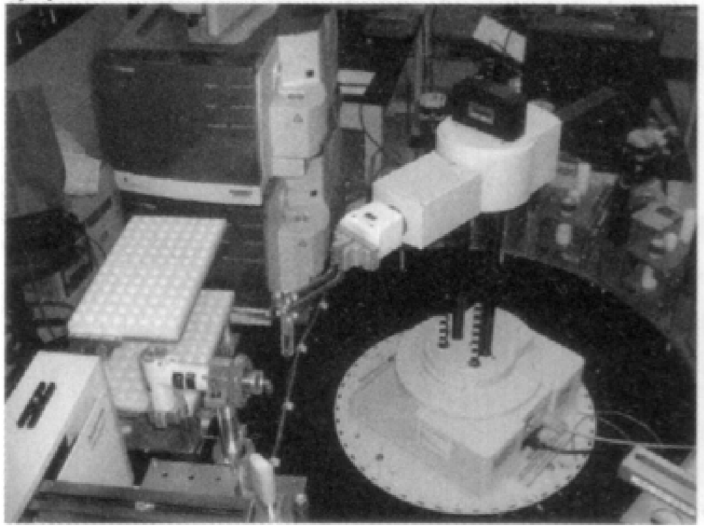
Microwave effects

thermal effects – dipolar polarization
superheating in a mw cavity
non-thermal effects – increasing pre-exponential factor A
decreasing activation energy

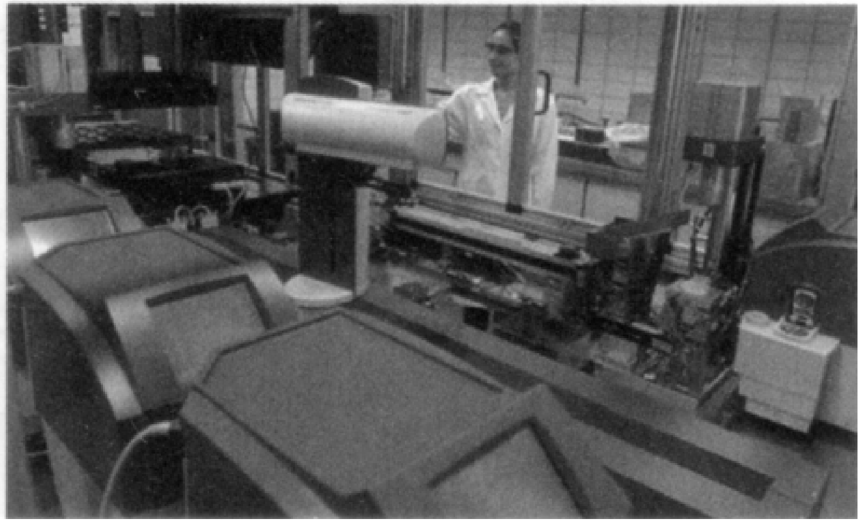
Robotic facility (Abbott Lab) (a) and high throughput factory (Novartis) (b)

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

(a)



(b)

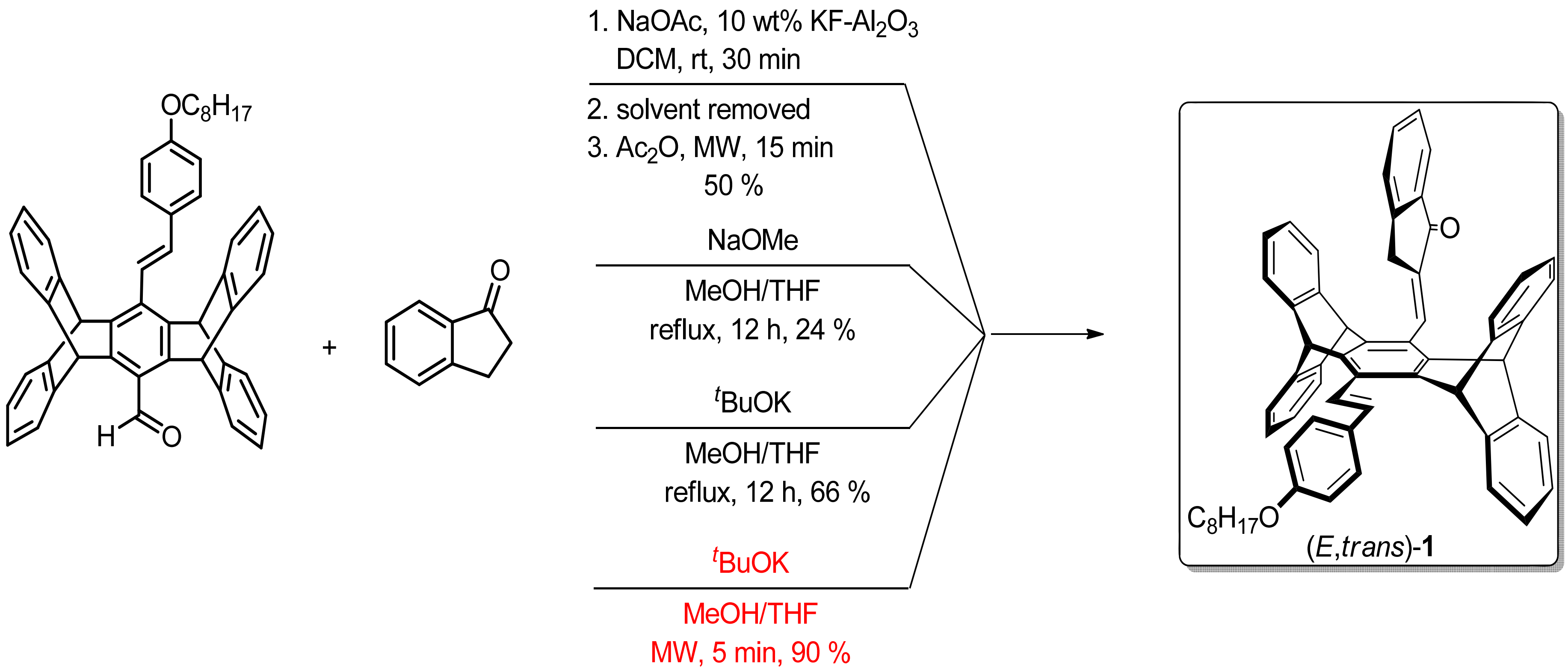


Laboratory scale preparations

簡單型儀器

Milestone START System

CEM
Discover SF



(Unpulished, courtesy of Professor J. S, Yang, **2011)**

(Table 5.3) **General Summary of Reaction Classes Suitable for Microwave Scale-Up**

	Beneficial/Suitable	No Benefit/Unsuitable
Major reaction classes	Additions condensations Alkylations/acylations Heterocycle formation Hydrogenations S_NAr reactions	Amide bond formation Deprotections (excluding hydrogenations) Functional group additions Functional group interconversions Protection reactions
Minor reaction classes	Cycloadditions Friedel–Crafts reactions Metal-catalyzed reactions (e.g., Heck and Suzuki couplings) [Peptide synthesis][a] [Polymer synthesis][b] Thermal rearrangements	Grignard reactions Low-temperature organometallic reactions (e.g., lithiation) Oxidations Reductions (metal hydrides, excluding hydrogenations)
Other reaction parameters	Autoclave/pressure reactions Reactions with gases Reactions with solid-support reagents Reactions with water as solvent Where thermodynamic product required	

Cann (Ed), *Microwave Heating as a Tool for Sustainable Chemistry*, **2011**,CRC

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MW Heating as a tool for Polymer Chemistry

(97 references)

Cann (Ed), *Microwave Heating as a Tool for Sustainable Chemistry*, 2011,CRC

MW Heating as a Tool for the Undergraduate Organic Chemistry Laboratory

(77 references)

Cann (Ed), ***Microwave Heating as a Tool for Sustainable Chemistry*****, 2011**,CRC

MW Heating as a tool for Material Chemistry

(55 reference)

Cann (Ed), ***Microwave Heating as a Tool for Sustainable Chemistry*****, 2011**,CRC

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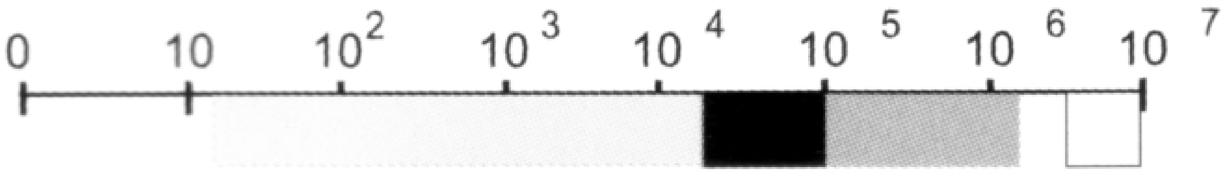
Sonochemistry

Sound frequencies



Hz (cps)

| → **Ultrasound (supersound)**

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

Cleaner with timer and heater

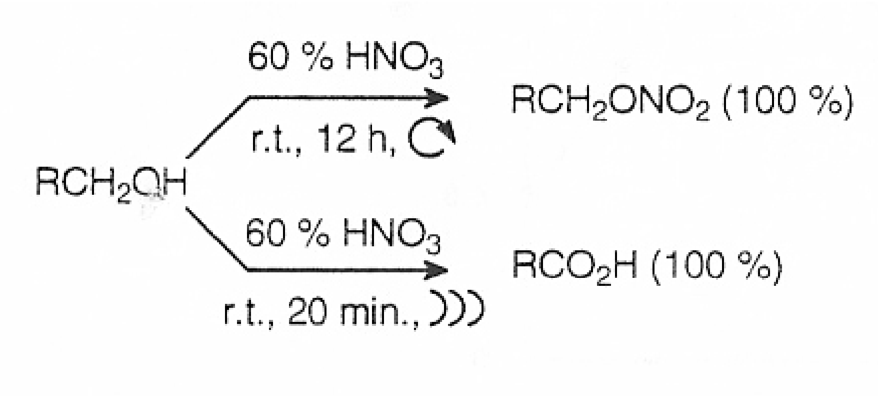
Less expensive

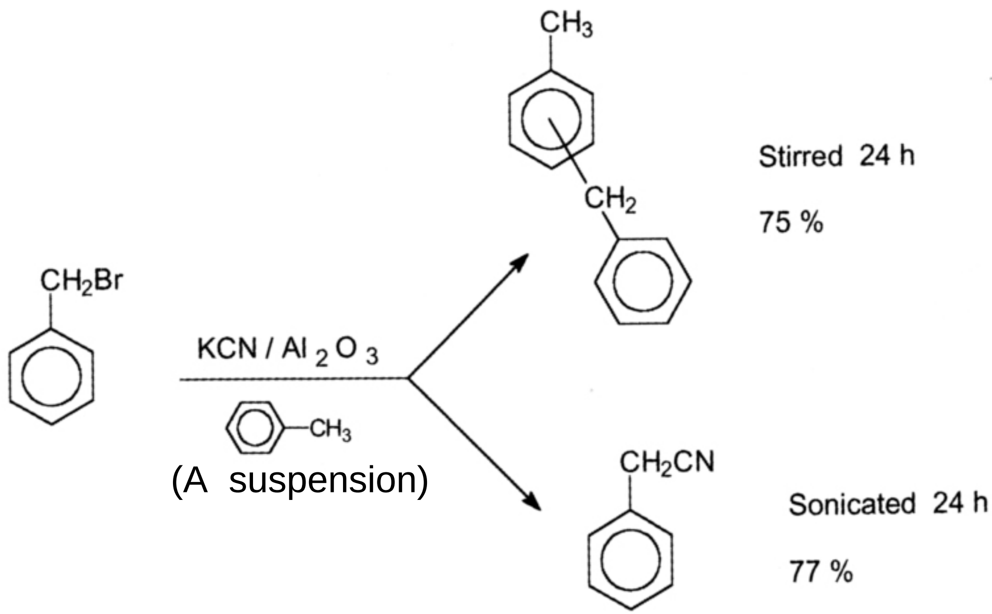
ultrasound horn

more effective

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:





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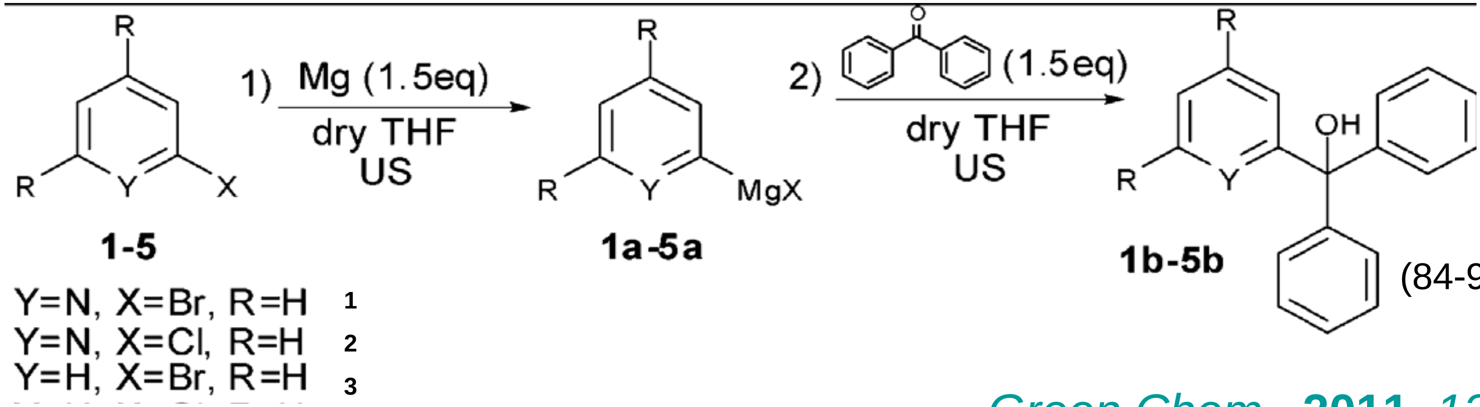
Simple sonochemical protocols for fast and reproducible Grignard reactions



(84-94% for **1-3)**

Green Chem., **2011**, *13*, 2806-2809

Ultrasonic activation of Heck type reactions in the presence of Aliquat-336

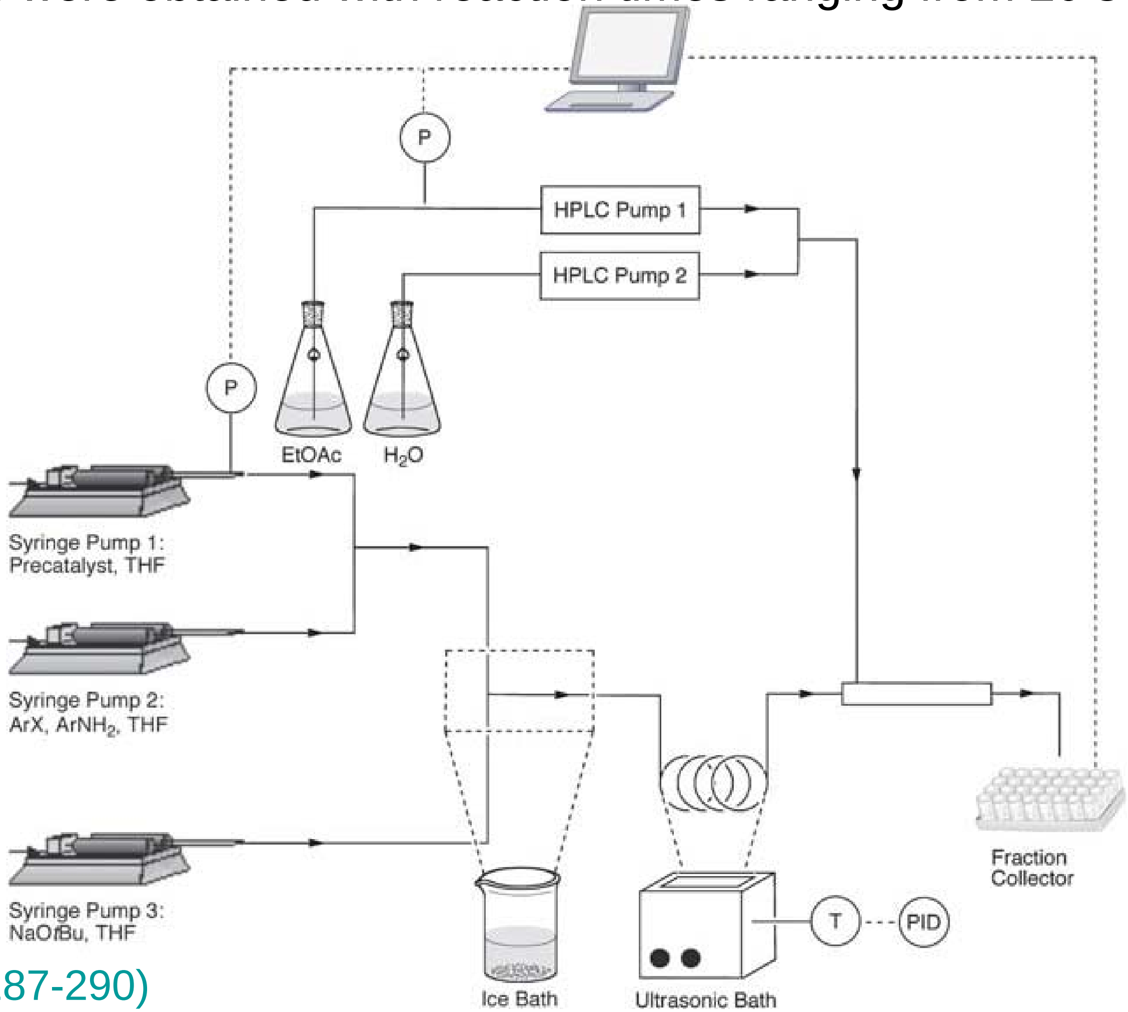
Without phosphine and base, Pd catalysts such as $PdCl_2$, $Pd(OAc)_2$ and $PdCl_2(PhCN)_2$ in water/DMF mixtures with Aliquat-336 proved to be excellent catalytic systems for Heck reactions involving several aryl bromides with styrene and acrylic compounds. Yields are remarkably improved under ultrasonic irradiation (40-60% to 84-91%)

$$ArBr + H_2C{=}CH\text{-}EWG \longrightarrow Ar\text{-}CH{=}CH\text{-}EWG.$$

Ultrasonic Sonochem. **2011**, *18*, 23-27

Overcoming the clogging in flow by ultrasound

A continuous-flow palladium-catalyzed amination reaction was made possible through efficient handling of solids via acoustic irradiation. Various diarylamines were obtained with reaction times ranging from 20 s to 10 min.



(*Chem. Sci*. **2011**, *2*, 287-290)

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Solvent alternatives

Water

Less-volatile solvents (including polymeric solvents)

Other benign solvents (ionic liquids, gas-expansion liquids, etc)

Supercritical and near-(or sub-)critical fluid systems

Renewables (organic carbonates, glycerol derivatives, etc)

Freemantle, *An Introduction to Ionic Liquids*, RSC, 2010

From Molten Salts to Ionic Liquids: A “Nano” Journey, *Accounts*, **2011**, *44*,1223-1231.

Room Temperature Ionic Liquids, *Chem. Rev*., **2011**, *111*, 3508-3576. (694 refs)

Subcritical Water as Reaction Environment, *ChemSusChem*, **2011**, *4*, 566-579.

Green material synthesis with supercritical water, *Green Chem*. **2011**, *13* 1380-1390.

Switchable solvents, *Chem. Sci*., **2011**, *2*, 609-614

A Versatile Lab to Pilot Scale Continuous Reaction System for Supercritical Fluid Processing, *Org. Process Res. Dev*. **2011**, *15*, 1270-1280.

Searching for green solvents, *Green Chem*. **2011**, *13* 1391-1398

and many more

Supercritical fluids and critical points

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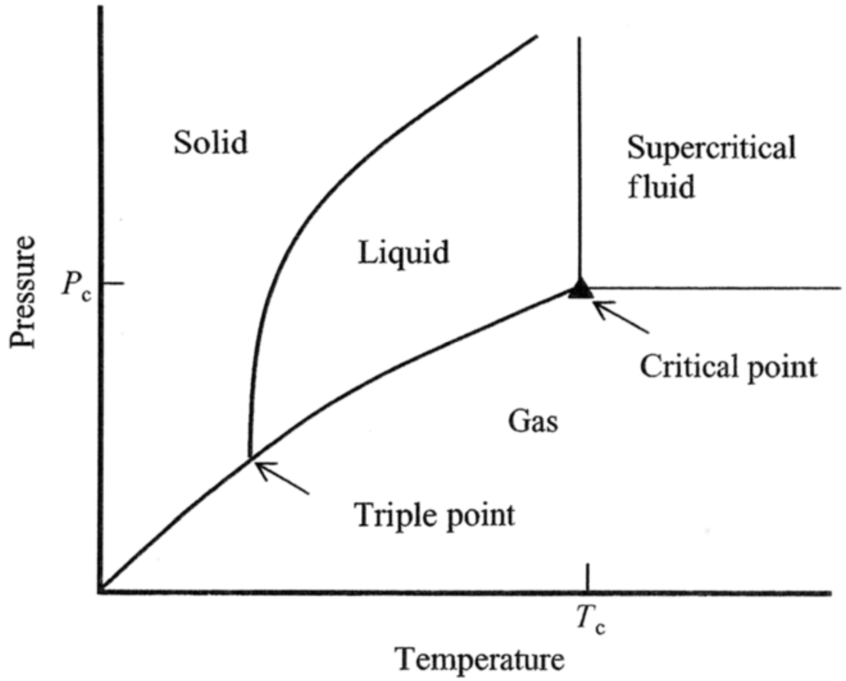
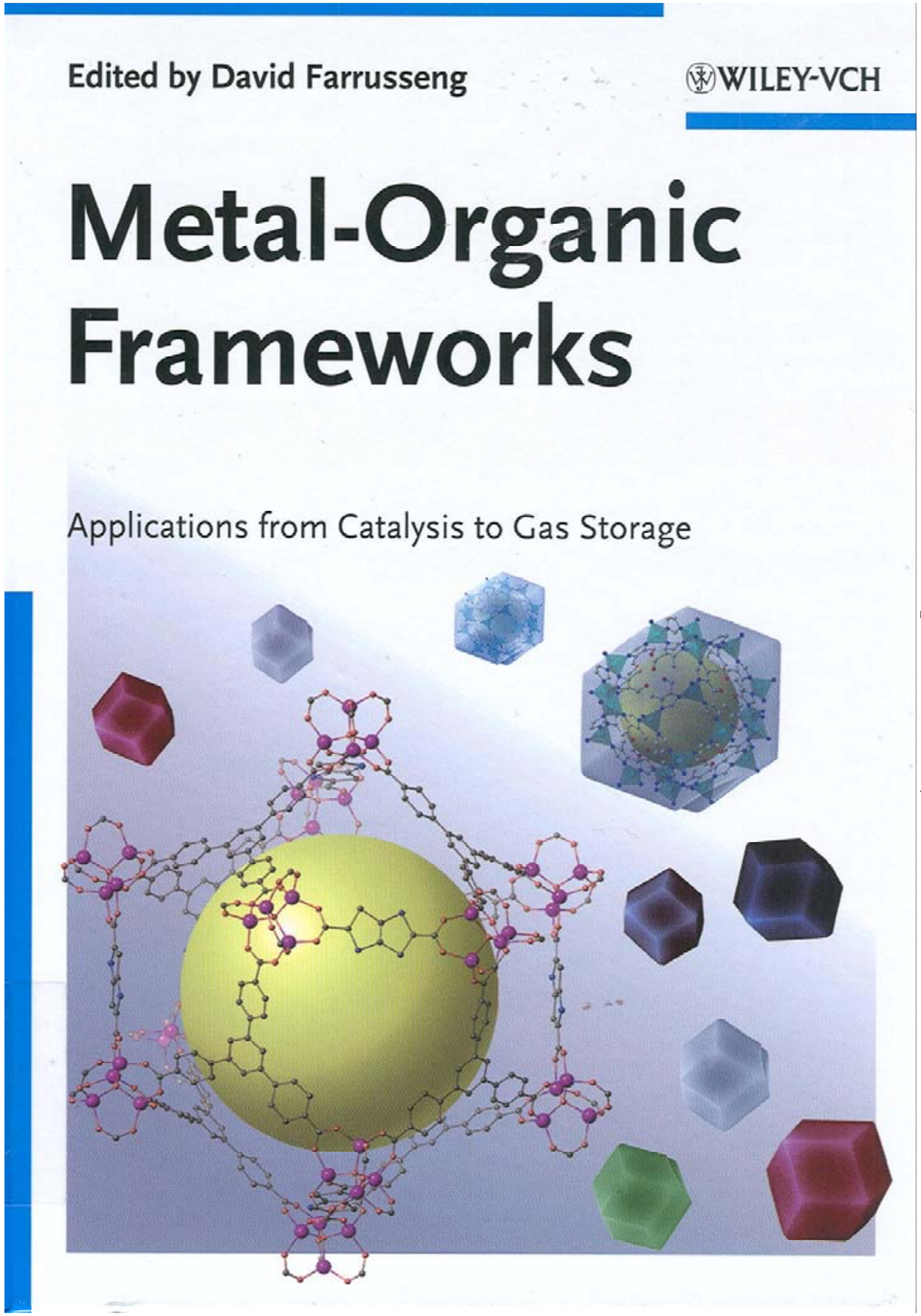


Material	T_c (°C)	P_c (bar)
Ammonia	132.4	113.2
Carbon dioxide	31.1	73.8
Ethane	32.2	48.7
Ethene	9.2	50.4
Fluoroform	25.9	48.2
Propane	96.7	42.5
Water	374.2	220.5



Hydrothermal processes using supercritical, or sub-(near-)critical water.

Near-critical water, a cleaner solvent for the synthesis of metal-organic Frameworks, *Green Chem.* **2011,** DOI:10.1039/c1gc15726d

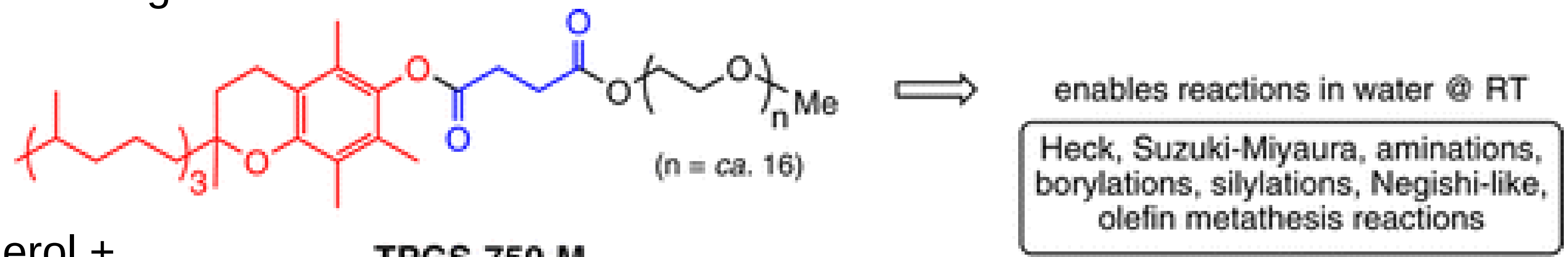
The microporous metal–organic framework $\{[Zn_2(L)]\cdot(H_2O)3\}\bullet$ (H_4L = 1,2,4,5-tetrakis(4-carboxyphenyl)benzene) has been synthesized using near-critical water (300 ^oC, ca 80 bar) as a cleaner alternative to toxic organic solvents.

PGCC Academic Award 2011

Professor Bruce H. Lipshutz, Department of Chemistry and Biochemistry, University of California, Santa Barbara

Innovation and Benefits

Most chemical manufacturing processes rely on organic solvents, which tend to be volatile, toxic, and flammable. Chemical manufacturers use billions of pounds of organic solvents each year, much of which becomes waste. Water itself cannot replace organic solvents as the medium for chemical reactions because many chemicals do not dissolve and do not react in water. Professor Lipshutz has designed a safe surfactant, **TPGS-750-M,** that forms tiny droplets in water. Organic chemicals dissolve in these droplets and react efficiently, allowing water to replace organic solvents.

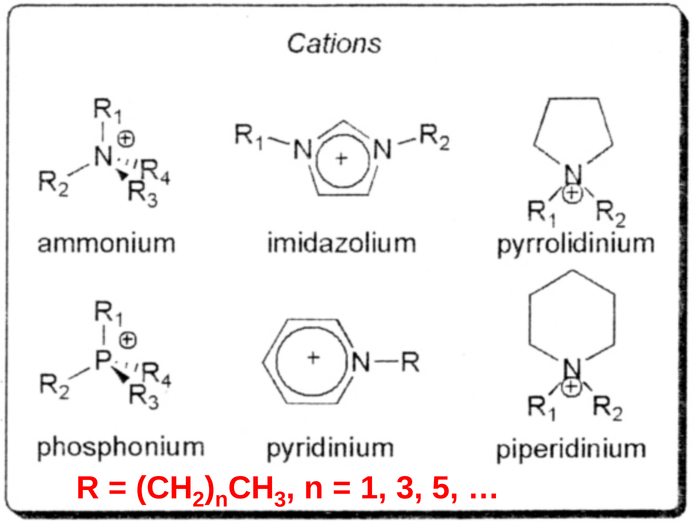


TPGS-750-M

α-tocopherol + $(CH_2CO)_2O$, then PEG-750-M

Lipschutz, *et al. J. Org. Chem.*, **2011**, *76*, 4379-4391.

Room temperature ionic liquids

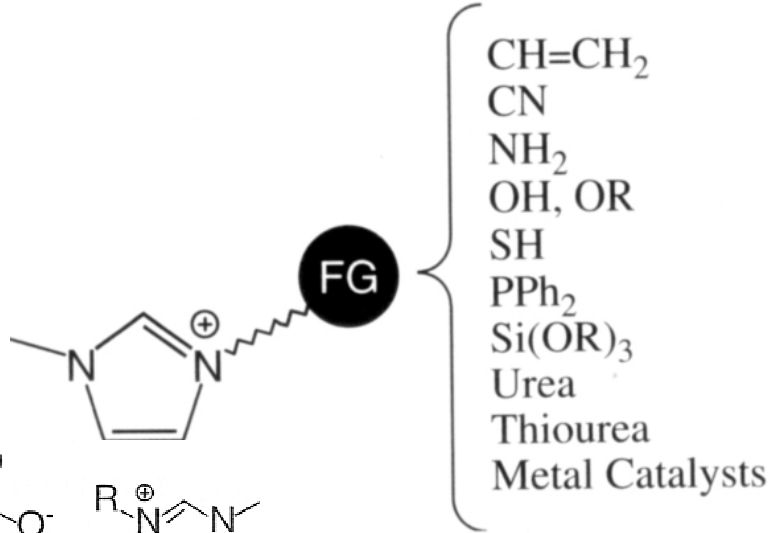


Anions			
NO_3^-	BF_4^-	$CF_3SO_3^-$	Cl^-, Br^-, I^-
$Al_2Cl_7^-$	SbF_6^-	$CF_3CO_2^-$	$CH_3CO_2^-$
$Me_2PO_4^-$	PF_6^-	$(CF_3SO_2)_2N^-$	$(CN)_2N^-$

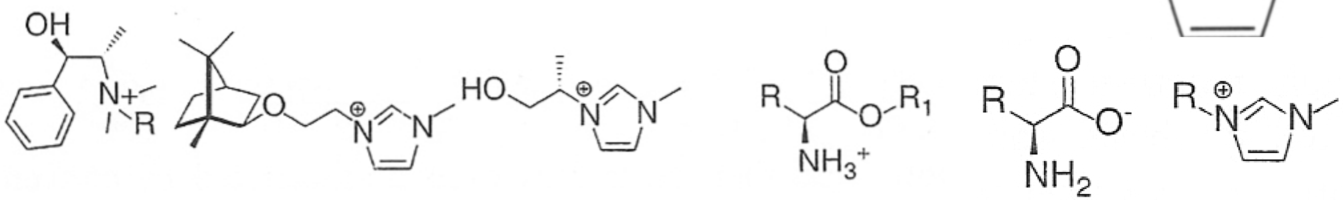
Alternative Solvents for Green Chemistry (Kerton, **2009, RSC**)
Chapter 5

Task-specific ionic liquids (TSIL)

Functionalized ionic liquid cations



Novel chiral ionic liquids



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

Solvents from renewable resources

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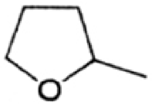
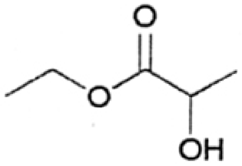
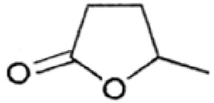


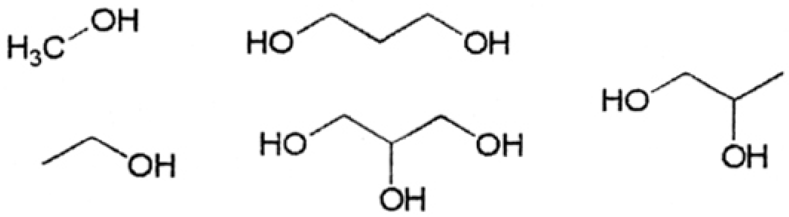
2-MeTHF



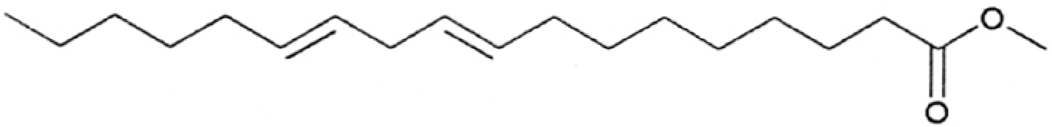
Ethyl lactate



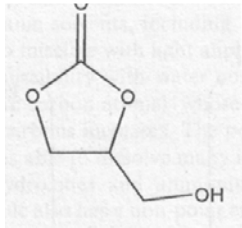
γ -Valerolactone



Alcohols and polyols



Fatty acid ester (Biodiesel component)



Glycerol carbonate
(and other organic
Carbontes)

Industrial uses of esteric green solvents

Solvent	*Industrial use*
Glycerol carbonate	Non-reactive diluent in epoxy or polyurethane systems
Ethyl lactate	Degreaser
	Photo-resist carrier solvent
	Clean-up solvent in microelectronics and semiconductor manufacture
2-Ethylhexyl lactate	Degreaser
	Agrochemical formulations
Fatty acid esters (and related compounds)	Biodegradable carrier oil for green inks
	Coalescent for decorative paint systems
	Agrochemical/pesticide formulations

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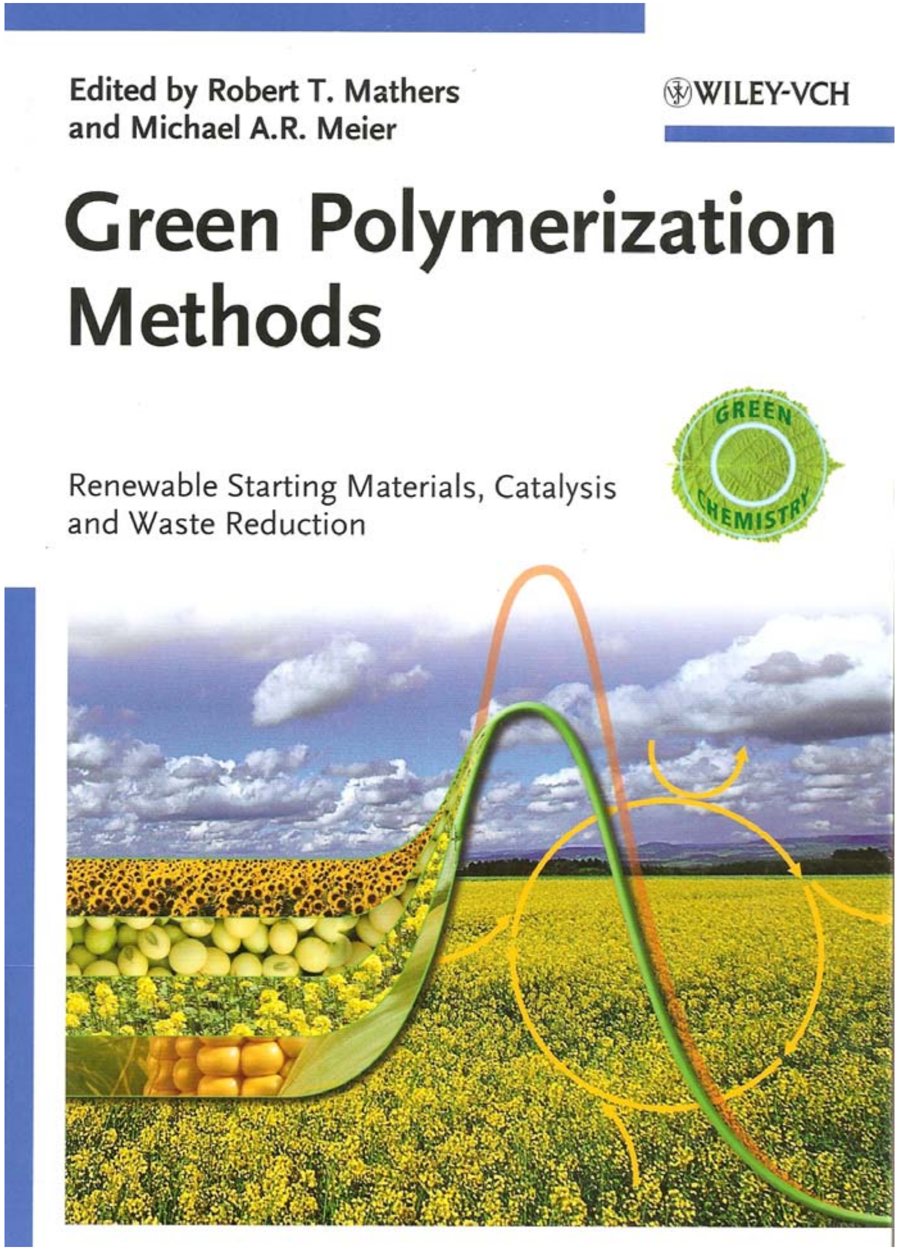
Solvents for polymerization



Chapter 5 Monoterpenes as Polymerization Solvents and Monomers in Polymer Chemistry

Chapter 6 Controlled and Living Polymorization in Water

Chapter 7 Towards Sustainable Solution Polymerization: Biodiesel as a Polymerization Solvent

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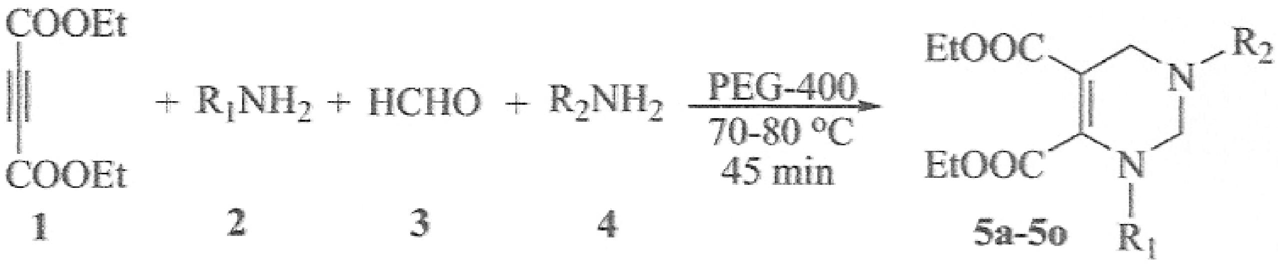
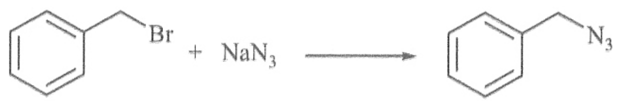
The use of PEG

- A green methodology for one-pot synthesis of polysubstituted-tetrahydropyrimidines using PEG
- *Green Chem. Lett. Rev*. **2011**, *4*, 109-115



- PEG 400 promoted nucleophilic substitution reaction of halides into organic azides under mild conditions
- *Green Chem. Lett. Rev*. **2011**, *4*, 281-287



Entry	NaN_3 (eq.)	Catalyst/Solvent	Method/Temperature	Reaction time	Yield[a]
1	1.1	DMSO (*31*)	Stirring, ambient temperature	1 hr	98[b]
2	1.3	H_2O (*55*)	Microwave, 120°C	30 min	95
3	1.3	Clays/PE-H_2O (*49*)	Stirring, 90–100°C	6 hr	84
4	2.0	[bmim][PF_6]-H_2O (*52*)	Stirring, 25°C	5 hr	84
5	1.1	EtOH (*34*)	Stirring, reflux	24 hr	No report
6	1.2	PEG 400	Stirring, room temperature	50 min	98, 95,[c] 91[d]

- A comprehensive tool that provides both simple and detailed guidance to help scientists choose greener solvents in route development.

GSK Solvent Selection Guide

	Few issues (bp°C)	Some issues (bp°C)	Major issues
Chlorinated	....before using chlorinated solvents, have you considered TBME, isopropyl acetate, ethyl acetate, 2-Methyl THF or Dimethyl Carbonate?		Dichloromethane ** Carbon tetrachloride ** Chloroform ** 1,2-Dichloroethane **
Greenest Option	Water (100°C)		
Alcohols	1-Butanol (118°C) 2-Butanol (100°C)	Ethanol/IMS (78°C) t-Butanol (82°C) 1-Propanol (97°C) 2-Propanol (82°C) Methanol (65°C)	2-Methoxyethanol **
Esters	t-Butyl acetate (95°C) Isopropyl acetate (89°C) Propyl acetate (102°C) Dimethyl Carbonate (91°C)	Ethyl acetate (77°C) Methyl acetate (57°C)	
Ketones		Methyl isobutyl ketone (117°C) Acetone (56°C)	Methyl ethyl ketone
Aromatics		p-Xylene (138°C) Toluene ** (111°C)	Benzene **
Hydrocarbons		Isooctane (99°C) Cyclohexane (81°C) Heptane (98°C)	Petroleum spirit ** 2-Methylpentane Hexane
Ethers		t-Butyl methyl ether (55°C) 2-Methyl THF (78°C) Cyclopentyl methyl ether (106°C)	1,4-Dioxane ** 1,2-Dimethoxyethane ** Tetrahydrofuran Diethyl ether Diisopropyl ether **
Dipolar aprotics		Dimethyl sulfoxide (189°C)	Dimethyl formamide ** N-Methyl pyrrolidone ** N-Methyl formamide ** Dimethyl acetamide ** Acetonitrile

** = EHS Regulatory Alerts: please consult the detailed solvent guide and the GSK Chemicals Legislation Guide for more information http://solventguide.gsk.com/

Green Chem. **2011**, *13*, 854-862

多謝聽講 歡迎討論

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