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## 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]。

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# 綠色製程與實驗方法

綠色製程與實驗方法：不同的反應方式  
(如微波、流動式反應器)帶來那些契機?

**10:10-11:00**

甘魯生

中央研究院化學研究所

第六條: 為用能效率而設計: 化學過程中能的需求應該被認定為對環境和經濟的衝擊縮為最小. 如果可能, 合成方法應該在常溫和常壓下進行.

耗能指數: 溫度

- 5 (反應溫度低於 $-20^{\circ}\text{C}$ 或高於 $280^{\circ}\text{C}$ )
- 3 (反應溫度 $0 - -20^{\circ}\text{C}$ 或 $160 - 280^{\circ}\text{C}$ )
- 2 (反應溫度 $0 - 10^{\circ}\text{C}$ 或 $90 - 160^{\circ}\text{C}$ )
- 1 (反應溫度 $10 - 20^{\circ}\text{C}$ 或 $30 - 90^{\circ}\text{C}$ )
- 0 (反應溫度 $20 - 30^{\circ}\text{C}$ )

問題是如能將每個化學反應耗能指數儘量縮小(最好是0). 因為我們目前用(尤其是很方便)能皆來自化石燃料. 開源既然不易, 所以要從節流上多下功夫. 節流可分二部份, 首先是化學反應的本身. 也就是說發明或設計新的節能反應來替換掉舊的耗能反應. 其二是改變實驗方法.

**Optimizing reaction conditions, minimizing energy usage.**

# Alternative organic synthetic methods



Microwave



Ultrasound

微波 (Microwave)

極性或解離物質  
微觀尺寸流動

(Microflow)

溶液  
超音波化學

(Sonochemistry)

溶液  
Mechanochemistry

固體

Electrochemistry

導電

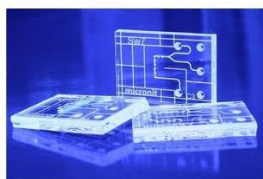
Photochemistry  
chromophore



Reactants



light



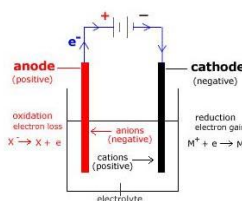
Microflow



Product



mechnochemistry Electrochemistry

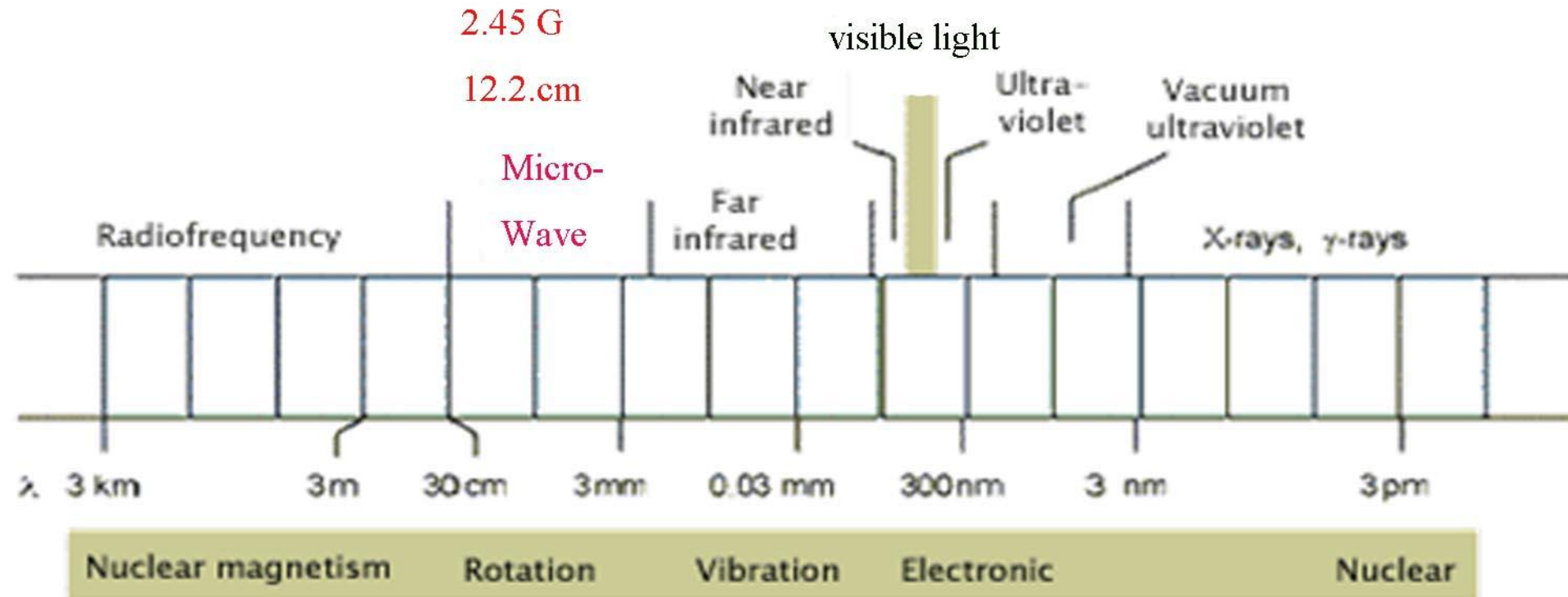


S. K. Sharma, A. Chaudhary,  
and R. V. Singh, "GRAY  
CHEMISTRY VERSES  
GREEN CHEMISTRY:  
CHALLENGES AND  
OPPORTUNITIES, RASĀYAN  
JOURNAL OF CHEMISTRY  
(RJC), (2008), 1, 68-92.

# Microwave heating method

*“The microwave oven is the Bunsen burner of the 21st century.”*

-Ajay K. Bose, 1925-2010 Chemistry professor, Stevens Institute of Technology



## ***Theory:***

***When irradiated at microwave frequencies, electromagnetic waves pass through the dipoles or ions of the sample and cause the molecules to oscillate. In this process, energy is lost in the form of heat through molecular friction and dielectric loss.***

## HISTORY

1947 Percy Spencer, heating food

1962 David Compson, lyophilization Microwave heating: in freeze-drying, electronic ovens, and other applications

1973 A.N. Ponomarev and V.A. Tarasenko "Application of Microwave frequency Irradiations for Stimulation of Chemical Processes" (in Russian).

???? Ardalyon N. Ponorev worked in the group of V.L. Tolroze, and they studied different physical methods of stimulations of chemical reactions. In their experiments with microwave irradiation they studied rubber vulcanization and polymerization reactions of methyl methacrylate and styrene in benzene in glass vessels or directly in the space of the metal microwave resonator.

Application of Microwaves in Chemistry <http://www.microwavetec.com/mwchem.php>

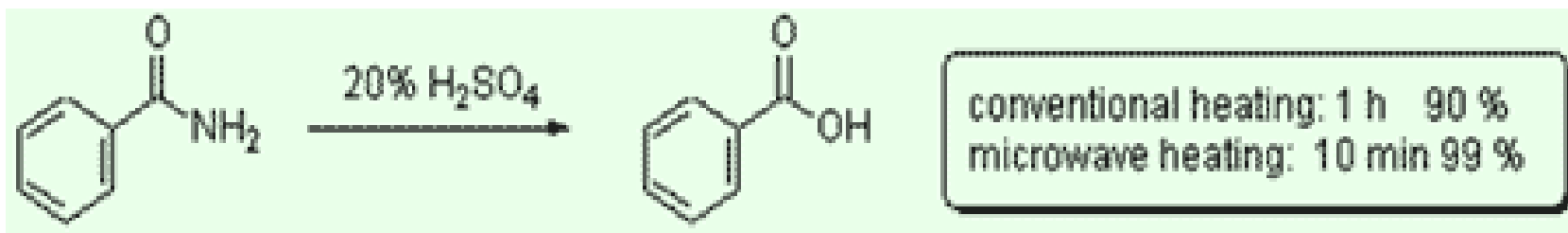
**1986 R. Gedye and R.J. Giguere (1986)**

Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L. & Rousell, J., The use of microwave ovens for rapid organic synthesis, Tetrahedron Letters, (1986) **27**, 279-282.)

Giguere, R. J.; Bray, T. L.; Duncan, S. M. & Majetich, G., Application of Commercial Microwave Ovens to Organic Synthesis. Tetrahedron Letters, (1986) **27**, 4945-4948.

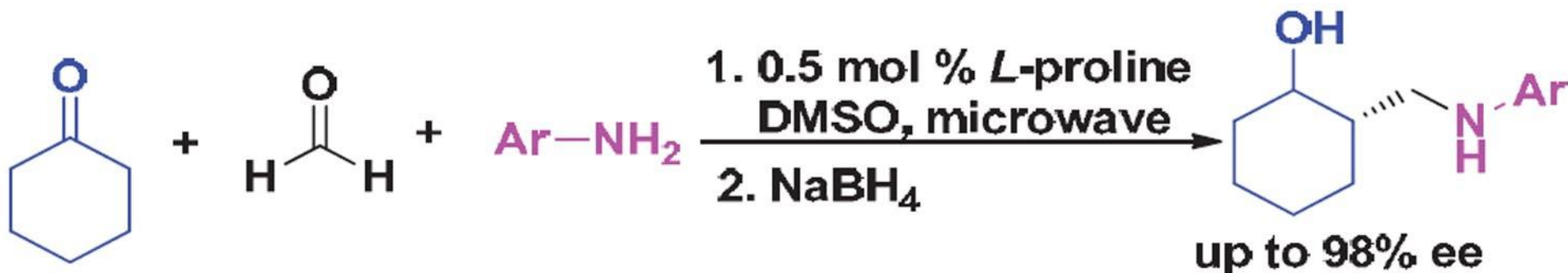
## Advantages:

- Control of temperature and pressure
- Perform reactions impossible by conventional heating
- Dramatic reduction in reaction time (from days and hours to minutes).



## • Increase yields

Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L. and Rousell, J., *Tetrahedron Letters*, (1986) **27**, 279-282.

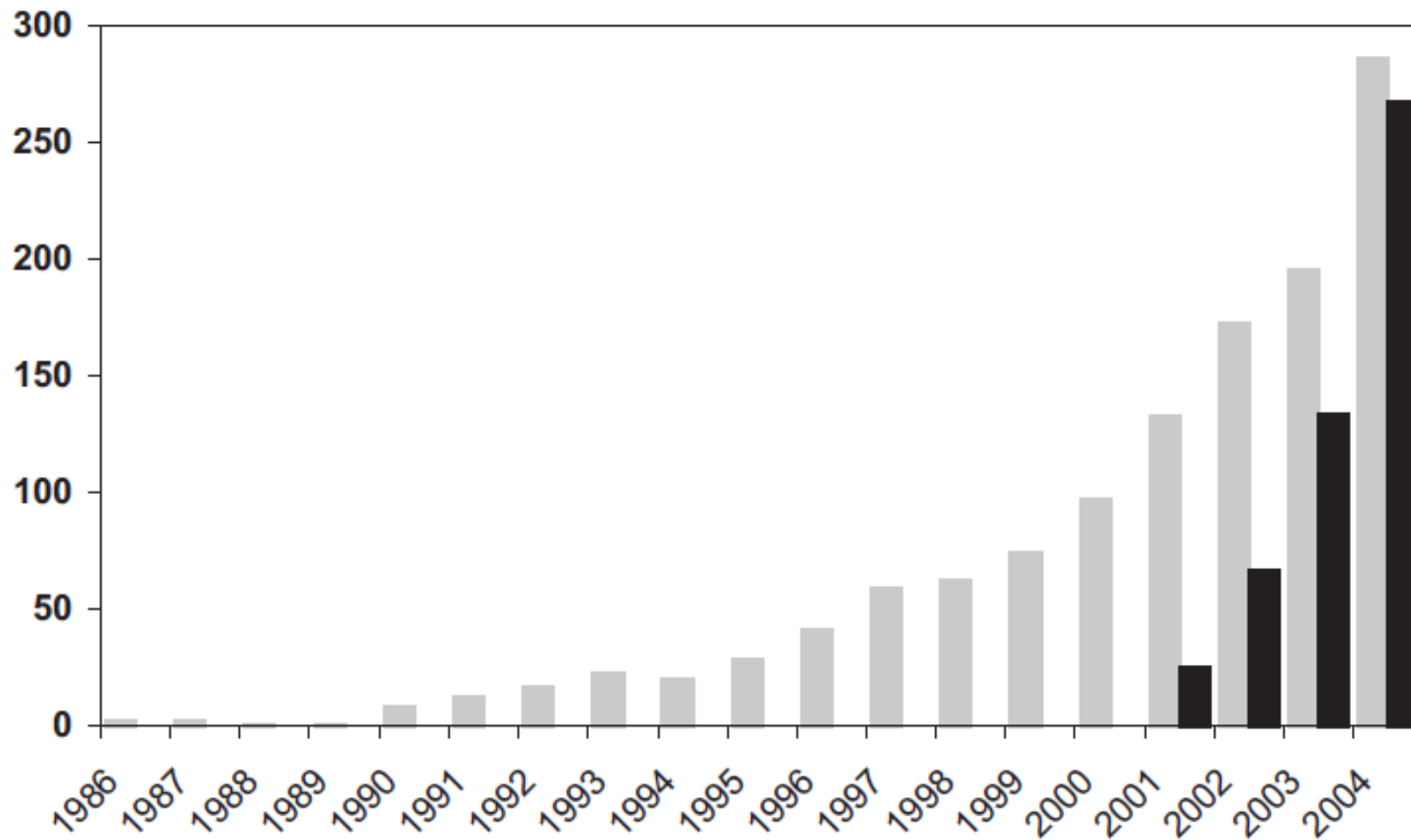


*Mannich* reactions: Synthesis of  $\beta$ -amino ketones via three-component condensation

B. Rodríguez and C. Bolm, *J. Org. Chem.* **2006**, *71*, 2888-2891

- Reduction of side reactions
- Improve reproducibility

# Publication Statistics



from the book C.O. Kappe and A. Stadler *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, 2005



## Organic synthesis:

Reviews: (a) C. O. Kappe and D. Dallinger, *Mol. Diversity*, 2009, **13**, 71; (b) S. Caddick and R. Fitzmaurice, *Tetrahedron*, 2009, **65**, 3325. (c) J. D. Moseley and C. O. Kappe, *Green Chem.*, 2011, **13**, 794-806.

Books: (a) *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2nd edn, 2006; (b) *Microwave Methods in Organic Synthesis*, ed. M. Larhed and K. Olofsson, Springer, Berlin, 2006; (c) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, 2005; (d) *Microwave Heating as a Tool for Sustainable Chemistry*, ed. N. E. Leadbeater, CRC Press, Boca Raton, 2011.

## Peptide synthesis:

(a) J. M. Collins and N. E. Leadbeater, *Org. Biomol. Chem.*, 2007, **5**, 1141; (b) F. Rizzolo, G. Sabatino, M. Chelli, P. Rovero and A. M. Papini, *Int. J. Pept. Res. Ther.*, 2007, **13**, 203; (c) S. Coantic, G. Subra and J. Martinez, *Int. J. Pept. Res. Ther.*, 2008, **14**, 143; (d) B. Bacsa, S. Bosze and C. O. Kappe, *J. Org. Chem.*, 2010, **75**, 2103; (e) C. U. Hjorringgaard, J. M. Pedersen, T. Vosegaard, N. C. Nielsen and T. Skrydsturp, *J. Org. Chem.*, 2009, **74**, 1329.

## Polymer chemistry:

(a) D. Bogdal and A. Prociak, *Microwave-Enhanced Polymer Chemistry and Technology*, Blackwell Publishing, Oxford, 2007; (b) R. Hoogenboom and U. S. Schubert, *Macromol. Rapid Commun.*, 2007, **28**, 368; (c) M. Bardts, N. Gonsior and H. Ritter, *Macromol. Chem. Phys.*, 2008, **209**, 25; (d) C. Holtze, M. Antonietti and K. Tauer, *Macromolecules*, 2006, **39**, 5720.

## Material sciences:

(a) S. Barlow and S. R. Marder, *Adv. Funct. Mater.*, 2003, **13**, 517; (b) J. Perelaer, B.-J. de Gans and U. S. Schubert, *Adv. Mater.*, 2006, **18**, 2101; (c) W. C. Conner and G. A. Tompsett, *J. Phys. Chem. B*, 2008, **112**, 2110; (d) N. L. Campbell, R. Clowes, L. K. Ritchie and A. I. Cooper, *Chem. Mater.*, 2009, **21**, 204; (e) O. Yoshikawa, T. Sonobe, T. Sagawa and S. Yoshikawa, *Appl. Phys. Lett.*, 2009, **94**, 083301; (f) M. Gharibeh, G. A. Tompsett, K. S. Yngvesson and W. C. Conner, *J. Phys. Chem. B*, 2009, **113**, 8930.

## **Nanotechnology:**

- (a) M. Tsuji, M. Hashimoto, Y. Nishizawa, M. Kubokawa and T. Tsuji, *Chem. Eur. J.*, 2005, 11, 440;
- (b) V. Polshettiwar, M. N. Nadagouda and R. S. Varma, *Chem. Commun.*, 2008, 6318;
- (c) M. D. Roy, A. A. Herzing, A. H. De, Paoli Lacerda and M. L. Becker, *Chem. Commun.*, 2008, 2106;
- (d) A. L. Washington and G. F. Strouse, *J. Am. Chem. Soc.*, 2008, 130, 8916;
- (e) J. G. Duque, M. Pasquali and H. K. Schmidt, *J. Am. Chem. Soc.*, 2008, 130, 15340;
- (f) I. Bilecka and M. Niederberger, *Nanoscale*, 2010, 2, 1358.

## **Biochemical processes:**

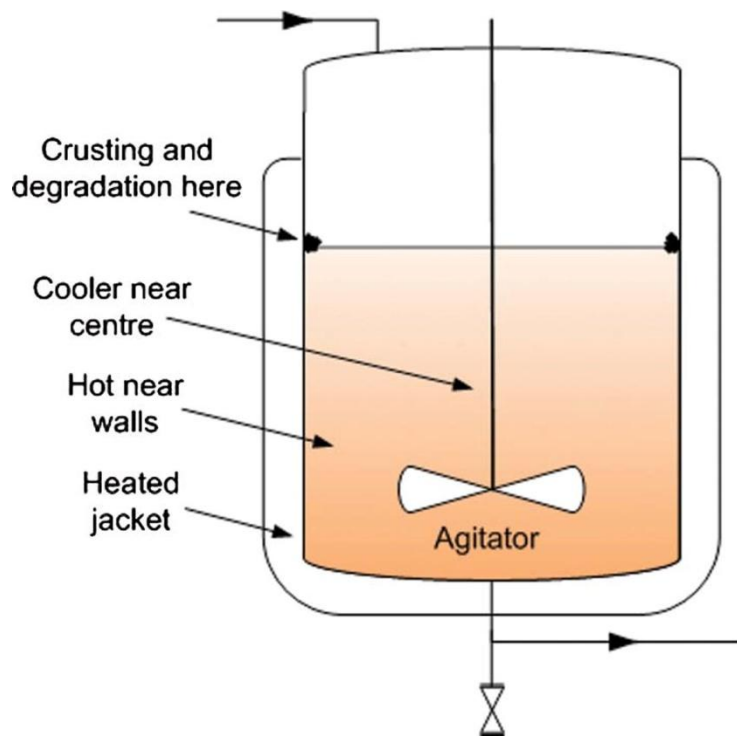
- (a) J. R. Lill, *Microwave Assisted Proteomics*, RSC Publishing, Cambridge, 2009;
- (b) J. R. Lill, E. S. Ingle, P. S. Liu, V. Pham and W. N. Sandoval, *Mass Spectrom. Rev.*, 2007, 26, 657;
- (c) D. D. Young, J. Nichols, R. M. Kelly and A. Deiters, *J. Am. Chem. Soc.*, 2008, 130, 10048;
- (d) W. F. Edwards, D. D. Young and A. Deiters, *Org. Biomol. Chem.*, 2009, 7, 2506;
- (e) K. M. Rahman and D. E. Thurston, *Chem. Commun.*, 2009, 2875.

**Review: R. B. N. Baig and R. S. Varma *Chem. Soc. Rev.*, "Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis", 2012, 41, 1559–1584.**

# Challenges:

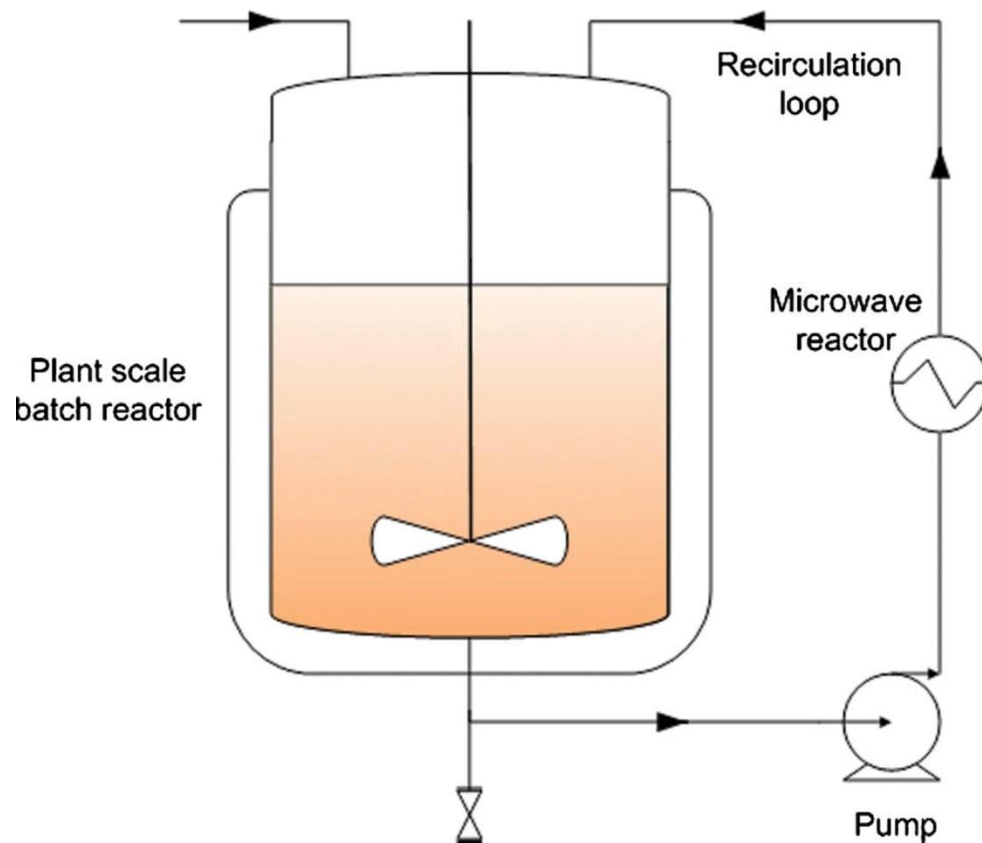
## The scalability

Large reactor up to 50 L.

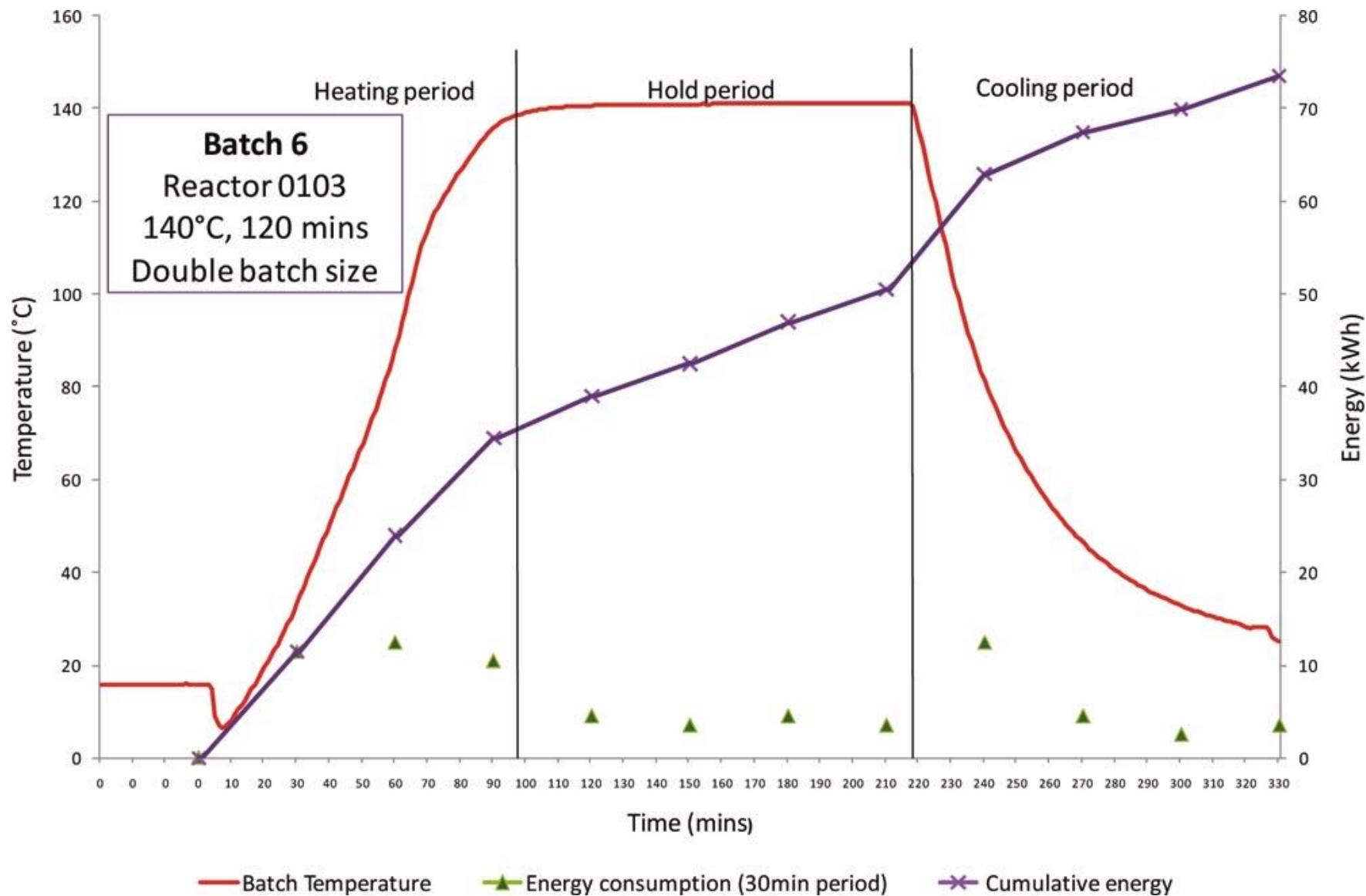


J. D. Moseley, M. J. Welham, and N. P. Weston,  
Energy Fuels 2010, 24, 5446–5453

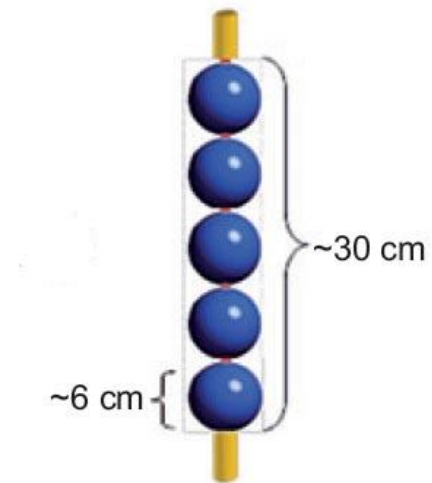
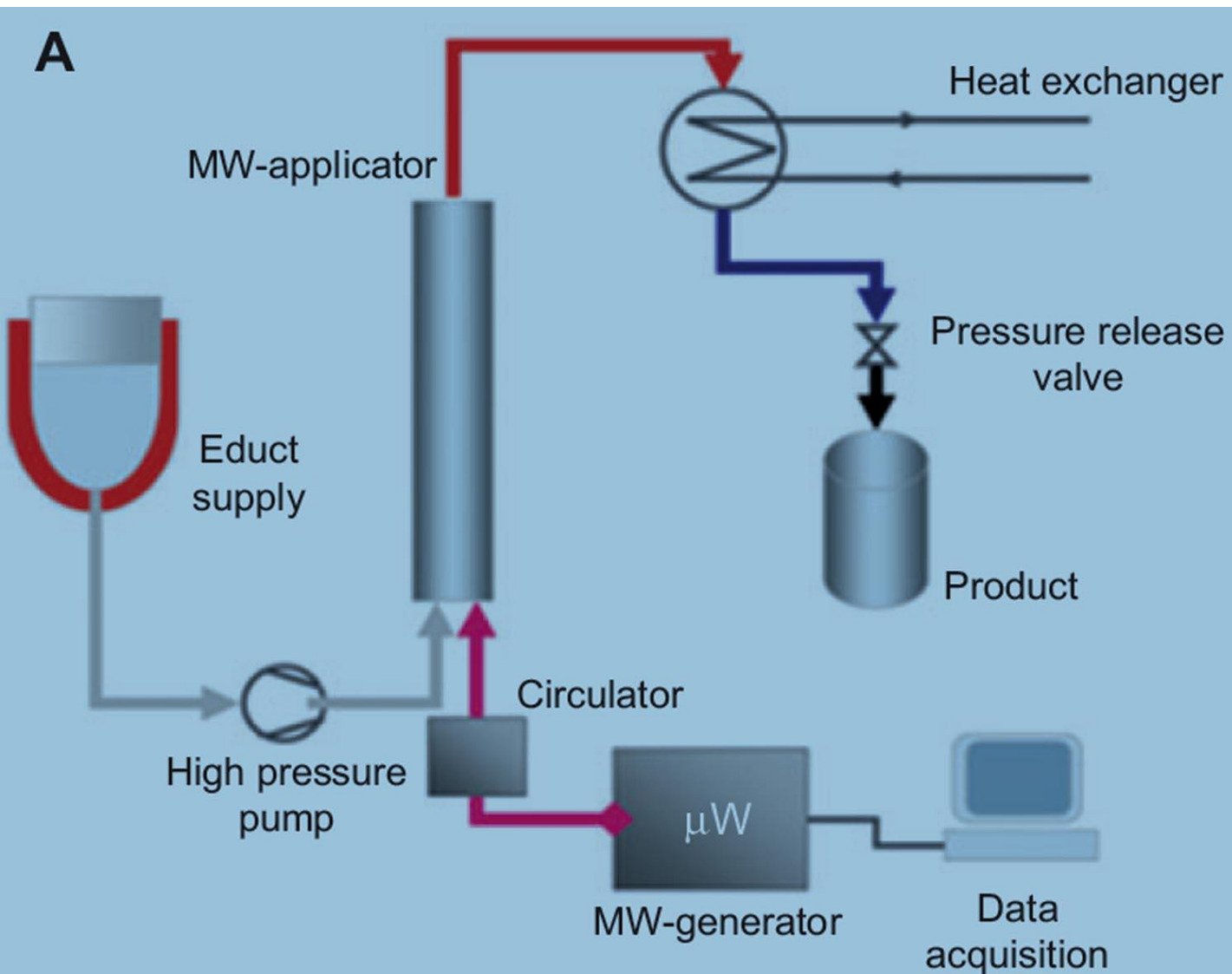
Continuous flow synthesis



R. Morschhauser, M. Krull , C. Kayser , C.  
Boberski, R. Bierbaum , P. A. Puschner , T. N.  
Glasnov, and C. O. Kappe  
Green Process Synth 1 (2012): 281–290



J. D. Moseley, M. J. Welham, and N. P. Weston,  
 Energy Fuels 2010, 24, 5446–5453



R. Morschhauser, M. Krull , C. Kayser , C. Boberski, R. Bierbaum , P. A. Puschner , T. N. Glasnov, and C. O. Kappe, *Green Process Synth* 1 (2012): 281–290.

## Overall energy efficiency of microwave-heating

$$Q_{TH} = mc_p \Delta T$$

$$\eta \text{ (overall efficiency)} = Q_{TH} / Q_{MW}$$

Electrical energy into microwave energy is only about 40–65% efficient for standard 2450 MHz magnetrons vs. electrical heater (nearly 100%) and steam-heated (about 65%) efficient, respectively.

R. Morschhauser, M. Krull , C. Kayser , C. Boberski, R. Bierbaum , P. A. Puschner , T. N. Glasnov, and C. O. Kappe, “Microwave-assisted continuous flow synthesis on industrial scale”, Green Process Synth 1 (2012): 281–290

## Reduce the cost

J. D. Moseley and E. K. Woodman, “Energy Efficiency of Microwave- and Conventionally Heated Reactors Compared at meso Scale for Organic Reactions”, Energy Fuels, 2009, **23**, 5438.

D. R. Godwin, S. J. Lawton, J. D. Moseley, M. J. Welham and N. P. Weston, “Energy Efficiency of Conventionally-Heated Pilot Plant Reactors Compared with Microwave Reactors”, Energy Fuels, 2010, **24**, 5446.

## 儀器公司

Anton Paar Microwave Oven

[http://www.anton-paar.com/Microwave-Synthesis/59\\_Corporate\\_en?productgroup\\_id=99](http://www.anton-paar.com/Microwave-Synthesis/59_Corporate_en?productgroup_id=99)

CEM MARS (台灣有代理商)

[http://www.kohan.com.tw/cem/mars\\_tubs.html](http://www.kohan.com.tw/cem/mars_tubs.html)

# Flash Chemistry (microflow reactor)

**Definition:** Micro Flow Reactors contain small internal channel in which chemicals will mix and chemical react under optimal conditions so that more of the desired reaction product can be generated.

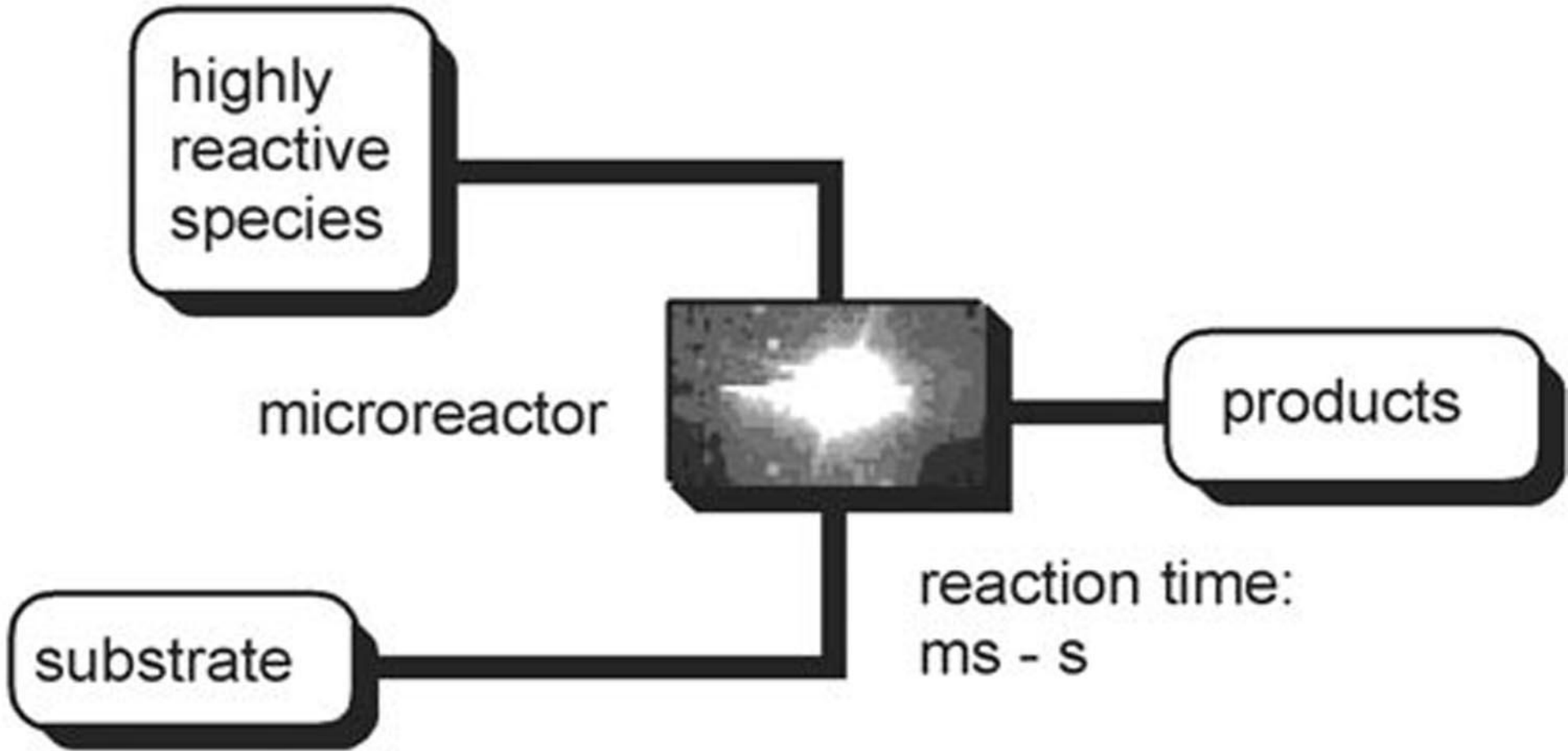
The volume/surface and size relationship



Size	1/100
Surface area	1/10000
Volume	1/1000000
Surface / Volume	100

high surface-to-volume ratio  
residence time control  
virtue of a short diffusion path

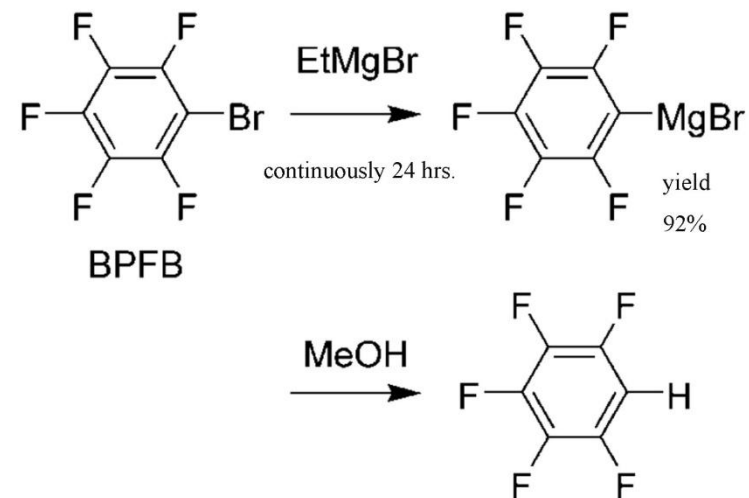
# Microflow Reactor





Advantages:

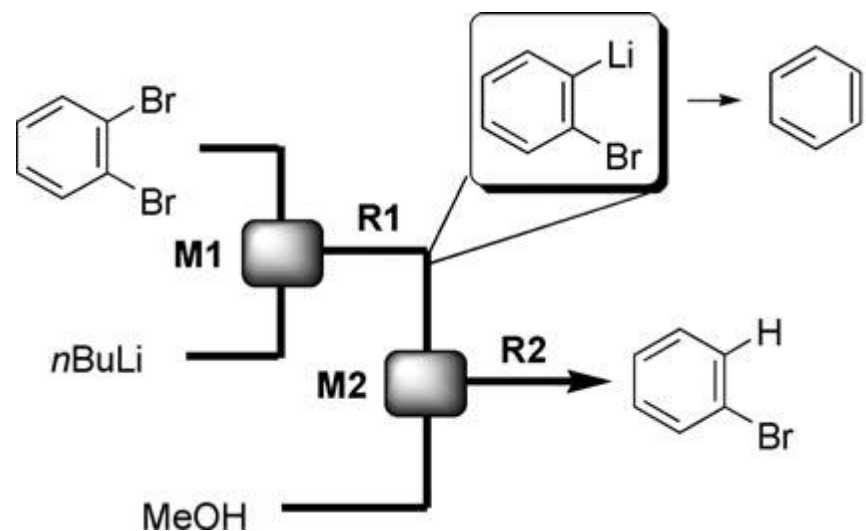
a) highly exothermic reactions that are difficult to control in conventional reactors,



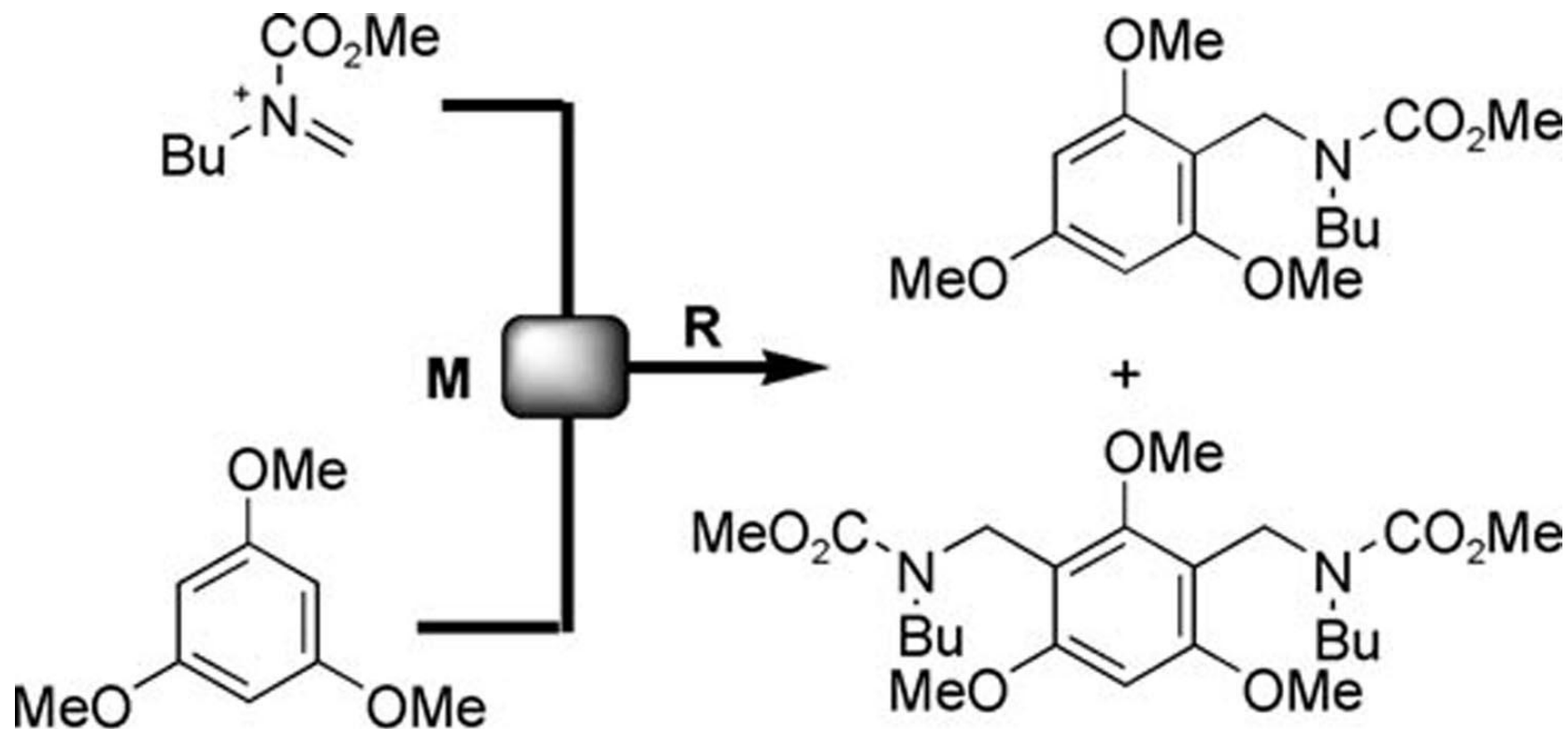
The halogen–magnesium exchange reaction of bromopentafluorobenzene (BPFBr) and  $\text{EtMgBr}$  reaction.

H. Wakami, J. Yoshida, *Org. Process Res. Dev.* 2005, **9**, 787–791.

b) reactions in which a reactive intermediate easily decomposes in conventional reactors,

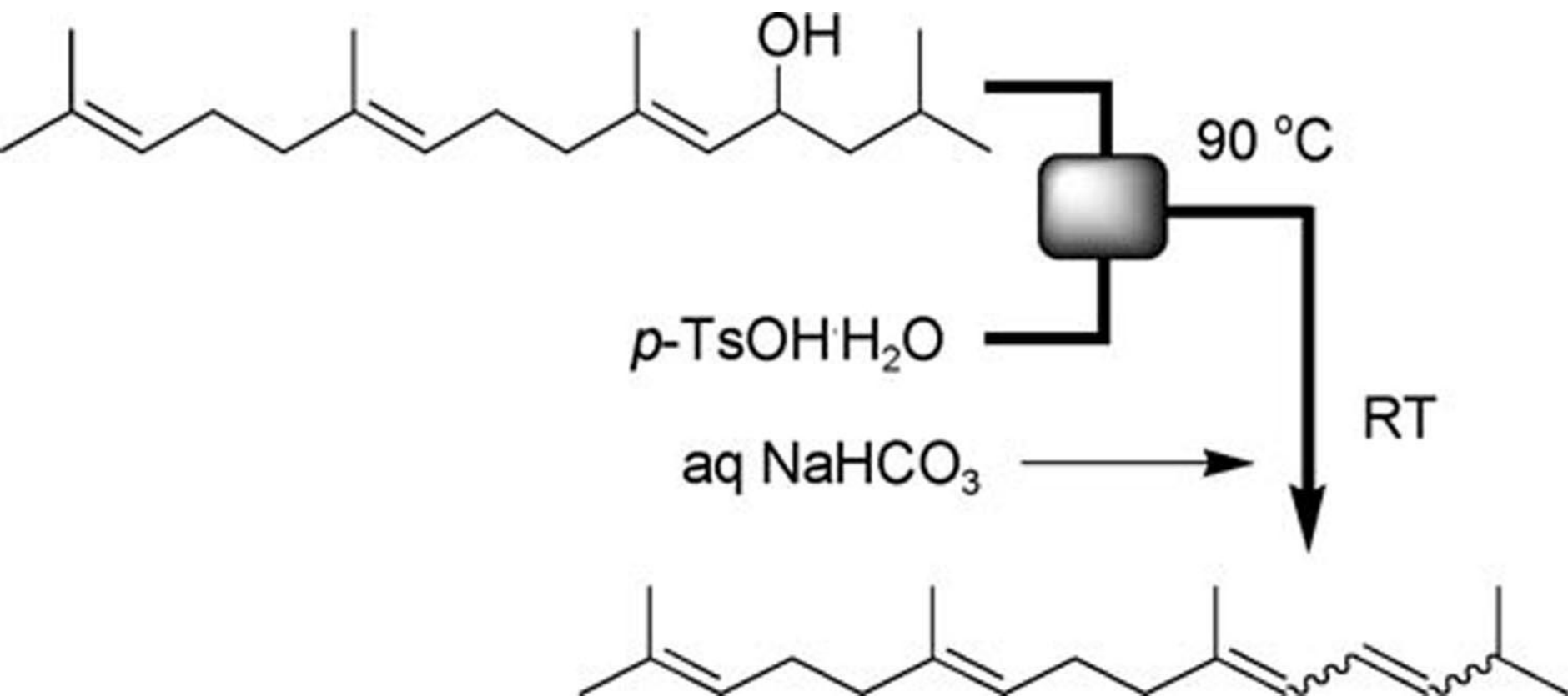


c) reactions in which undesired byproducts are produced in the subsequent reactions in conventional reactors, and



	monoalkylation product	dialkylation product
microreactor	92%	4%
flask	37%	32%

d) reactions whose products easily decompose in conventional reactors.



## Advantages

- 1) Little or no use of auxiliary substances: Flow chemistry avoids the use of auxiliary substances that slow down reactions to obtain better controllability.
- 2) Energy saving: Conventionally, cooling is often used to attain acceptable controllability of fast reactions. The use of microreactor enables reactions to be conducted at higher temperatures, minimizing the energy required for controlling these reactions.
- 3) High selectivity: Better controllability by virtue of the inherent properties of microreactors leads to a high selectivity of the products. Therefore, less waste is produced.
- 4) One-demand and on-site synthesis: Synthesis based on extremely fast reactions using microreactors enables on-demand and on-site synthesis. This leads to less energy for transportation.

# Scale-up

## Increasing the volume of reactor

1. Convert batch chemistry to flow chemistry on  $\mu\text{L}$ -scale;
2. Scaling up the internal dimensions of the reactor to mL-scale;
3. Numbering out mL-scale reactors towards the capacity desired.

## Increasing the number of reactors

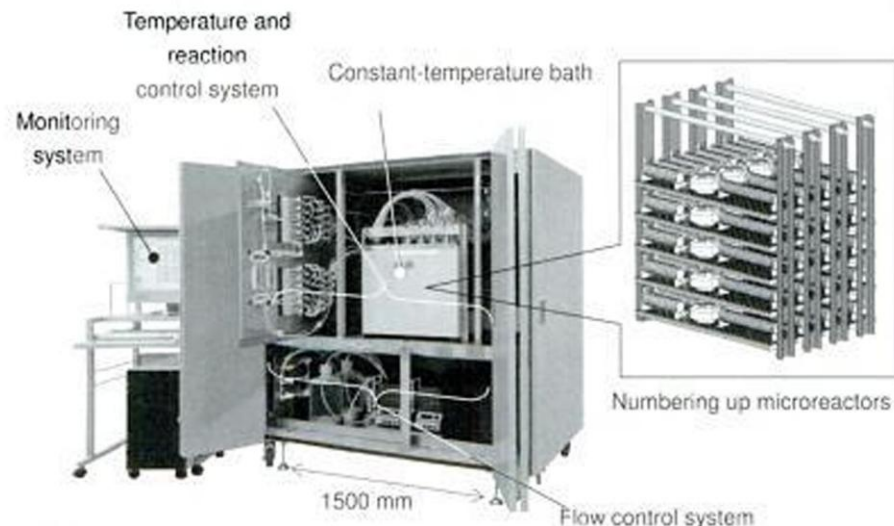
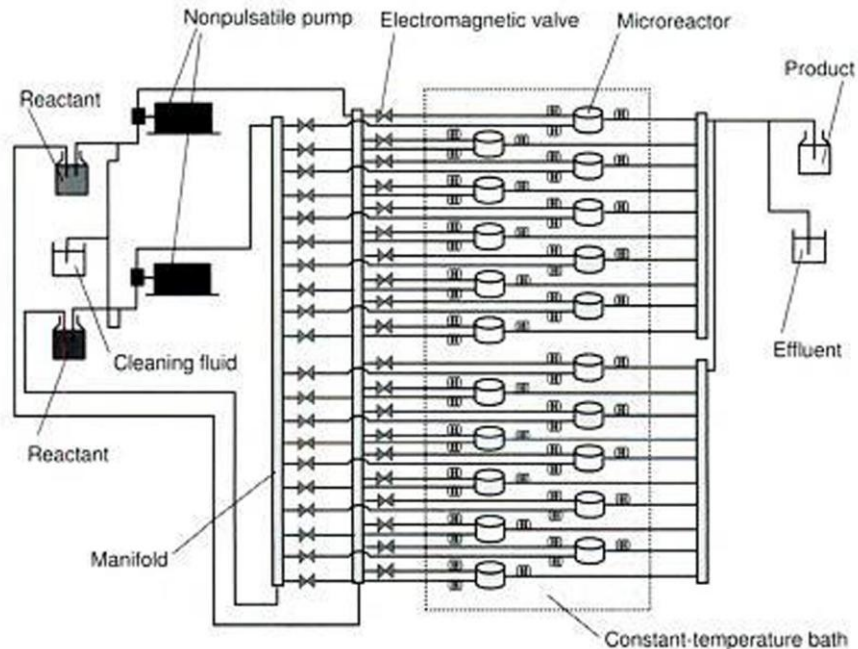


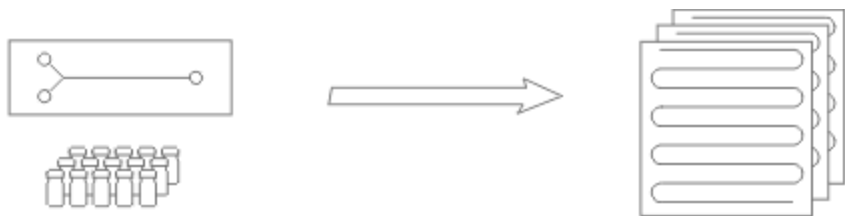
Figure 11.6 Internal structure of pilot plant.

J. Yoshida, A. Nagaki, and T. Yamada, "Flash Chemistry: Fast Chemical Synthesis by Using Microreactors", Chem. Eur. J. 2008, **14**, 7450-7459.

**Working continuously.**

# Industrial companies

*Access2Flow* with its members Flowid B.V., a spin-off company of the Eindhoven University of Technology,

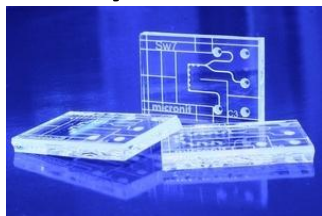


<http://www.access2flow.com/>

Microreactor  
complete optimization

Scaled out  
parallel manufacturing

**FutureChemistry** <http://www.futurechemistry.com/>, and **Micronit Microfluidics** has shown the fast scalability and applicability of microreactors in a case study for flow chemistry.



<http://syrris.com/flow-products/asia-flow-chemistry?gclid=CKeCjo-2w7MCFQFKpgodiRAALA>

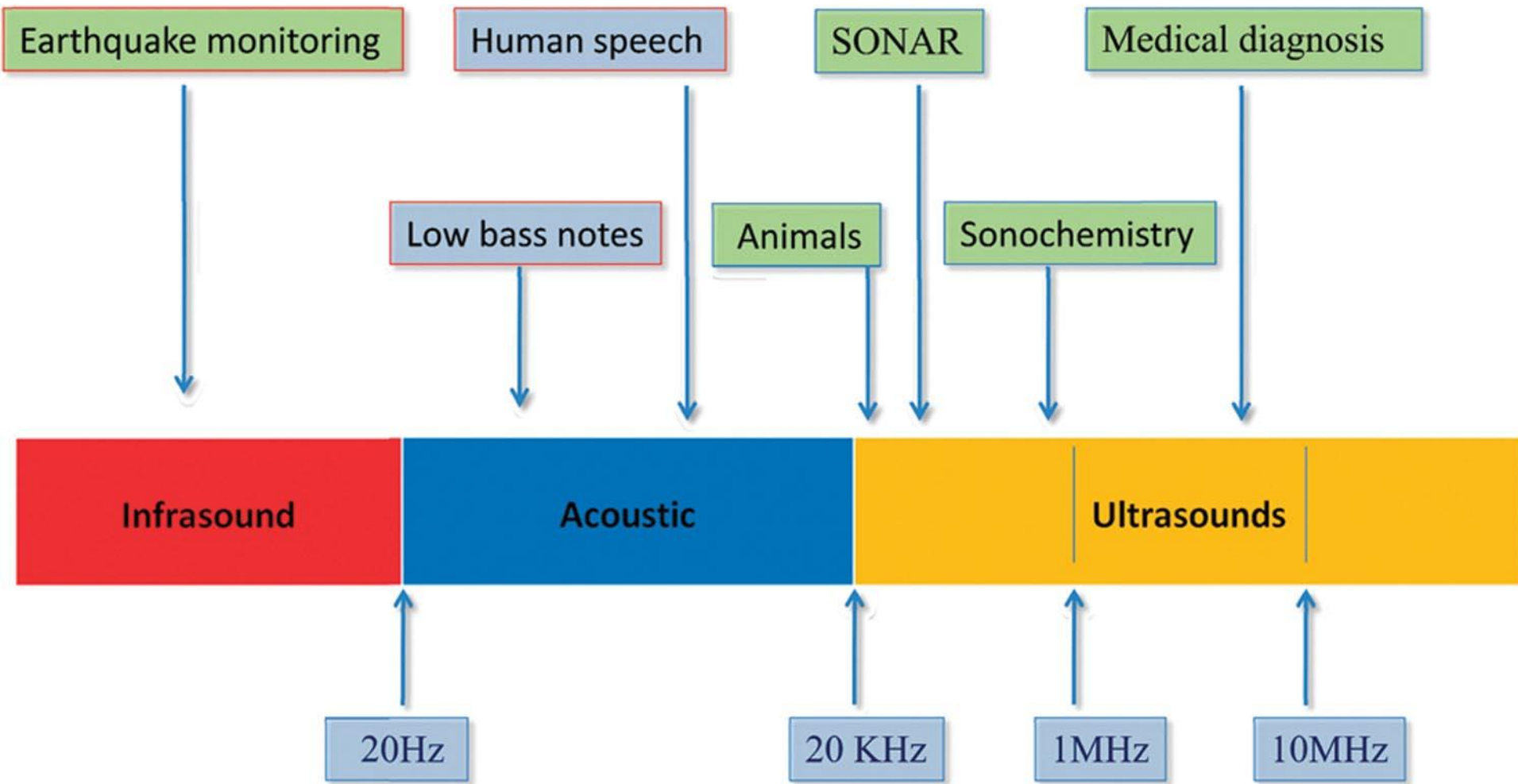
<http://www.micronit.com/assets/Downloads/Fast-Scale-Up-of-Microreactor-Technology.pdf>

J. Yoshida, H. Kim, and A. Nagaki, Green and Sustainable Chemical Synthesis Using Flow Microreactors, *ChemSusChem* (2011) **4**, 331–340. (DOI: 10.1002/cssc.201000271)

Jun-ichi Yoshida, “Flash Chemistry: Fast Organic Synthesis in Microsystems”

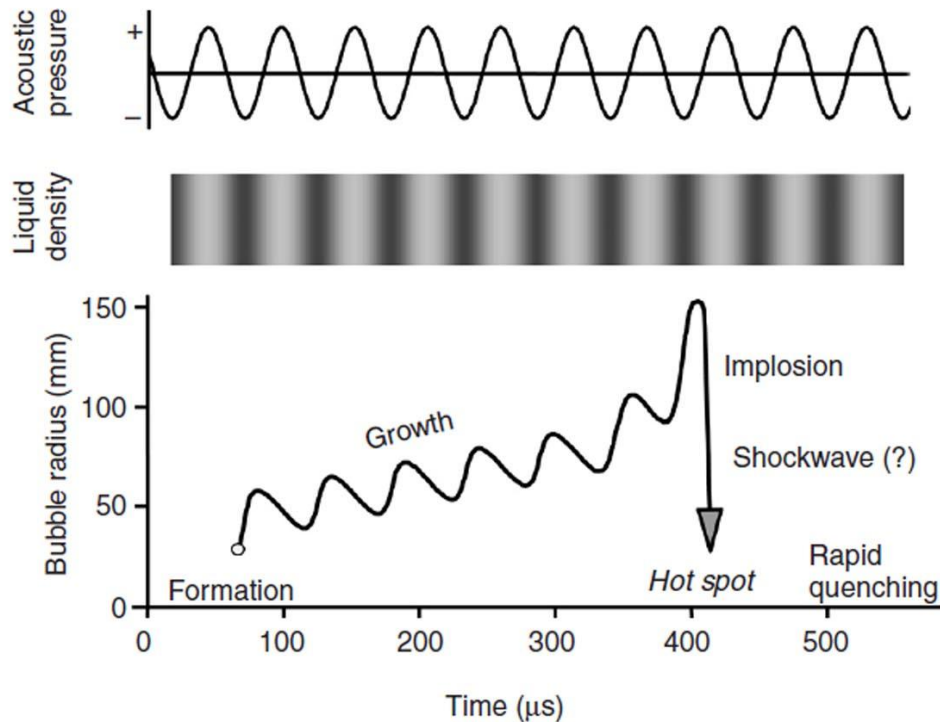
Stoma Care, Edited Jennie Burch, Blackwell Publishing

# Sonochemistry



Range: 15 kHz to 1 GHz (10 to  $10^{-4}$  cm).

## Theory:



Transient acoustic cavitation: the origin of sonochemistry

The origin of sonochemistry is acoustic cavitation: the formation, growth, and implosive collapse of bubbles in liquids irradiated with high-intensity sound. The collapse of bubbles caused by cavitation produces intense local heating and high pressures, with very short lifetimes (Rayleigh–Plesset equation). In clouds of cavitating bubbles, these hot-spots have equivalent temperatures of roughly 5,000 K, pressures of about 1,000 atm, and heating and cooling rates above  $10^{10} \text{ Ks}^{-1}$ . In single bubble cavitation, conditions may be even more extreme. Thus, cavitation can create extraordinary physical and chemical conditions in otherwise cold liquids.

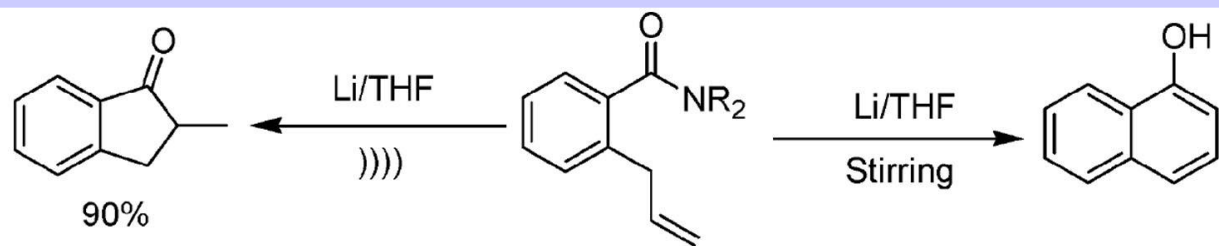
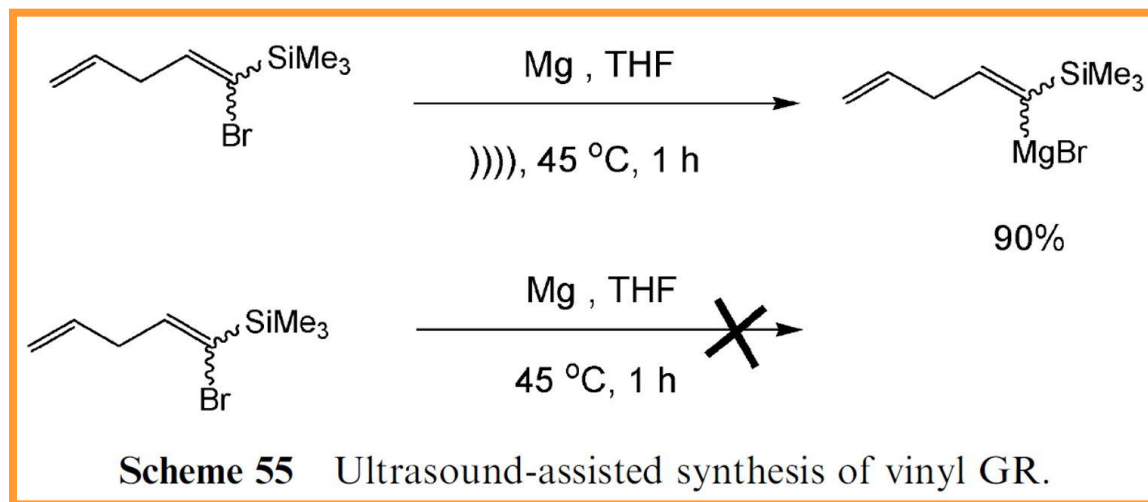


## -- APPLICATIONS --

### (a) Organic synthesis

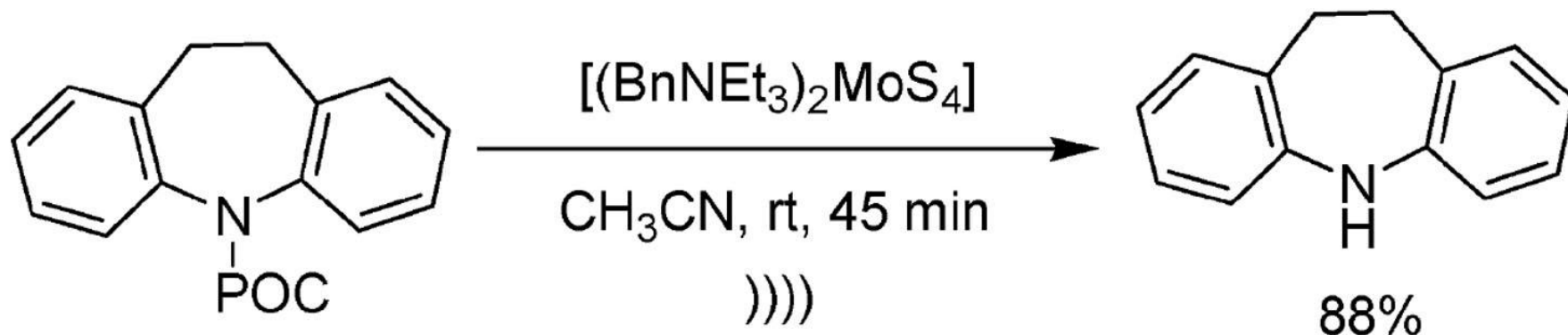
**Coupling reactions** (Heck, Suzuki, Sonograpia, Ullmann, Reformatsky, Michael addition, Baylis–Hillman, Wittig, Diels-Alder, Mannich-type, and Grignard reagent synthesis)

### Special cases



J. Einhorn, C. Einhorn and J.-L. Luche, *Tetrahedron Lett.*, 1988, **29**, 2183.

## (b) deprotective group reactions



**Scheme 71** Ultrasound assisted deprotection of POC.

(POC: “prop-2-ynyloxy carbonyl”, 45 mins., 88% yield)

S. Sinha, P. Ilankumaran and S. Chandrasekaran, *Tetrahedron Lett.*, 1999, **40**, 771.

## (c) oxidation and reduction reactions

## (d) carbohydrate chemistry

## (e) synthesis of ionic liquid

R. B. Nasir Baig and Rajender S. Varma, “Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis”, *Chem. Soc. Rev.*, 2012, **41**, 1559–1584.

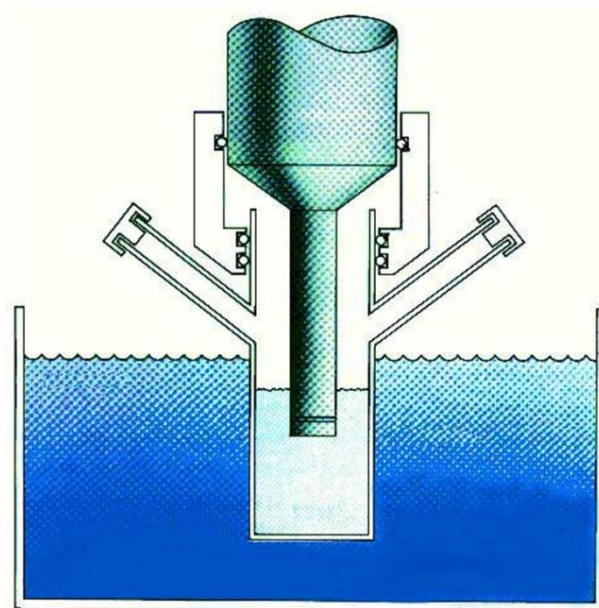
## (f) sonochemistry

Ultrasonics Sonochemistry

<http://www.journals.elsevier.com/ultrasonics-sonochemistry/>

## Challenges:

wider application  
scale-up  
energy efficiency



## General References:

Sonochemistry: Theory, Reactions and Syntheses, and Applications (Chemistry Engineering Methods and Technology), Filip M. Nowak (Author, Editor)

K. S. SUSLICK, Sonochemistry

<http://www.scs.illinois.edu/suslick/documents/comprehencoordchem.pdf>

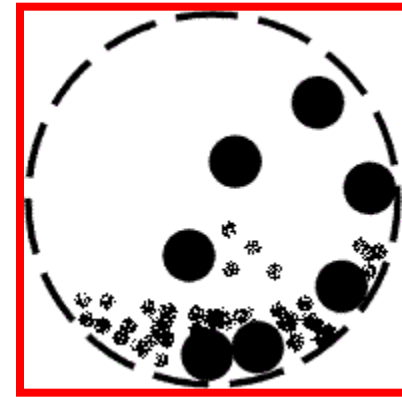
Kenneth S. Suslick, THE CHEMISTRY OF ULTRASOUND

<http://www.scs.illinois.edu/suslick/sonochembritannica.html>

# Machnochemistry

**Definition:** Chemistry in ball mill

Definition of ball mill: A ball mill, a type of grinder, is a cylindrical device used in grinding (or mixing) materials like ores, chemicals, ceramic raw materials and paints.



## Planetary Ball Mill:

Video

<http://www.youtube.com/watch?v=lZo6eYsj1QY>



## Mixer ball mill:



## Vibrating ball mill:

Video

<http://mtixtl.com/demo-sfm-3.aspx>



研磨在化學反應種類上沒有什麼限制,只要注意下列要點:

- 至少有一種反應物之熔點高於70 °C.
- 不能有不耐撞擊的物品.反應物和生成物要耐機械應力要高.
- 在密閉的研磨鉢中不能有產生氣體的反應,除了有安全釋壓裝置.
- 三種研磨鉢均可應用到有機化學反應上.
- 反應的規模依研磨鉢的大小而定.但振動型的研磨鉢不要超過50 CC.

## 研磨器的材質

- 研磨鉢材質的密度和研磨過程產生之熱量有關.通常高密度的物質可承受大的熱量.
- 研磨鉢和研磨球的材質應相同,若不同時前者之密度較大.
- 研磨鉢和研磨球的材質和反應物無作用.包括催化劑的有機化學反應以陶製器(如二氧化鋯)為佳.因為它們不但不和反應物起作用而且耐磨.
- 如果用多孔性物質(瑪瑙)則易有殘餘將影響下一個實驗.

## 合成規模:

- 合成反應的規模反應的種類及研磨鉢的大小而定.不過在實務上應由小規模( $\leq 10$  mmol) 開始.能不能放大依小規模反應之成敗而定.
- 填滿研磨鉢的程度依產生的能而定.考量反應物能在研磨鉢中充分翻動以填充最高 $1/3$ 容積為佳.
- 為了保持重現性,所用的研磨鉢及實驗步驟(如先放反應混合物或研磨球)應保持一致.

## 研磨球之數目及大小:

- 研磨球的總體積也不要超過研磨鉢的1/3容量.
- 和磨碎物質不同,研磨球之大小與化學反應關係不大.最好是依製造商的推薦及參考文獻.
- 為避免研磨鉢之磨損,可用多具研磨鉢.

## 研磨鉢之旋轉或振動頻率和反應時間:

- 新實驗請參考相關的文獻.
- 找最佳條件時先換反應時間,次考量旋轉或振動頻率•旋轉或振動頻率要在儀器之能力75-100%.
- 實驗可間歇(每次停歇5-10分鐘)進行以避免過熱.

A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, "Ball Milling in Organic Synthesis: Solutions and Challenges" <http://www.rsc.org/suppdata/cs/c0/c0cs00195c/c0cs00195c.pdf>

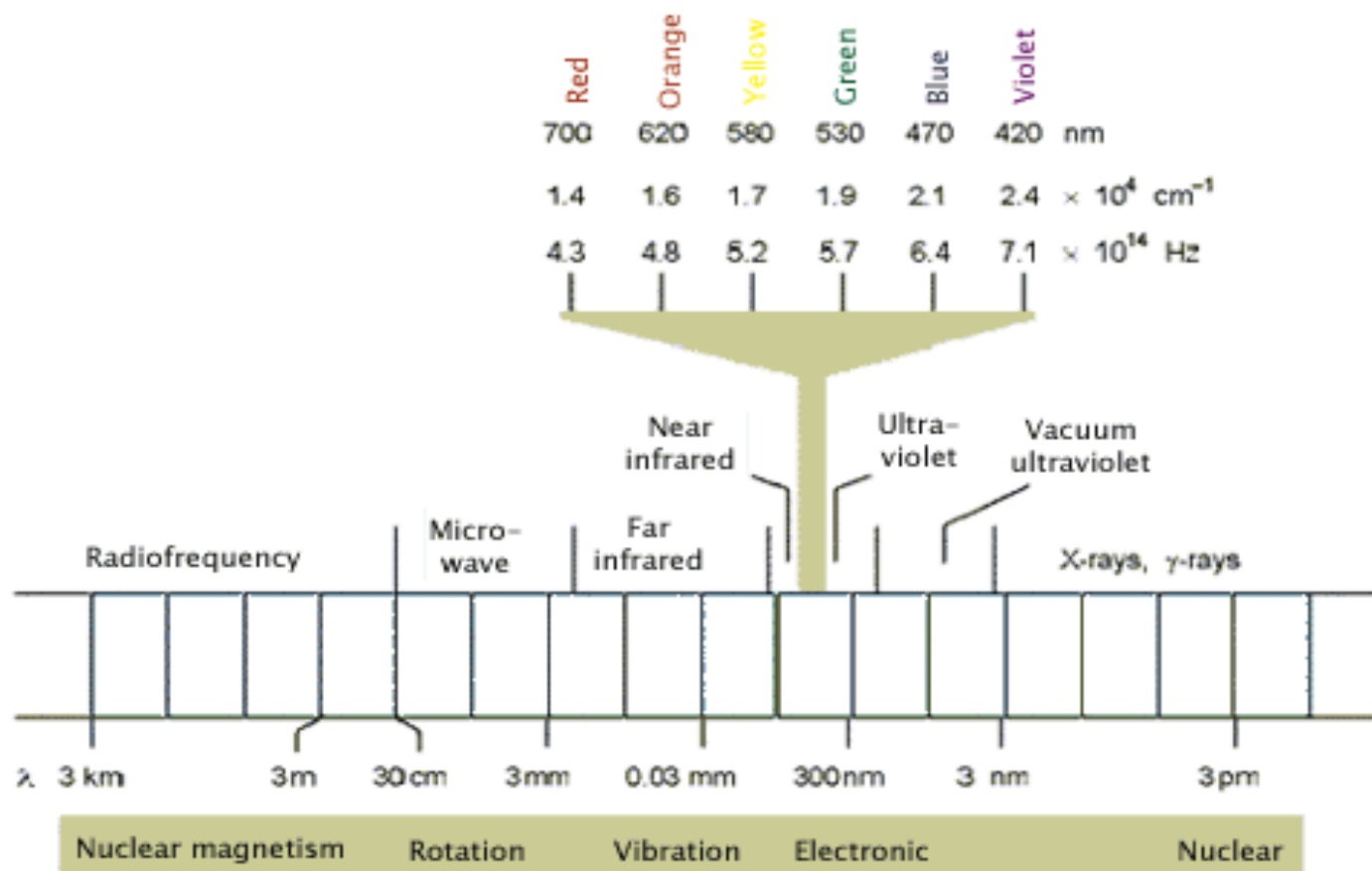
應用的部份請見許拱北老師"綠色溶劑與無溶劑反應"。



# Photochemistry

**Definition:** Chemical reactions proceed with the absorption of light by atoms or molecules.

**Requirement:** At least one molecule with chromophore.



Near infrared: 700–2500 nm Visible light: 400–700 nm Ultraviolet: 100–400 nm

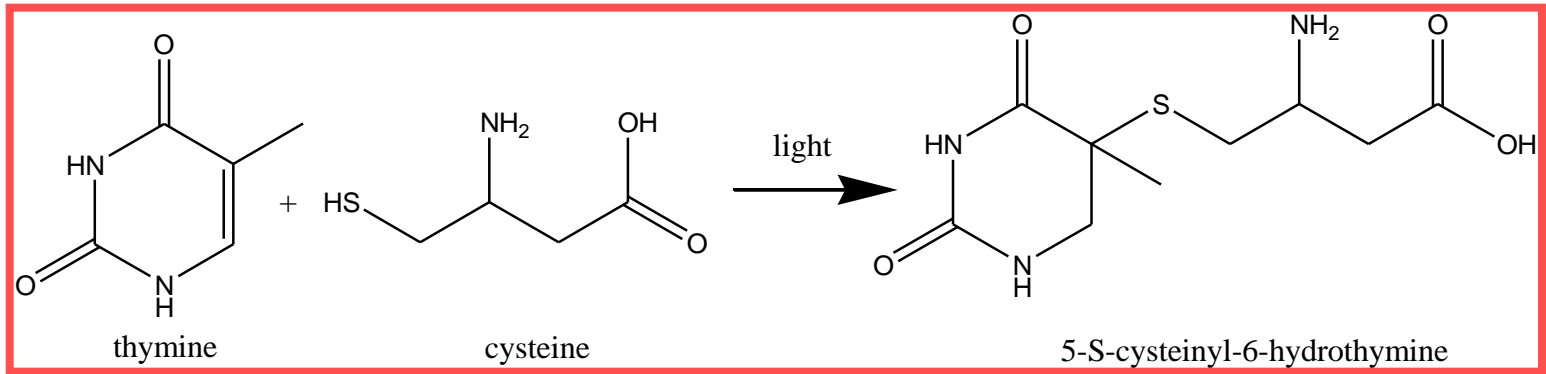
# Advantages

Clean

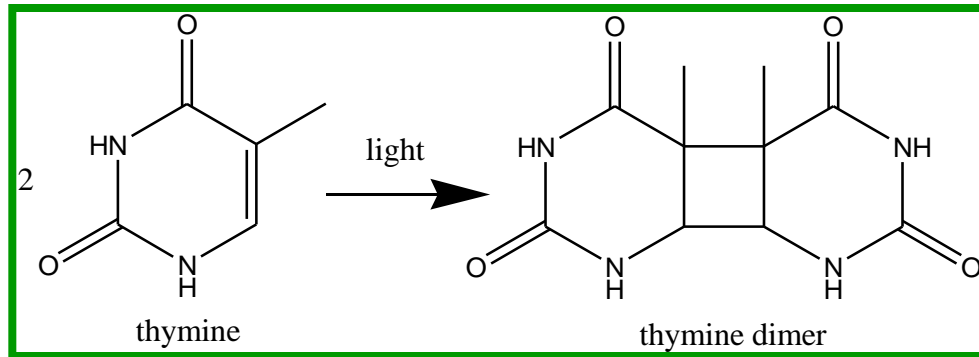
Save energy (sunlight)

# Applications:

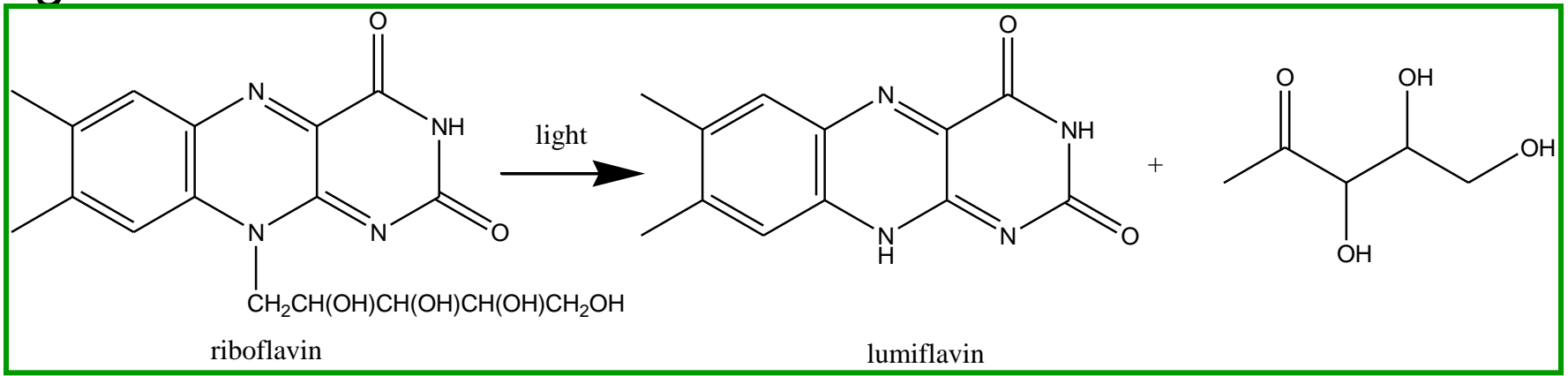
*Addition* reaction



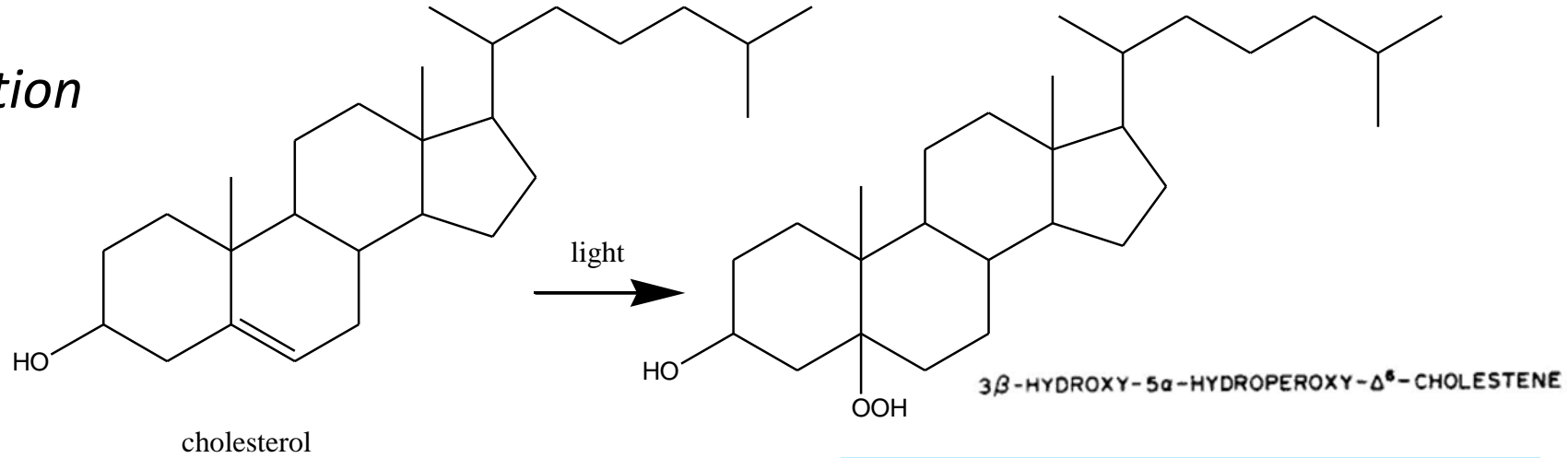
# *Cycloaddition*



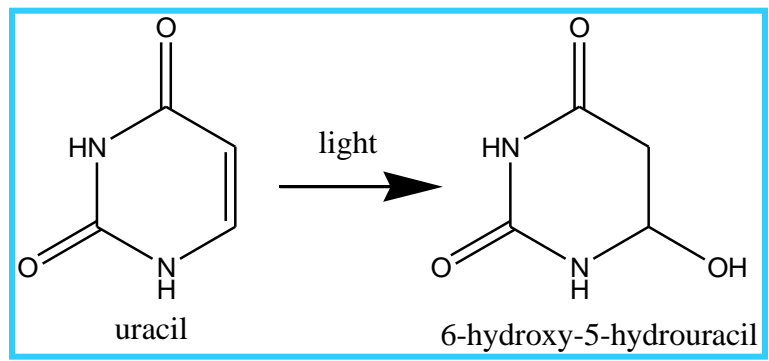
# Fragmentation



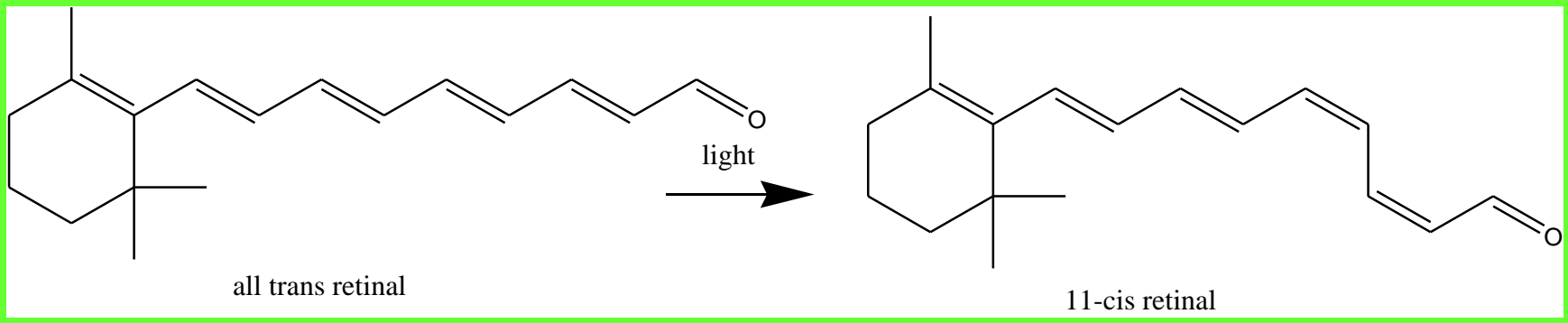
# Oxidation



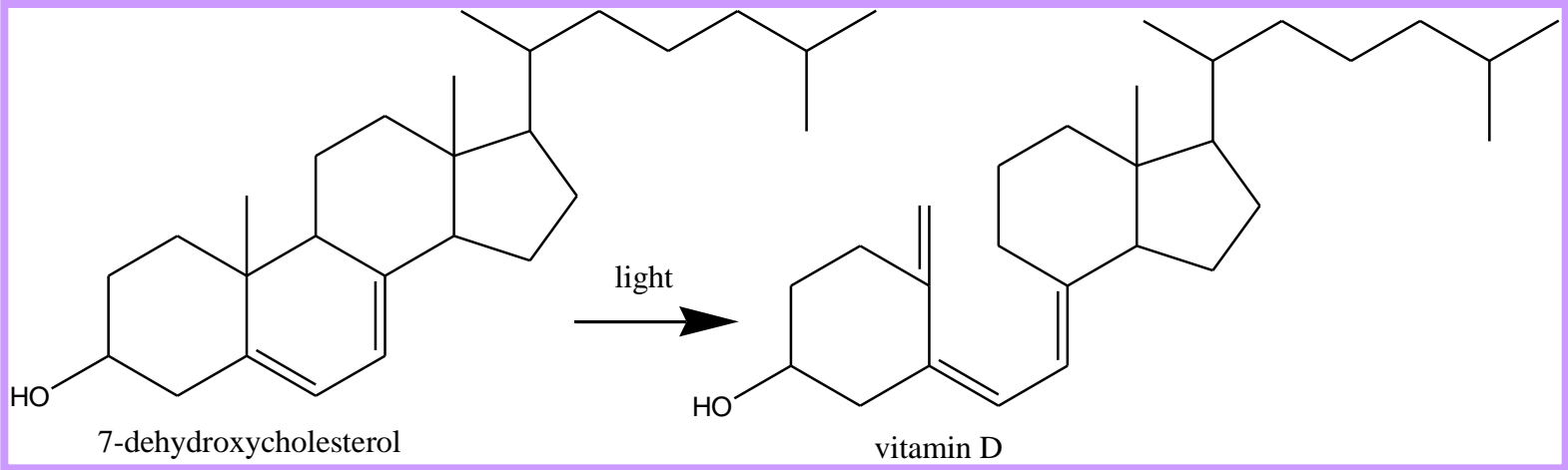
# Hydration



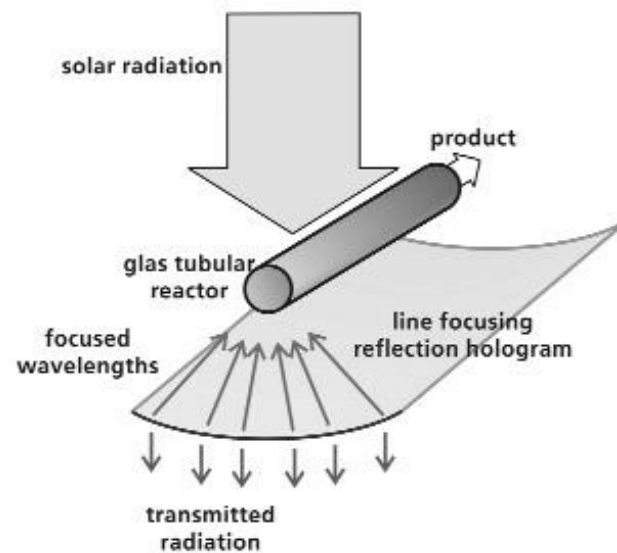
# Cis-trans isomerization



# Rearrangement



# Scale-up



**A parabolic trough reactor**



**Solar chemical reaction plant (Cologne, Germany)**

## References

Kendric C. Smith, BASIC PHOTOCHEMISTRY

*<http://www.photobiology.info/Photochem.html>*

Michael Oelgemoller, Christian Jung, and Jochen Mattay, Green photochemistry: Production of fine chemicals with sunlight, Pure Appl. Chem., (2007) **79**, 1939–1947.

doi:10.1351/pac200779111939c 2007 IUPAC

*<http://pac.iupac.org/publications/pac/pdf/2007/pdf/7911x1939.pdf>*

Emma Coyle, BSc Ph.D. Thesis (January 2010)

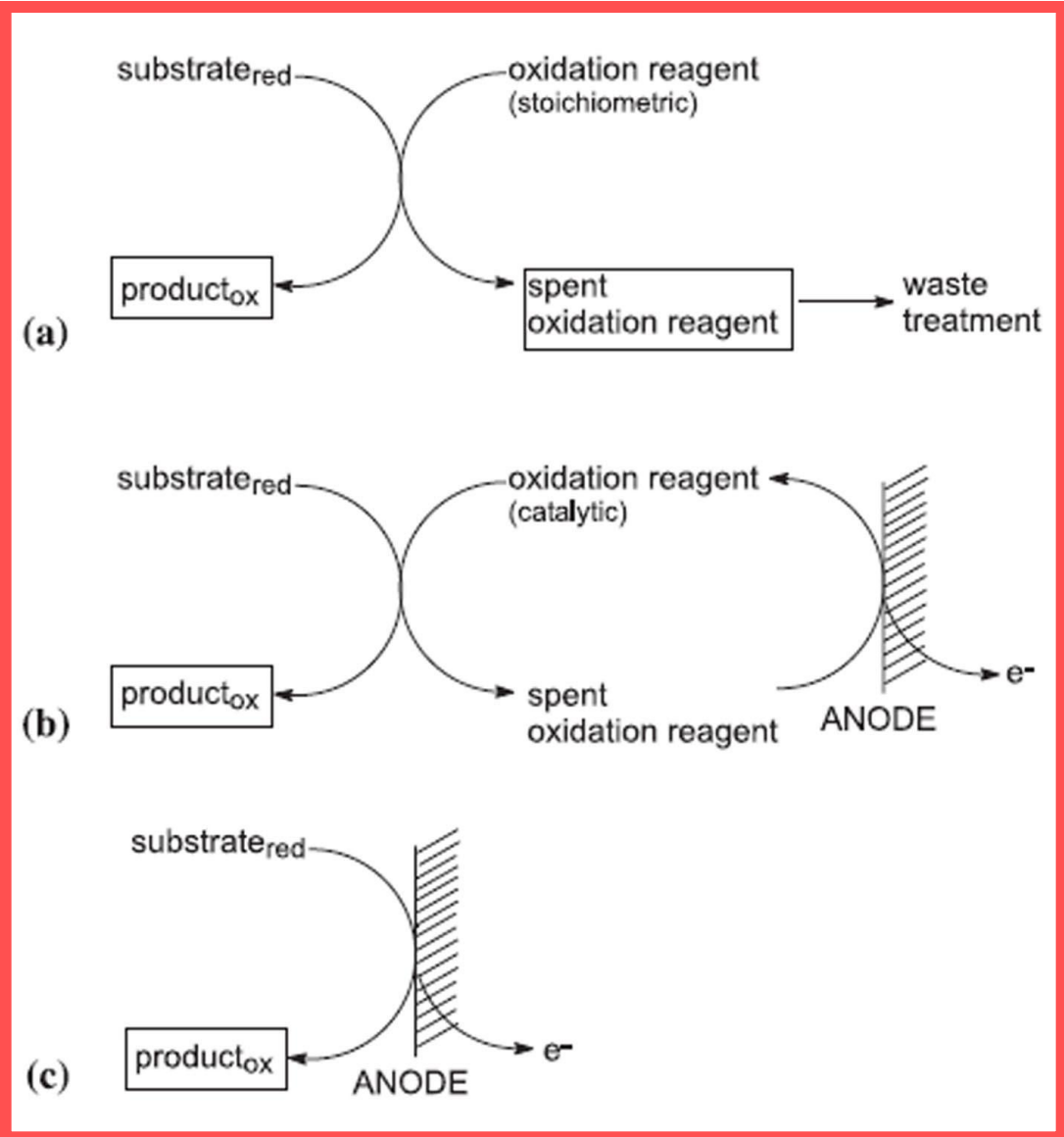
Green Photochemistry the synthesis of fine chemicals with sunlight

Dublin City University, Ireland

*[http://doras.dcu.ie/15389/1/Emma\\_Coyle\\_PhD\\_thesis.pdf](http://doras.dcu.ie/15389/1/Emma_Coyle_PhD_thesis.pdf)*

# Electrochemistry

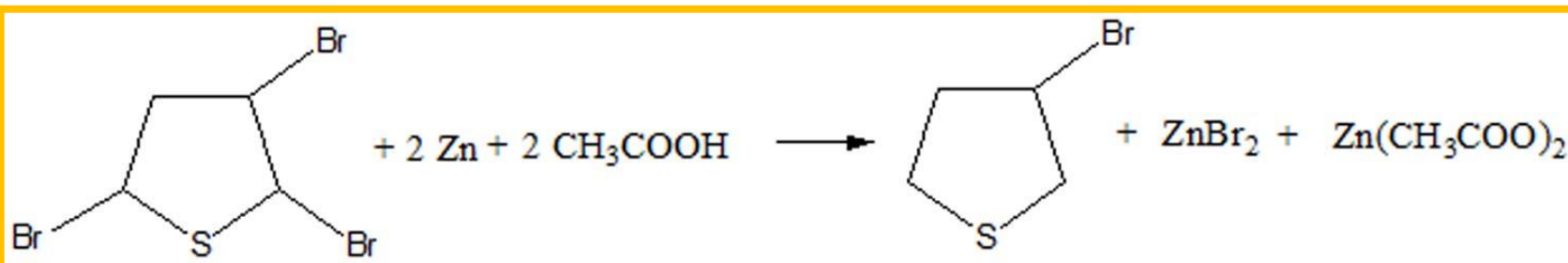
Advantages  
*Less wastes*  
Environmentally favorable



## Example:

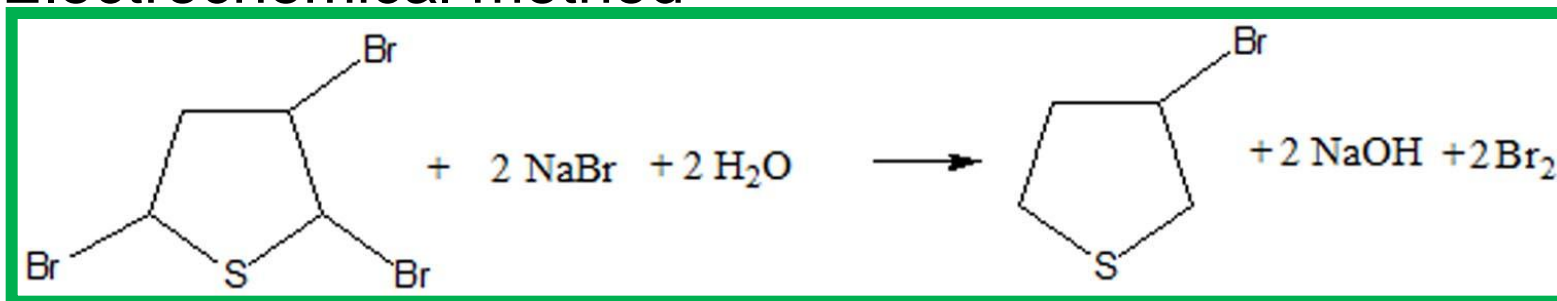
Synthesis of 3-bromothiophene (starting material for pharmaceutical and high polymer products) from 2,3,5-tribromothiophene.

The traditional way is that the 2,3,5-tribromothiophene is reduced by zinc powder in acetic acid.



Excess acetic acid is required to push the reaction to right hand side. Poor E-factor is obtained as a consequence.

Electrochemical method



Bromine molecular is collected at anode and readily being reuse. No excess reagent is needed. Better E-factor is obtained.



*Low reaction temperature*

The above electrochemical reaction can be carried out at ambient temperature.

*Easy products separation*

Products are collected on electrodes.

*Non-volatile solvent*

Water is common used solvent in electrochemical reaction.

## **Challenges**

Difficult to scale-up.

Costly.

## **References**

Electrochemical Reactions, Patricia Ann Mabrouk, Wiley

<http://www.iupac.org/publications/pac/2001/pdf/7308x1305.pdf>

Michael A. Matthews, Green electrochemistry. Examples and challenges, Pure Appl. Chem., (2001) **73**, 1305-1308.

E. Steckhan, et al., Environmental protection and economization of resources by electroorganic and electroenzymatic syntheses, Chemosphere, (2001) **43**, 63-73.

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