

# Microwave chemistry— out of the lab and into production

Microwave assisted organic synthesis (MAOS) has been used to good effect at small scale for a number of years. Now Cambrex and C-Tech Innovation have developed a large scale continuous flow system (CF-MAOS) capable of processing hundreds of litres a day while retaining all the benefits associated with small scale microwave synthesis. Systems based on the CF-MAOS technology are capable of producing 1000 kg of product per week.

## Why Microwave Chemistry?

- Faster** Whether there is a "microwave effect" may still be a matter of debate—what isn't in doubt is that microwave heating can produce substantially faster reactions than conventional heating. Due to selective heating, very rapid temperature rise, the removal of wall effects or simply the ease of operating at high temperatures and pressures—there are hundreds of literature examples where the use of microwave equipment has shortened reaction times from hours to minutes.
- Cleaner** Rapid temperature rise and the absence of hot heat transfer surfaces can mean less undesired side reactions resulting in higher yields and lower impurity levels. No steam or heat transfer fluids means fewer leaks and less mess. No fouling or burn on to heat transfer surfaces.
- Greener** There are many literature examples of solvent free syntheses and the case studies opposite show the potential for reducing catalyst use. C-Tech Innovation have also been awarded Carbon Trust funding to quantify the energy saving potential of microwave chemistry due to the shortened reaction times and reduced downstream work up as a result of the higher yields and purity often achieved.
- Safer** Microwave heating is a direct heating method with no need for heating jackets or heat exchangers with large thermal mass. This means that turning off the microwave power immediately stops energy input to the system and the temperature can be lowered quickly. Using a continuous flow system lowers the inventory of any hazardous or unstable products and intermediates, making scale up inherently safer than using a batch approach.

## The Challenges of Scale up

Moving directly from laboratory-scale work, where small quantities of compounds (typically milligrammes) are produced for compound libraries, to scaled up or even production quantities (kilogrammes and more) has previously proved difficult to achieve using microwave technology.

As the scale becomes larger, so the advantages of microwaves can be lost. The power from microwaves dissipates with the distance the microwaves have to travel into the reaction mixture (penetration depth) and this would result in significant overheating at the surfaces, just as with conventional heating. Also, as the reaction mixture heats up, so the properties relevant for microwave heating change and this may exacerbate the overheating effect. Materials that are used for small scale reactions are often not suitable to fabricate larger reactors, and problems of measurement and control can be more acute as the scale of operation is increased

## Penetration Depth

Microwave heating is described as a volumetric heating method in that it does not rely on conduction or mass transport for heat transfer. However as we move through a microwave absorbing medium the microwave field is attenuated, the more absorbing the medium the quicker the field is attenuated. The penetration depth is often defined as the distance from the surface that the power has dropped to 1/e of the incident power. Figure 1 shows the attenuation of microwave power for two substances, one strongly absorbing the other less absorbing. Penetration depth typically varies from ~1cm to ~10cm for most chemical reaction systems of interest. This means that scale up of batch processes is generally not possible without losing many of the benefits of microwave heating.

**For larger scale processes continuous flow reactors are needed.**

## Materials

Microwave chemistry puts particularly strenuous demands on the materials of the reactor. Many of the small scale synthetic methods use high temperatures and pressures. For useful scale up larger systems must be capable of operating under these conditions too. Contact materials must also be resistant to as wide a range of chemicals as possible. Microwave heating also adds the requirement that parts of the reactor must be microwave transparent to allow energy transfer and parts of the system must be able to contain and shape the microwave field. Lab scale reactors employ PTFE or glass as microwave transparent reaction vessels but it is difficult to use these materials at larger scale as they do not have sufficient strength at high temperatures to resist the larger forces from internal pressure.

**The continuous flow reactors we have developed use a bespoke pressure, temperature, chemical resistant and microwave transparent conduit to allow the widest possible range of conditions**

## Measurement and Control

Temperature measurement of the reaction mixture within microwave cavities is recognised as an important aspect of microwave chemistry. Many "microwave effects" have later been attributed to poor or indirect temperature measurements. Temperature profiling of the continuous flow reactor shows a rapid temperature rise as the fluid enters the microwave reactor and a stable final temperature at the exit (Figure 2).

**Routine temperature measurement and control is achieved using standard probes at the exit of the microwave reactor or by using fibre-optic based probes within the microwave cavity.**

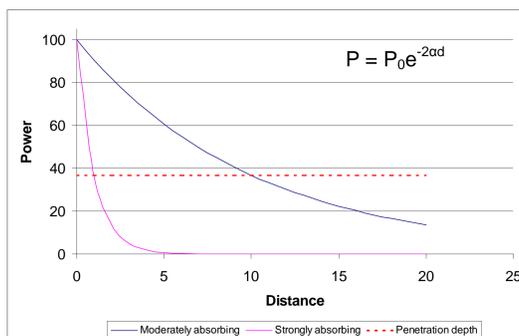


Figure 1—Power dissipation in dielectric material

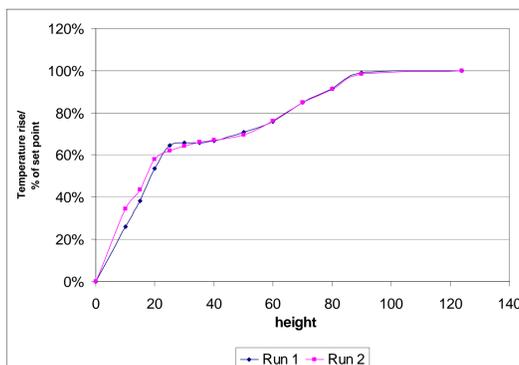


Figure 2—Temperature profile of CF-MAOS reactor



Figure 3— GENESIS™ CF-MAOS reactor



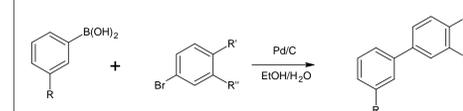
Figure 4—Twin receivers

## CASE STUDY 1

**SCENARIO:** A series of palladium-catalysed Suzuki reactions were studied under CF-MAOS using heterogeneous catalysts.

Residence times were in seconds or minutes. Catalyst loadings were usually reduced from the corresponding conventional heated reaction. In one case less than 10ppm catalyst was needed. Impurity profiles were as least as good as, if not better than, conventional heating. Specifically, no new impurities were observed.

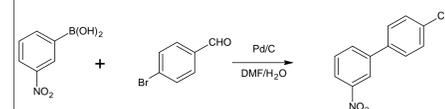
**EXAMPLE 1:** Improved impurity profile:



The conventional reaction requires 24 hours reflux in EtOH with 5200ppm Pd/C catalyst. The isolated yield was 85%, purity 97% (a/a) by HPLC with one major impurity >2.5% (a/a).

The microwave-assisted continuous-flow reaction at 170°C requires 60s residence time with 350ppm Pd/C catalyst. The isolated yield was 81%, purity 99.5% (a/a) by HPLC with the major impurity above greatly reduced.

**EXAMPLE 2:** Large Volume Manufacture:



The dual receiver system allows 24 hour operation of the Cambrex GENESIS™ microwave reactor. The above reaction was used to prove the large-scale concept of continuous-flow microwave-assisted synthesis. More than 140L was processed continuously over 32 hours at 180°C, 20s residence time to produce 22.3 kg product (88% yield) with purity 99.3 % (a/a) by HPLC.

**OUTCOME:** The Cambrex CF-MAOS methodology proved highly efficient and cost-effective, resulting in:

- Less reaction time
- Less catalyst usage
- Less impurities
- Less cost

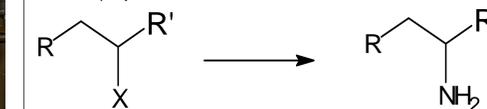
## Contacts

Dr Jayne E Muir  
Cambrex  
Tel: +44 (0)1223 237 527  
Email:  
jayne.muir@cambrex.com

Darren Kell  
C-Tech Innovation Ltd  
Tel: +44 (0)151 347 2900  
Email:  
darren.kell@ctechinnovation.com

## CASE STUDY 2

**SCENARIO:** Cambrex was presented with a difficult conventional nucleophilic amination reaction. However, reaction parameters by microwave heating were quickly determined such that on the following day, 18L was processed in 3.5 hours to give 2.6kg product. This gave an estimated saving of 4 weeks in project time.



**OUTCOME:** The Cambrex GENESIS™ microwave reactor significantly reduced production time. Other advantages over the conventional reaction included:

- Yield doubled over literature methods
- Off-the-shelf reagent used versus reagent preparation
- Substantial reduction of organic solvent usage
- Simplified workup
- No scale up experiments needed

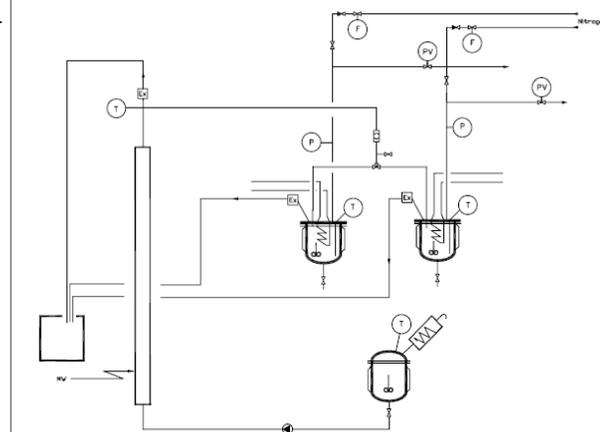


Figure 5— CF-MAOS Process flow sheet

## Operating Parameters

- Temperatures up to 200°C
- Pressures up to 20 bar
- Flowrates up to 200ml/min
- Dual Feed Vessels
- Dual Receiver Vessels
- Designed to process up to 10L per single run
  - Can be operated for longer periods
- Homogeneous reactions
- Light Heterogeneous reactions

## COMMERCIAL-SCALE CONTINUOUS-FLOW MAOS

Cambrex is committed to bringing this exciting manufacturing technique to commercial scale. A step-up from the Cambrex GENESIS™ microwave reactor is the Cambrex VANGUARD™ microwave reactor as a skid-mounted design to be available for use with conventional plant vessels, delivering 100kgs per week.

Large-scale microwave-assisted synthesis is no longer in the future; it is here today at Cambrex. Call us to discuss the benefits and value we can bring to your program