The Evolution of Microwave Technology for Synthetic Chemistry

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Microwave Energy Versus

Radiation Type	Typical Frequency (MHz)	Quantum Energy (ev)
Gamma Rays	3.0×10^{14}	1.24×10^{6}
X-Rays	3.0×10^{13}	1.24×10^{5}
Ultraviolet	1.0×10^{9}	4.1
Visible Light	6.0×10^{8}	2.5
Infrared Light	3.0×10^{6}	0.012
Microwaves	2450	0.0016
Radio	1	4×10^{-9}

Chemical Bond Type	Chemical Bond Energy (ev)
H-OH	5.2
$H-CH_3$	4.5
$H-NHCH_3$	4.0
H_3C-CH_3	3.8
$PhCH_2-COOH$	2.4
H–O(-)–H+---O(-)(H)(H) (hydrogen bond)	0.21

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Hardware

- Multiple mode applicators
  - Industrial-design commercial instruments
- Single mode applicators
  - Fixed tuning single mode systems
  - ***Self-tuning single mode technology***

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Commercial Multiple Mode Systems

- Advantages of commercial multiple mode systems
  - Larger cavity geometry w/ higher input power levels
  - Industrial design leads to robust system
  - Systems designed for safe operation
  - Can be useful for larger scale batch reactions
  - Wide range of chemistry-related accessories
- Disadvantages of commercial multiple mode systems
  - **Field intensity (typically only 25 – 30 w/L) – leads to difficulty in heating small loads**
  - Field uniformity – "hot spots" lead to poor reproducibility
  - Parallel chemistries must have like absorption characteristics
  - Variations between units

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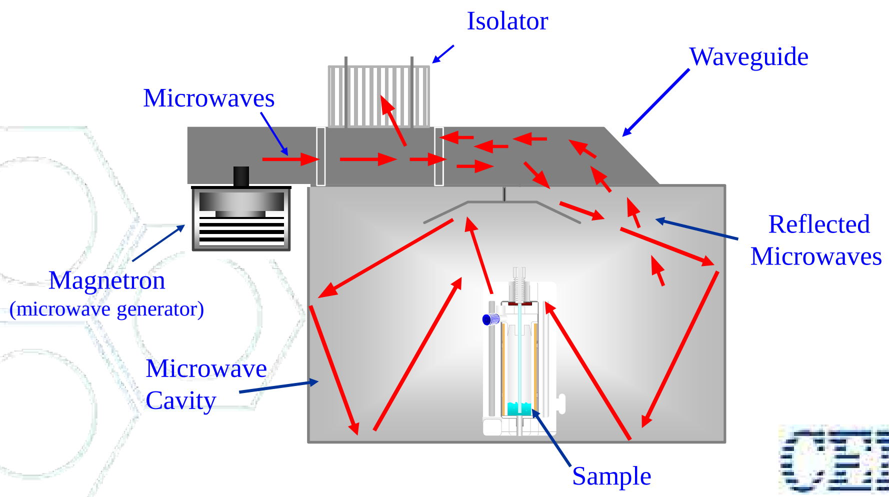
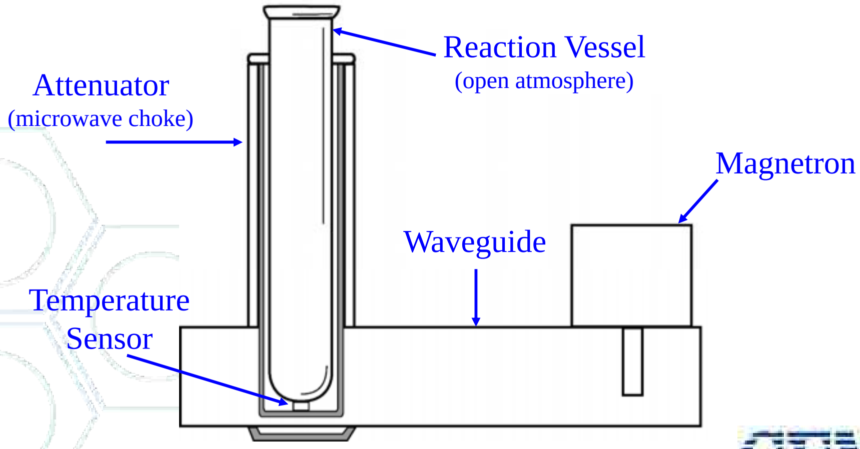
Typical Multiple Mode System Design



Conventional Single Mode Systems

- Advantages of conventional single mode systems
  - Uniform energy distribution
  - Good coupling with small samples
  - High power density equals faster heating
- Disadvantages of traditional single mode systems
  - **Typically require tuning for different sample loads**
  - Very sensitive to sample size and coupling characteristics
  - Small cavity geometry requires small sample sizes, small vessels (<20 mL)

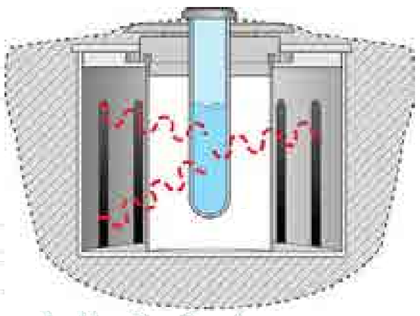
Original Single Mode System



Patent Nos. EP 2643829, US 4681740, US 5059400; **c. 1988**

CEM Focused™ Microwave System

(Self-Tuning Single Mode Cavity†)



The Evolution is Complete

Adapts automatically to *Your* chemistry

- Polarity and Ionic properties
- Varying reaction volumes

Accepts the *Widest* variety of vessels

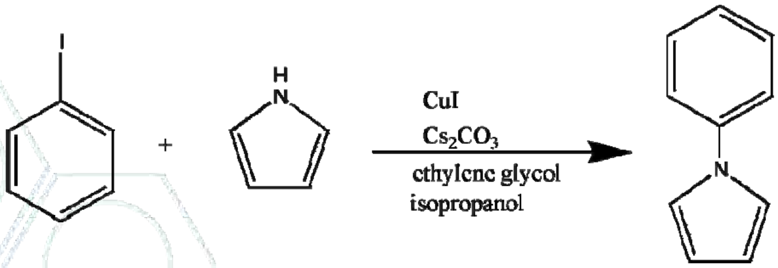
- 5 – 125 mL open vessel capacity
- 0.25 – 80 mL sealed vessel capacity

Provides the *Largest* cavity access

- Easy to clean
- Easy to use

† Patents 6648659, 6666223, others pending

Multiple Mode or Single Mode – Does It Effect the Chemistry?



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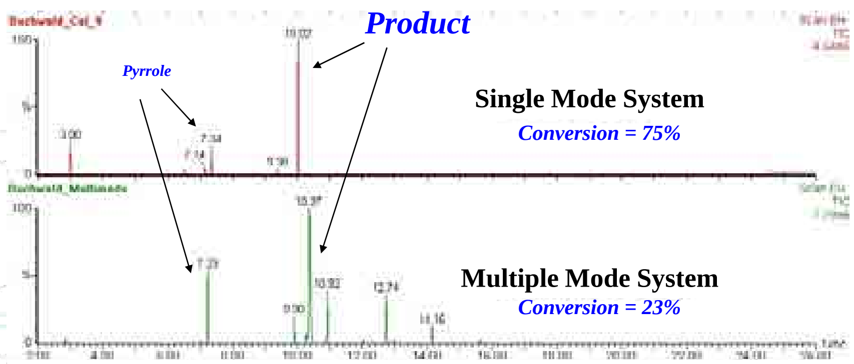
Focus™ On the Results



Higher Yields and Cleaner Products with Single Mode Technology

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Discovery Chemistry

mg scale

Optimization Workstation

Explorer™

Automated Optimization System

- 1 to 24 samples: Load it and leave it
- Automatic or manual operation
- Pressure and temperature control
- Change procedure on the fly
- Pause: interrupt sample queue and run priority sample(s) then continue
- Unlimited method storage

Navigator™

Automated Compound Factory

Microwave Compound Factory

- Complete library synthesis platform
- Incorporate multiple reactors for parallel microwave chemistry
- Deconvolution
- Automated liquid, gas, and solid reagent addition
- Integrate into existing robotic suites

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Scaling up to grams

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Reaction Scale Accommodated

- Widest dynamic range
- ***Only 2*** vial sizes needed
- Both work in the same applicator so conditions scale up simply

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80 mL Scale Up Accessory

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So…
Microwave Synthesis Is Great for Discovery but Can You Scale Up?

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Continuous-Flow System

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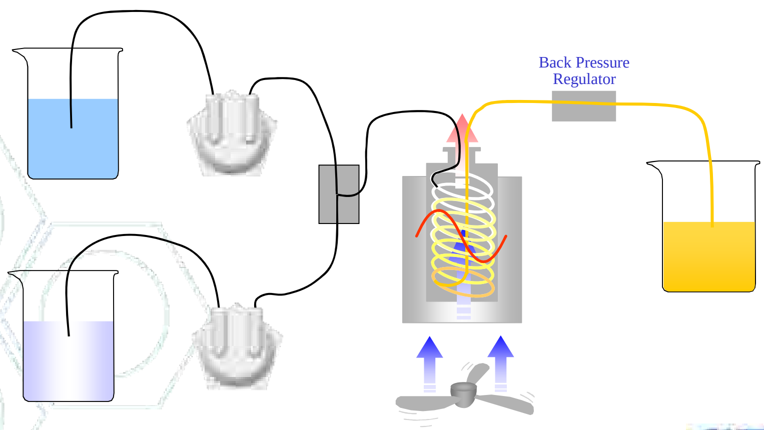
- Homogeneous reaction mixtures
- mg to kg quantities
- Discover or Explorer

Schematic of Flow Reactor System



Flow Cell

- 5 and 10 mL of volume inside the microwave cavity
- Kevlar reinforced Teflon tubing
- Fiber Optic temperature control
- Unique weave maximizes cooling and coupling abilities

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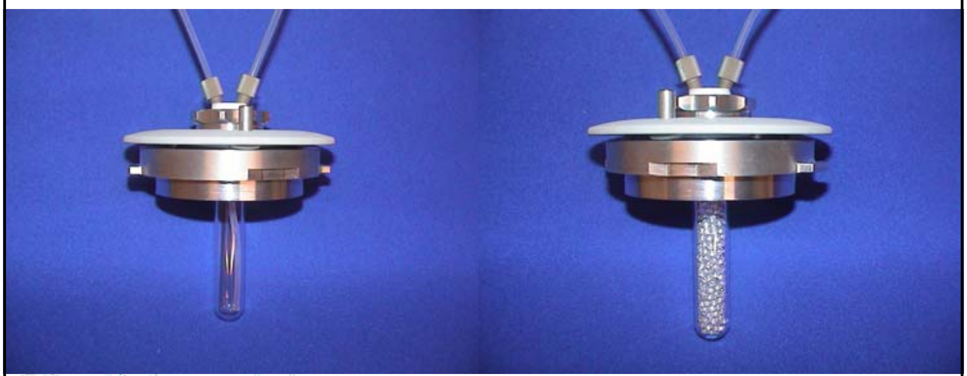
Continuous flow in a 10ml Tube



Solution pumped into bottom of standard 10ml cell, and it rises up over glass beads or immobilised catalyst

Developed by C. Mason CEM, Robin Wood AstraZeneca.

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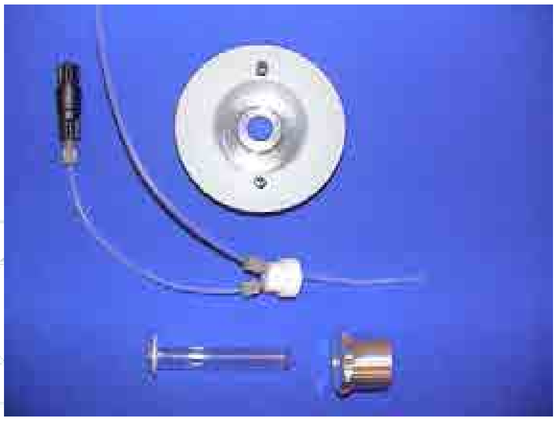
10 ml Flow Cell Accessory



BPR or Pump maintains back pressure

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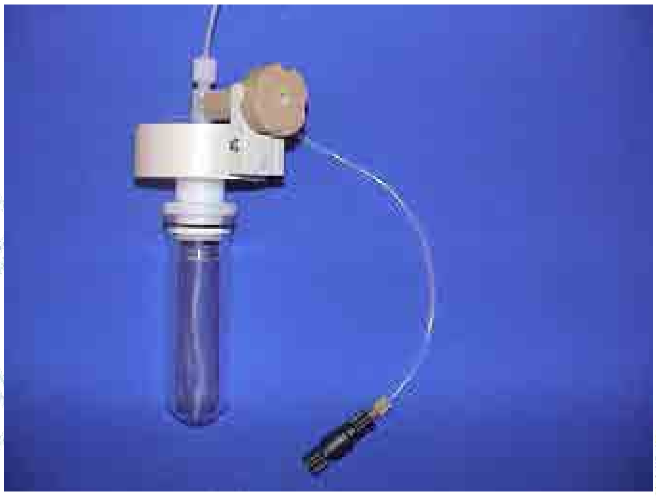
80ml Flow Cell Set-up



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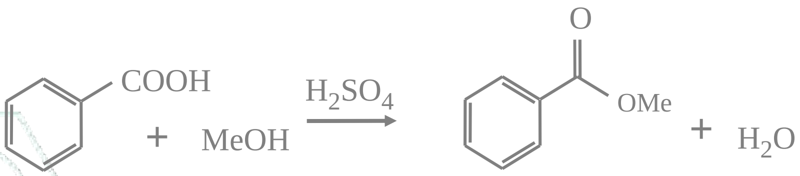
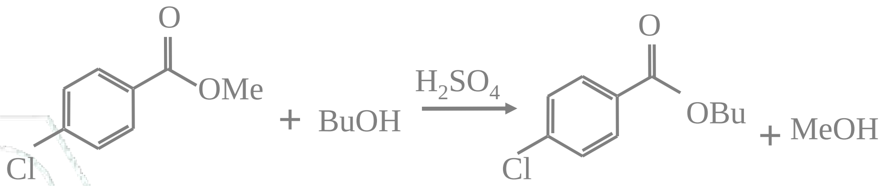
Esterification



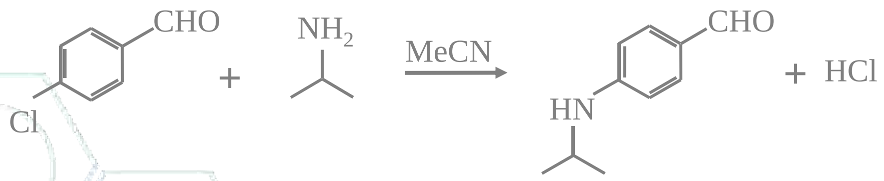
Flow rate	1.5 mL/min	Flow cell	5 mL
Residence time	3:20	Temperature	80 °C
Pressure	250 psi	Power	75 W
Cooling	15 psi	Yield	100%

Transesterification



Flow rate	2.0 mL/min	Flow cell	5 mL
Residence time	2:30	Temperature	80 °C
Pressure	250 psi	Power	100 W
Cooling	1 - 2 psi	Yield	89%

Nucleophilic Aromatic Substitution



Flow rate	1.5 mL/min	Flow cell	5 mL
Residence time	3:20	Temperature	90 °C
Pressure	250 psi	Power	300 W
Cooling	10 - 13 psi	Yield	100%

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Continuous Reactors

- Higher throughput with less effort
- Inherently safer because of small reaction zone
- Microwave penetration depth
- Real time reaction monitoring

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Stop-Flow System

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Voyager™

Stop-Flow Technology

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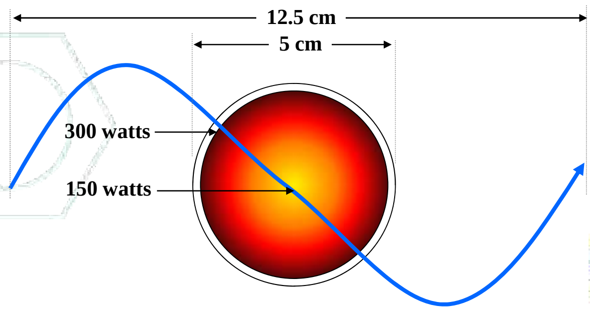
Scalability Using a Single Mode Cavity

10 mg → 10 g → 1 kg

1 Reactor - 10,000x Scale Up Capability

Microwave Scale Up Options

- Penetration depth of microwave (half power depth 2.5 cm) limits size of batch reactors
- Flow thru format becomes possible due to the short reaction times (<5 mins.)



Batch Reactors

- Homogeneous reaction mixture (stirring)
- Uniform temperature
- Able to handle heterogeneous reaction mixtures

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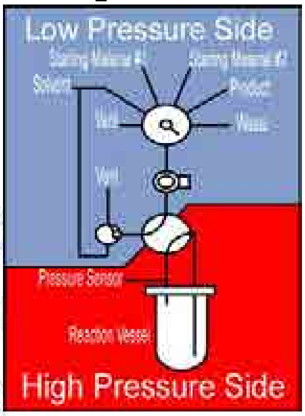
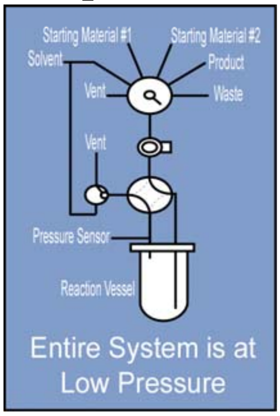
High Pressure Operation



Low Pressure Operation



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Stop-Flow Pressure Vessel

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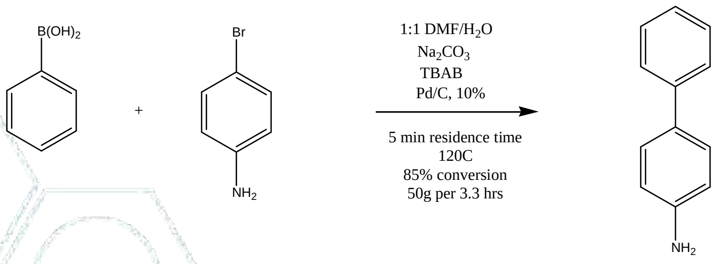
Stop-Flow Suzuki Reaction



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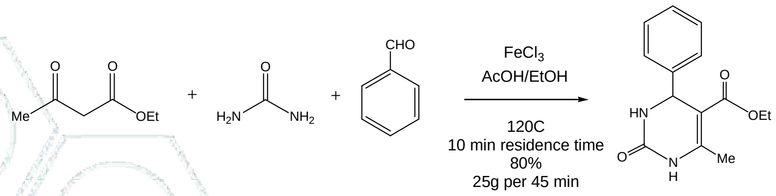
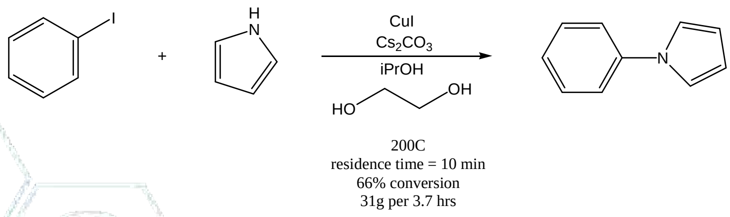
Stop-Flow Biginelli Condensation



Stop-Flow Buchwald Reaction



Purification Opportunities

- Solid Phase Synthesis
- Scavengers
- Fluorous Separations
- Preparative / Flash Chromatography

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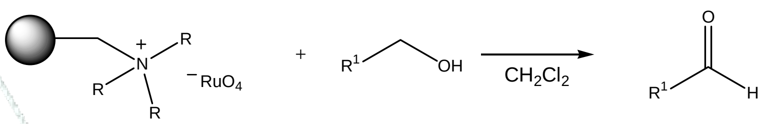
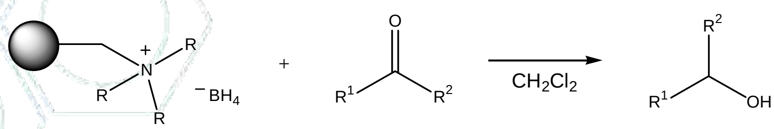
Stop-Flow Solid Phase Reactions

Oxidation



Reduction



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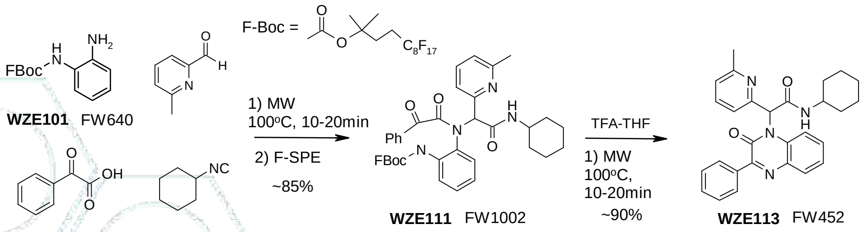
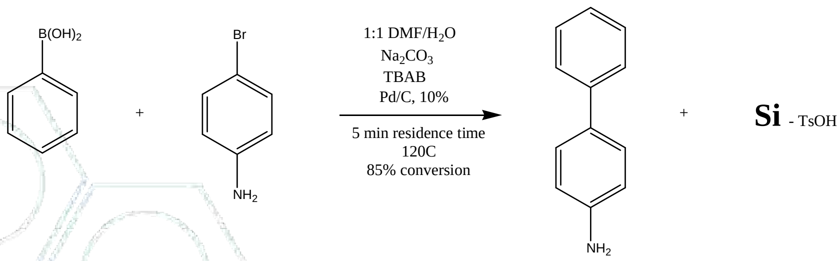
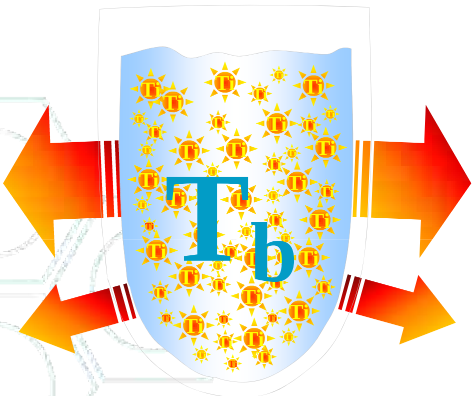
Fluorous Ugi Example



SiliCycle Suzuki Example



How Do You Enhance Microwave Synthesis?



- Simultaneously cool the reaction during the irradiation cycle
- Create higher T_i
- Effectively remove bulk temperature to reduce thermal degradation
- Maximize the amount of input microwave energy

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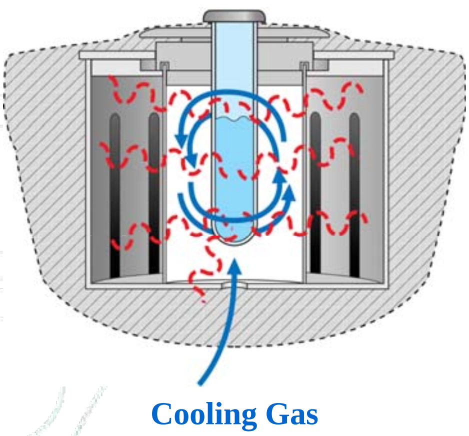
PowerMAX™ Automates the EMS Process



- Cooling gas flow regulated through system software
- Temperature feedback control maximizes input microwave power
- Bulk temperature effectively removed reducing thermal degradation

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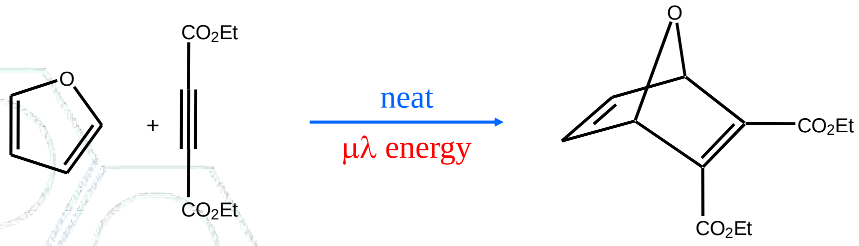
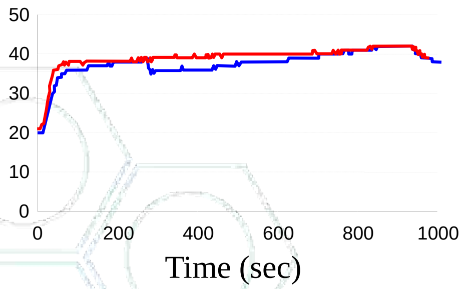
PowerMAX Chemistry

Diels-Alder Reaction

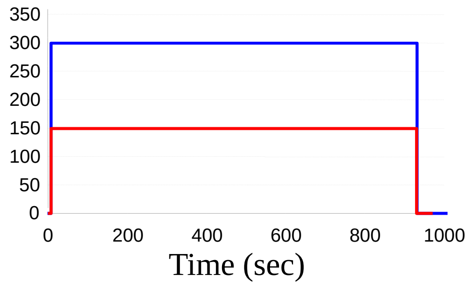


PowerMAX Chemistry

Temperature (°C)



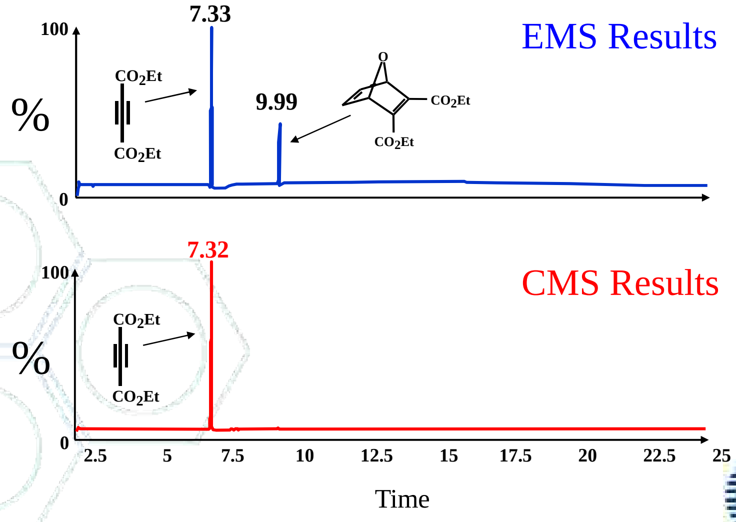
Power (Watts)



PowerMAX Enhanced

Conventional Operation

PowerMAX Chemistry



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Enhancing the Process Further

Sub-ambient Temperature Reactions

In a Microwave System

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Cool Chem™ Reaction Accessory

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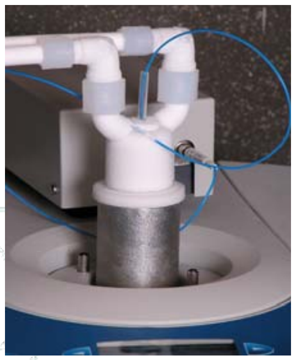
Cool Chem™ Jacketed Reaction Vessel



Vessel Specifications

- Working volume up to 5 mL
- Temp. range from -100 → +30 °C
- Jacketed design allows for circulation of microwave transparent cooling media
- Ability to run under inert atmosphere
- Access for Fiber-optic temp sensors, condensers, reagent addition

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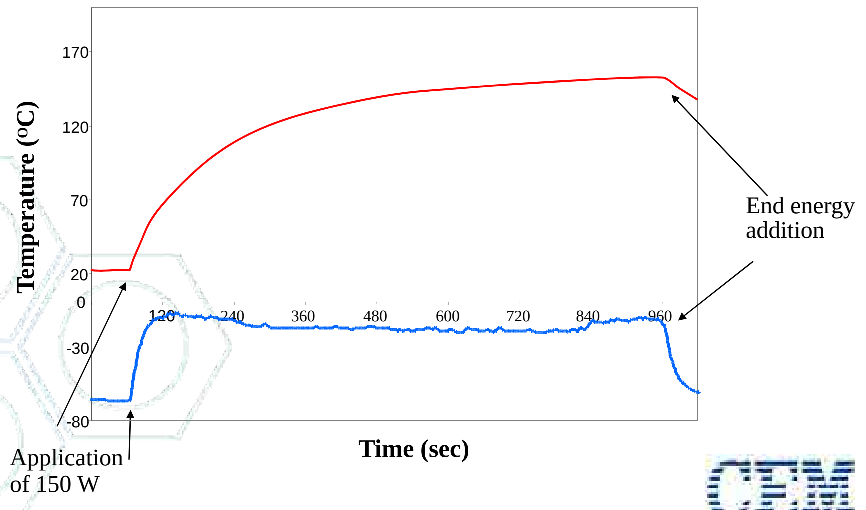
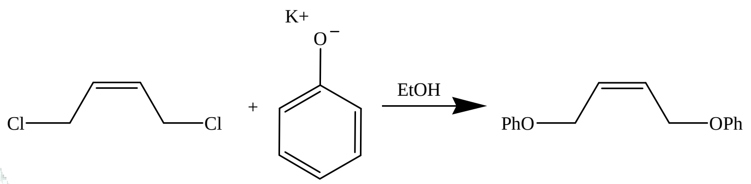
DMF: 15 Minutes, 150 W



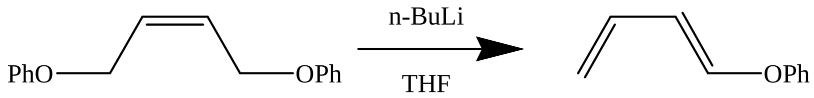
Avalanche™ Chemistry Example



	Conventional Synthesis	Microwave Synthesis
Temperature	0 – 20 °C	30 °C
Time	21 hours	35 minutes
Yield	75%	87%

Conventional synthesis: Roversi, E.; Monnat, F.; Vogel, P.; *Helv. Chim. Acta*, **2002**, *85*, 733.

Avalanche™ Chemistry Example



	Conventional Synthesis	Microwave Synthesis
Temperature	0 – 25 ˚C	- 60 ˚C
Time	2.5 hours	5 minutes
Yield	78%	81%

Conventional synthesis: Roversi, E.; Monnat, F.; Vogel, P.; *Helv. Chim. Acta*, **2002**, *85*, 733.

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If I Could Only Tell What Was Happening During the Process…

Monitoring Reactions Via Raman Spectroscopy

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Investigator™

Real Time Reaction Monitoring

- Raman-based spectroscopy system for real time reaction monitoring
- In situ measurement
- Facilitates reaction optimization

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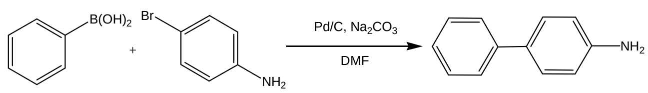
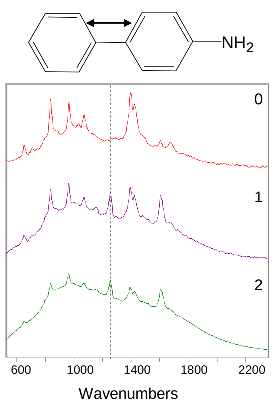
Example of Investigator™ Analytics





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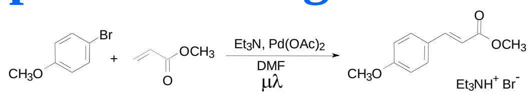
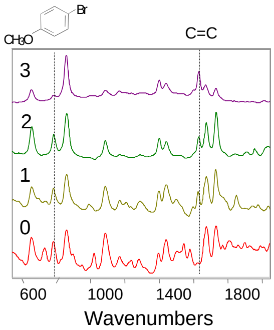
Example of Investigator™ Analytics





Okay… Where Else Might Microwave Technology Be Used in My Organization?

Microwave Enhanced Biochemical and Proteomic Applications

Speed of Traditional SPPS

- For each amino acid addition:
  - Deprotection reaction = 10 minutes
  - Coupling reaction = 30-90 minutes
- Cleavage of the peptide from the resin = 2 hours – overnight reaction

A 15 amino acid peptide takes almost 24 hours to make

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Advantages of Microwave Energy for Solid Phase Peptide Synthesis

Enhanced Deprotection, Coupling, and Cleavage Reactions

- Each step can be performed **10** times faster with microwave energy
- Coupling times as low as two minutes have been obtained
- Enhanced peptide-resin cleavage in ten minutes

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Odyssey™

Automated Peptide Synthesis

Solid Phase Peptide Synthesizer

- Walk away synthesis
- 12 peptides in a day
- 1 peptide in 2.5 hours
- Automated cleavage in 10 minutes
- Wide scale range of .005 to 5 mmol with reaction vessel sizes of 10 to 100 ml

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$^{65\text{-}74}$ACP Peptide

Sequence: NH_2-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-H

Parameters:

- *Deprotection: 1 min w/ 15% Piperidine/DMF*
- *Coupling: 2min w/ PyBOP/HOBt/DIPEA, 0.9/1/2, x4 excess*
- *Cleavage: 90 min TFA/TIS/H2O, 95/2.5/2.5*

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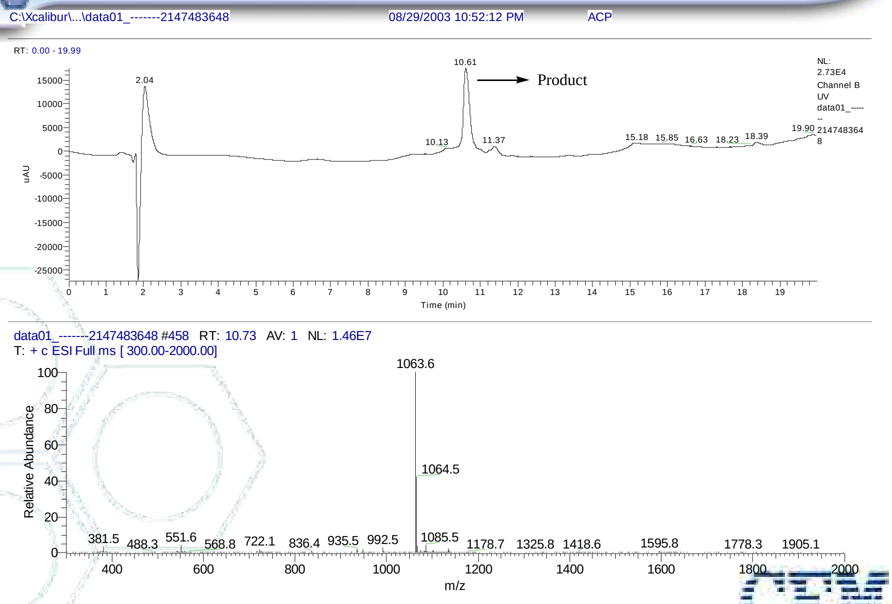
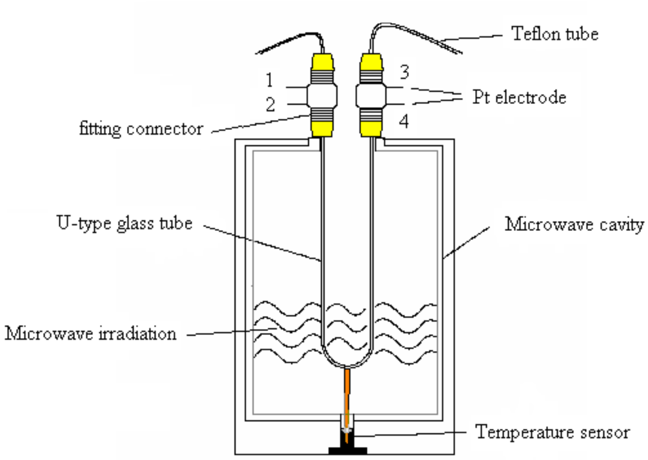


Micro-reactors

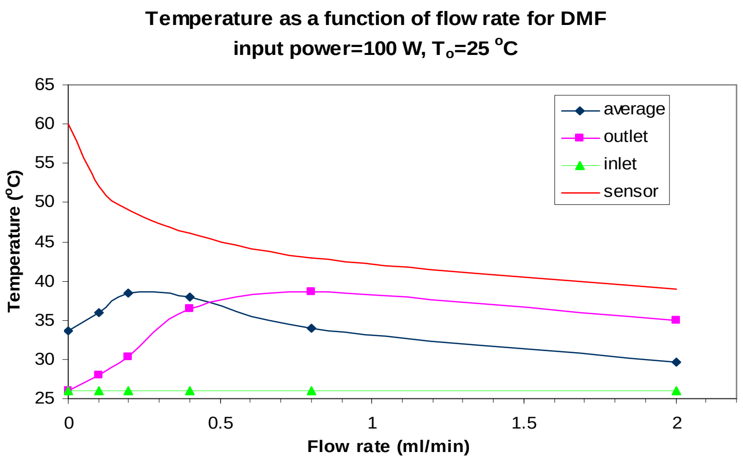
Prof. Stephen Haswell
University of Hull
School of Chemistry
United Kingdom

Capillary flow through reactor
Hull version

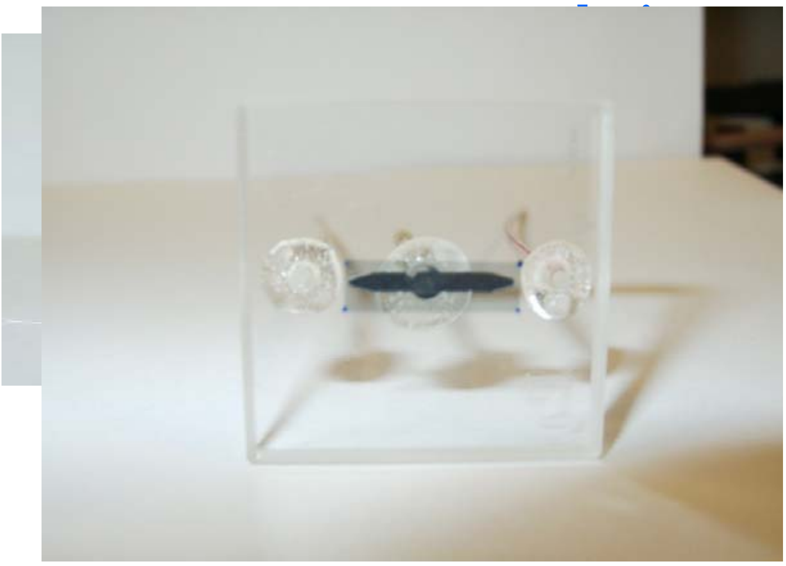


Temperature monitoring using a resistance measurement

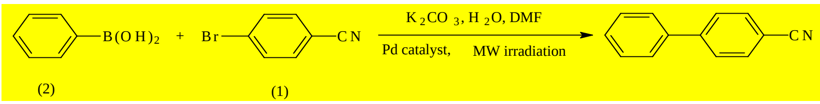
Capillary reactor temperature monitoring
(electrical resistance and infrared)



Controlled spatial microwave induced heating on a micro reactor



Suzuki reaction in a flow through micro reactor



Reactant **1**=0.1M; **2**=0.12M; K_2CO_3=0.3M; DMF: H_2O=3:1 as weight.

Catalyst	Au coating (nm)	MW power (W)	T (ºC)	Conversion (%)
Pd/Si02	0	280	50	<2
Pd/Si02	10	280	66	27
Pd/Al_20_3	0	250	58	51
Pd/Al_20_3	10	200	58	54
Pd/Al_20_3	15	90	70-74	99

Rapid reaction evaluation

X	R	Power/ W	Yield/ %
Br	NO_2	150	74
Br	CN	90	59
Br	CHO	150	54
I	OCH_3	250	32
I	CH_3	150	30

- Contact time 15 s
- Gold coating 15 nm
- Temperature 50±5°C
- Complete experiment 30 min

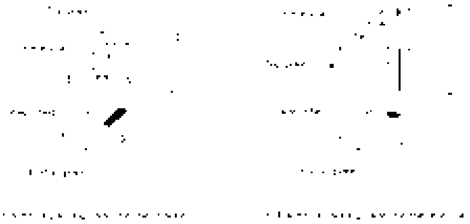
Reaction containing 0.1M BBN, 0.12 M PBA, 0.25 M K_2CO_3 and 8 mg of Pd/Al_2O_3.

Product conversion for different heating methods - micro reactor design B

Heating method	**MW power/W**	**Temp/°C**	**Conversion %**
Room temperature	0	25	0
Oil bath	0	130	65
MW heating only	150	94-98	71
MW heating plus gold coating	55	90-102	99

Comparison of product conversion in micro reactor designs A and B

Substrate	Flow/μlmin^{-1} Contact time/s	MW power/W Temp/°C	Packing design	Conv %
Br-C_6H_4-NO_2	5/36	50/90-98	B	98
Br-C_6H_4-NO_2	3/44	7/90-105	A	90
Br-C_6H_4-CN	5/36	55/90-102	B	99
Br-C_6H_4-CN	3/44	5/90-108	A	92
Br-C_6H_4-CHO	5/36	40/90-96	B	75
Br-C_6H_4-CHO	3/44	5/80-90	A	72[c]



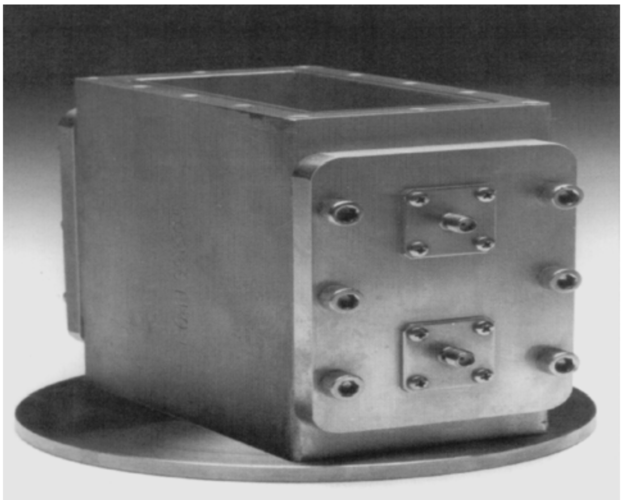
Microwave synthesis
Flow through reactions

- Benefits-
  - Greater control over reaction energy
  - Can remove sensitive products as they are produced
  - Can easily regulate exposure time
  - Can observe and regulate conditions "on the fly"
- Issues-
  - Sensitive when materials are gases or solids
  - Limitations on flow though rates

Microwave enhanced synthesis

- Low volume (0.1-5ml) systems
- mm geometry's
- Low energy systems (<50W)
- Variable continuos focused power
- Variable frequency (0.2 - 40 GHz)
- Flow through and stopped flow
- Pressurised
- Energy coupled measurements
- Absorption data processing

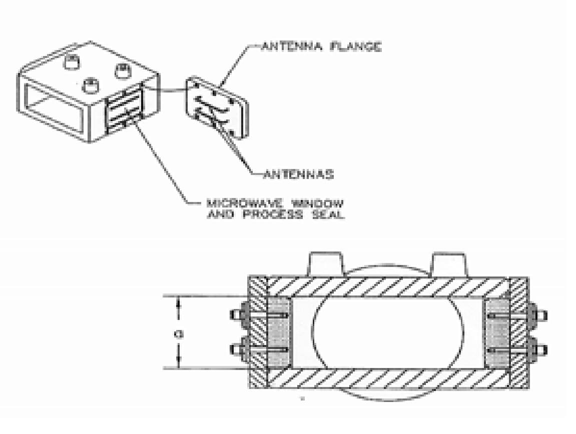
Microwave spectroscopy



Examples of spectral microwave properties that could be determined

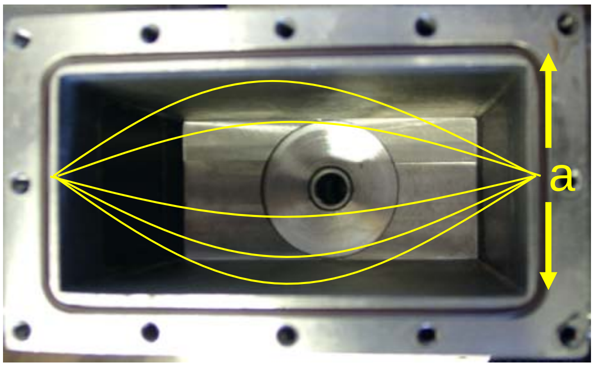
- Determination of chemical species
- Emulsion phase change
- Particle size effects
- Bound versus free water effect
- Temperature and physical state effects
- Entrained air, pressure and packing density

Dual antenna assembly



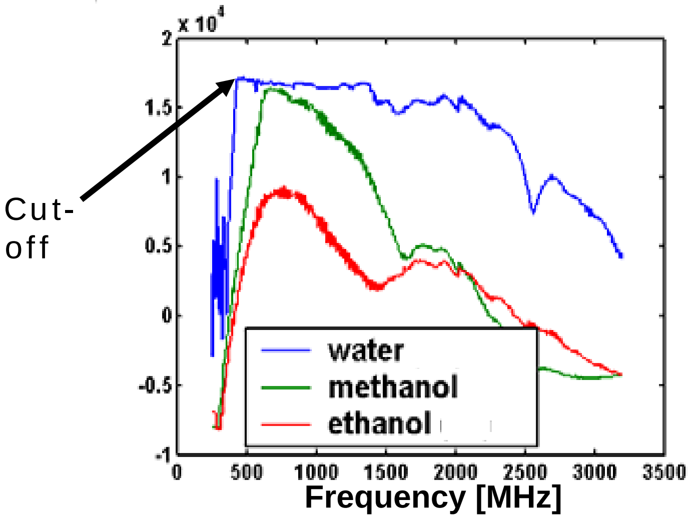
Waveguide frequency cut - off

$$f_c = v_{\text{vacuum}} / 2a\sqrt{\varepsilon'}$$



Spectrometer with reaction vessel in place

Example guided microwave spectrum



Key research areas

- Equipment design
- Combined thermal spectroscopic systems

Targets

- Improve reaction selectivity
  - Greater product specificity
  - Increase in reaction products
  - Enable novel routes to synthesis
  - Modified supported reagents
- Improve Analytical capability
  - Chromatographic and membrane separations
  - Spectroscopic based models

Research collaborators and funding

- Tony Walmsley
- Paul Fletcher
- Vesko Paunov
- Della Grice
- Ping He
- Vicky Loads
- Adrie Dane
- Gerard Rea

- EPSRC
- CEM
- GlaxoSmithKline
- CPACT