

# Toward Rapid, “Green”, Predictable Microwave-Assisted Synthesis

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## ABSTRACT

Continuous and batch microwave reactors were constructed for efficient, “green” synthesis with low-boiling solvents at high temperature in closed vessels. Capabilities for rapid heating and cooling, concurrent heating and cooling, and differential heating facilitated novel chemical reactions and processes. Commercial microwave systems based on these developments are available. Times required for conventional reactions typically are decreased by 2–3 orders of magnitude. Green processes also have resulted through use of less or no catalyst, readily recyclable solvents, or media and yields that are often higher than normal. Complementary interactive software for calculating optimal conditions was developed.

## Introduction

Before 1990, analytical methods for separation and identification of organic compounds underwent major advances through the development of tandem techniques such as GC–MS, HPLC–MS, and the introduction of computer operation and Fourier transform. In contrast, chemical synthesis and manufacture were still conducted with traditional equipment and often by wasteful methods that had changed little over decades. Advances had been mainly incremental, e.g., rotary evaporation, complementary ground-glass joints, adapters, and stoppers instead of corks or rubber bungs for glassware. Environmental aspects were not given their current high priority either. Typically, attention was more focused upon yield and profit than safety or ecological effects of chemical products

Brett Roberts was born in Australia in 1974. He obtained his B.Sc. (honors) in 1996 and Ph.D. in 2000 from Monash University, under the supervision of Prof. C. L. Raston. A year of his doctorate was undertaken at the University of Strathclyde, with Prof. R. E. Mulvey. Between 2000 and 2002, he investigated solvent-free organic synthesis at the Centre for Green Chemistry, Monash University, and then began with CSIRO Molecular Science exploring Microwave Chemistry with Dr. C. R. Strauss, before returning to the Centre for Green Chemistry as a Research Fellow in 2004.

Chris Strauss was born in Australia. He obtained his B.Sc. (honors) and M.Sc. degrees from Sydney University in 1968 and 1977, respectively, and his Ph.D. from the University of Adelaide in 1984. He researched grape, wine, and spirit composition at the Australian Wine Research Institute between 1971 and 1987 before joining CSIRO. He has had leading roles in the establishment of Microwave Chemistry and Green Chemistry as fields. In 2001, he was seconded to his current post as the Deputy Director of the Centre for Green Chemistry at Monash University.

and processes. Synthetic protocols were often indirect and employed low temperatures.

With increasing community concern over possible influences of chemicals and chemical practices on the environment, we sought enabling technologies for direct, efficient, and environmentally unobtrusive synthesis. Our activities have mainly focused on technologies and methodologies for controlled heating. The products include hardware (continuous and batch microwave reactors), software (predictive technology for deriving optimal reaction conditions), and “green”, thermal synthetic methods, including new reactions and media.

The first microwave-assisted organic syntheses, reported in 1986,<sup>1</sup> attracted our attention. Considerably shorter reaction times than normal had been obtained for common organic transformations such as esterification, hydrolysis, etherification, addition, and rearrangement. Inadequate controls in the rudimentary equipment employed, however, generated hazards, including explosions.<sup>1,2</sup>

This suggested that microwave heating could be advantageous for synthesis if it could be conducted safely. Workers concluding that the technology was incompatible with organic solvents, investigated solvent-free conditions, particularly applications of “dry media” in open vessels. Their approach was readily implemented and has been reviewed extensively.<sup>3</sup> Inexpensive domestic microwave ovens typically were employed, without measurement of temperature and stirring of reactions. However, subtle differences in size, shape, homogeneity, dielectric properties, and even location of the sample within the oven, influenced the results.<sup>4</sup> Uniform heating is difficult to accomplish in domestic ovens, owing to variability in flux densities throughout the microwave cavity and the use of duty cycles to apply the power. These vagaries appear to have contributed to findings of abnormal “microwave effects”,<sup>5</sup> examples of which subsequently proved difficult to reproduce.<sup>6</sup>

Pivotal to our alternative strategy were assumptions (a) that temperature measurement was critical if reactions were to be reproducible between laboratories and (b) that organic solvents would continue to have vital roles in synthetic chemistry, notwithstanding the development of solvent-free methods. Therefore, from our perspective, for microwave technology to be generally applicable, it should be capable of operating safely, controllably, measurably, and reproducibly, in the presence of organic solvents.

Our work was concurrent with that of others into solvent-free approaches, and two quite independent sub-fields of microwave chemistry resulted. The differences hinged upon the use of either closed or open vessels usually but not exclusively with or without solvent, respectively. Nonetheless, the strategies had a common objective; the safe application of microwaves in organic synthesis. The whole work showed that contrasting inter-

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pretations of the same problem can afford vastly different but nonetheless beneficial solutions. Open-vessel microwave chemistry and closed-vessel microwave chemistry, as we could term them, tend to have specific rather than shared advantages and disadvantages and as will be discussed elsewhere, they are more complementary than competitive.

## Development of Microwave Reactors

An established approximation is that, for each 10 °C increase in reaction temperature, the required time is halved. A reaction taking 18 h at 80 °C could give a comparable result within 30 s at 200 °C provided that the components survived the conditions. At around 200 °C, though, reactions are inconvenient to carry out with conventionally heated flasks at atmospheric pressure. Solvents boiling in that region are difficult to recover and purify. Many have potentially reactive functional groups as well. Under moderate pressures, increases of 100–150 °C occur in the boiling points of common solvents such as EtOAc, MeOH, EtOH, MeCN, and Me<sub>2</sub>CO, all of which boil below 80 °C at ambient pressure. Low boiling solvent can also be readily removed from products after the reaction and recycled.

It followed that systems tolerant of internal pressure could deliver the benefits of short reaction time, convenient workup, and avoidance of waste for processes requiring moderate to high temperature in solvents. Conductively heated autoclaves would not be ideal. Thermally heated autoclaves would not be ideal. Thermal inertia of thick metal surfaces results in long heating and cooling times. Thermal gradients lead to pyrolytic wall effects, which can be particularly severe with viscous materials. Also, heat losses increase with a temperature rise; therefore, high temperatures are difficult to attain and maintain.

With microwave heating, the energy can be applied directly to the sample rather than conductively, via the vessel. Heating can be started or stopped instantly, or the power level can be adjusted to match that required. If the sample is mixed efficiently during irradiation, bulk heating occurs. That minimizes convection and temperature gradients particularly near surfaces, rendering the vessel no hotter than its contents. Also, heat retention is more efficient in vessels made from insulating materials than from metals, facilitating maintenance of high temperatures.<sup>7</sup>

Before the 1986 reports disclosing organic reactions, microwave irradiation was used in analytical laboratories to digest samples.<sup>1,8</sup> Digestion is a destructive process requiring reproducibility but not monitoring. Synthesis is constructive and tends to require highly specific manipulations. An appreciation of these conflicting requirements was essential for the construction of dedicated microwave systems for synthetic applications.<sup>9</sup>

Safety, the highest priority, was achieved through appropriate engineering, comprehensive control of reactions, reproducibility of performance, and effective, automated emergency procedures if necessary. Other major

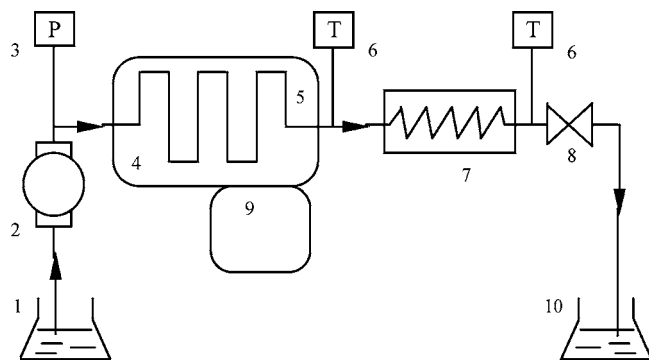


FIGURE 1. MBR (B. A. Roberts operating).

technical issues concerned scale, vessel design, means for stirring of reaction mixtures, temperature measurement, control of microwave power, sample or product withdrawal, reactant addition, and postreaction cooling. Some are irrelevant for digestion, and all were resolved by the mid 1990s. The capability for changes in scale and unique properties, applications and advantages such as remote, robotic operation, differential heating, and rapid heating and cooling (discussed below) enhanced the appeal of this approach toward microwave chemistry.

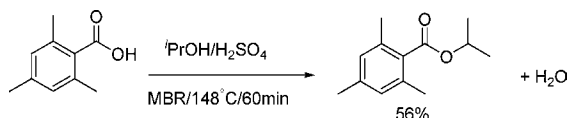
In 1995, we reported a microwave batch reactor (MBR; Figure 1), which operated on a scale of 25–200 mL (a range selected to facilitate scaling up and scaling down), at temperatures up to 260 °C and pressures up to 10 MPa (100 atm) in a standard organic laboratory.<sup>10</sup> It superseded an earlier prototype<sup>11</sup> and enabled rapid heating (typically 1–2 °C per second on the 100–200 mL scale), infinitely variable control of microwave power, and measurement of absorbed and reflected microwave energy. A load-matching device (cavity tuner) optimized heating efficiency. The temperature was measured directly by optic fiber thermometry, and pressure was measured through a transducer. Magnetic stirring of the sample, unprecedented in a microwave environment before our 1992 report,<sup>11</sup> ensured a uniform temperature by thorough mixing. Chemicals could be added and samples withdrawn while heating. All wettable surfaces and connections were chemically inert. Other facilities included plumbing for gases and a cold finger for rapid, postreaction cooling. Safety devices and protocols extended from materials of construction, the design of flanges, disks, and seals, the microwave cavity, vessels, and their containment to electronic interlocks and emergency shut-down. Microwave power input was computer-controlled. Heating could be carried out at high or low rates as required, and designated temperatures could be maintained for hours.

The continuous microwave reactor (CMR; Figure 2)<sup>12a</sup> was designed for flow-through chemical processing and complemented the MBR. Several embodiments have appeared since the first prototype was produced in 1988.<sup>12b</sup> Commercial systems manufactured by an industrial partner had volumes up to 120 mL within the microwave zone, 80 mL within the cooling zone, and could be operated at flow rates up to 100 mL/min (also to facilitate scaling up and down). Residence and, by definition, reaction times<sup>12a</sup> in the microwave zone were typically 2–10 min.<sup>13</sup>

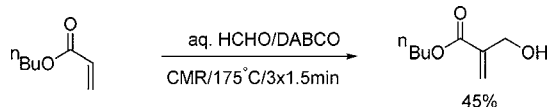


**FIGURE 2.** Schematic diagram of the CMR.<sup>12a</sup> 1, Reaction mixture; 2, metering pump; 3, pressure transducer; 4, microwave cavity; 5, reaction coil; 6, temperature sensor; 7, heat exchanger; 8, pressure regulator; 9, microprocessor controller; and 10, product vessel.

**Scheme 1. Esterification of 2,4,6-Trimethylbenzoic Acid<sup>10,11</sup>**



**Scheme 2. Preparation of *n*-Butyl 2-(Hydroxymethyl)acrylate<sup>14a</sup>**



## Chemistry with the MBR and CMR

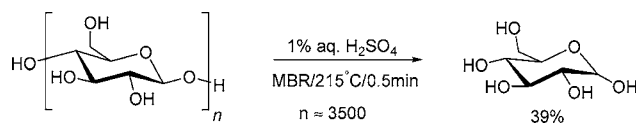
The MBR<sup>10</sup> and CMR<sup>12</sup> were the first microwave systems specifically designed for organic synthesis. Workers could select and control conditions. Reactions could be sampled while in progress. Their thermal history could be recorded. Improvements to literature methods typically involved time savings, higher yields, greater selectivity, the need for less catalyst,<sup>14a</sup> or the employment of a more environmentally benign solvent or reaction medium.<sup>14b</sup>

Speed and convenience are the major advantages of microwave technology for synthesis. Typically, the MBR and CMR reduced reaction times with conventional glassware by 2–3 orders of magnitude. Significant savings in energy, labor, management and utilization of plant can be achieved through accelerating normally sluggish reactions in particular.<sup>10,12,13c</sup> Esterification of sterically demanding 2,4,6-trimethylbenzoic acid was well-advanced after 1 h at higher temperatures, instead of after days at reflux (Scheme 1).<sup>10,11</sup>

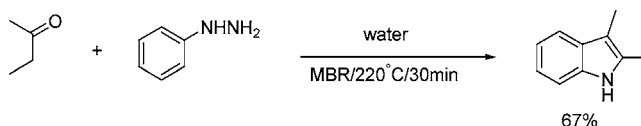
Methylation of 2,4,6-trichlorophenol proceeded in 54 min in a microwave reactor instead of 192 h under conventional conditions; it became 10 times faster with phase-transfer catalysis.<sup>13c</sup> For alkyl 2-hydroxymethylacrylates, reaction times were shortened from several days (at ambient temperature) to a few minutes (at 160–180 °C), without detriment to yields (Scheme 2).<sup>14a</sup> Adaptation of the new conditions from batch to continuous was readily accomplished with the CMR, and kilograms of material were produced safely for pilot studies.

The cold finger, located within the vessel during operation in the MBR, cooled reactions directly and could be activated or decommissioned conveniently.<sup>10</sup> Heating

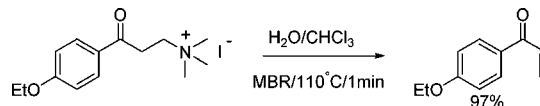
**Scheme 3. Hydrolysis of Cellulose<sup>10</sup>**



**Scheme 4. Indolization in Water (Equation Not Balanced)<sup>14a</sup>**



**Scheme 5. MW-Assisted Hofmann Elimination (Equation Not Balanced)<sup>10</sup>**

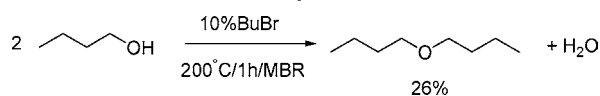
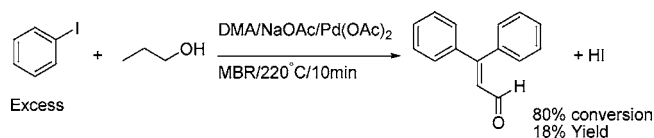


and cooling could be performed simultaneously (*concurrent heating and cooling*<sup>14a</sup>), thereby reducing possibilities for thermal runaway in the case of exothermic reactions requiring heat input. Other preparations, difficult with conventional equipment, were facilitated by rapid microwave heating and cooling, e.g., compounds that were inherently thermally unstable or became so under the conditions. Examples included preparations of alkyl 2-hydroxymethylacrylates<sup>14a</sup> and acid-catalyzed hydrolysis of cellulose (Scheme 3) to give the more acid-labile glucose in around 40% yield.<sup>10</sup> In these cases, rapid cooling allowed isolation of the products before they could be degraded to polymeric material.

Multiple sets of optimal conditions are not obtained commonly with reflux processes. With the CMR and MBR though, the use of low-boiling solvents at considerably higher temperatures enabled several sets of optima to be obtained.<sup>14a</sup> Time, temperature, and catalyst concentration could be manipulated according to priorities, without necessarily compromising yields. An example involved a Fischer-type synthesis from phenyl hydrazine and butanone to give 2,3-dimethylindole in water at about 220 °C (Scheme 4).<sup>14a</sup> Employment of 1 M sulfuric acid catalyst decreased the reaction time from 30 min (in water alone) to 1 min, without significantly altering the yield. The optimum became a choice between short reaction time with more waste on one hand and longer reaction time with less waste generated on the other.

In two-phase systems, absorption of microwave radiation by dielectric heating and ionic conduction enables individual phases to be heated at different rates, potentially affording sizable temperature differences.<sup>10</sup> Cundy<sup>15</sup> has suggested that *differential heating*<sup>14a</sup> in liquid/solid systems may account for seemingly nonthermal "microwave effects" claimed by others for "dry media" reactions.<sup>5</sup> In our work, differential heating was exploited in water/CHCl<sub>3</sub> for the preparation of aryl vinyl ketones by Hofmann elimination (Scheme 5).<sup>10</sup> Reactions on the starting salts progressed rapidly in the more strongly microwave absorbing aqueous phase. The thermally unstable monomeric products were simultaneously extracted and diluted



Scheme 6. Catalytic Etherification<sup>16</sup>Scheme 7. Pd-Catalyzed Arylation (Equation Not Balanced)<sup>17</sup>

into the cooler, denser, organic phase. Near quantitative yields precluded the need for purification of the products and were twice those obtained by traditional methods. The process, carried out batchwise in the MBR, could be scaled-up with the CMR.<sup>12a</sup>

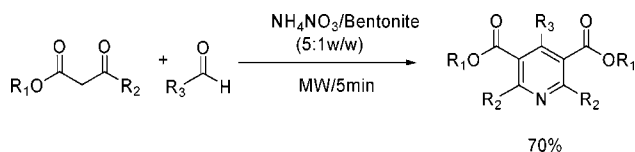
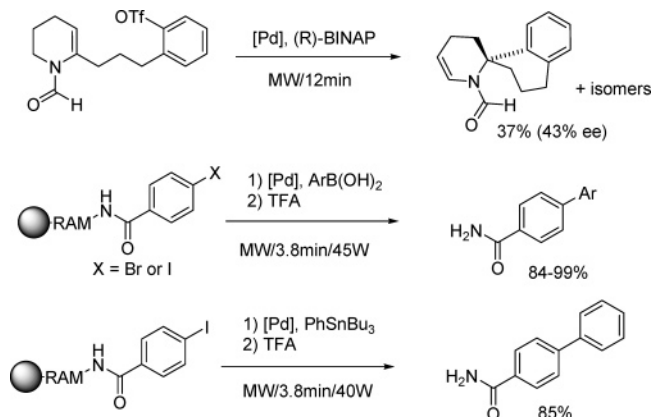
The microwave systems enabled discovery of new reactions that require elevated temperature. Examples included a catalytic etherification (Scheme 6)<sup>16</sup> and a multicomponent oxidation, dehydrogenation, and double Heck coupling (Scheme 7).<sup>17</sup> Improvements were also introduced to processes known to require high temperature. Willgerodt reactions conventionally are conducted at about 180 °C for several hours in sealed tubes or bombs. In the MBR, they were completed within minutes.<sup>18</sup>

In exploration of new "green" applications, water at high temperature was found to be a useful synthetic medium.<sup>19</sup> It behaves as a *pseudo-organic solvent*.<sup>14a</sup> Its dielectric constant decreases substantially; its ionic product increases by 3 orders of magnitude; and above 200 °C, the solvating power toward organic molecules becomes comparable with that of EtOH or Me<sub>2</sub>CO at ambient temperature. Acid or base-catalyzed reactions in high-temperature water typically required less catalyst than normal, and they often proceeded rapidly.<sup>7,10,13a,14</sup> Some products were isolated from cooled reaction mixtures by adsorption onto hydrophobic resins rather than by solvent extraction.<sup>13a</sup> The microwave studies complemented those of Katritzky and Siskin, who employed conventional heating in high-temperature water for investigations into geothermal processes.<sup>20</sup>

## Commercial Developments

The dedicated microwave reactors and associated chemistry<sup>10,12,14</sup> stimulated other researchers to construct systems for laboratory and even pilot-scale studies.<sup>21</sup> Units were also designed for solvent-free reactions.<sup>22</sup> Such developments have been discussed elsewhere.<sup>23</sup>

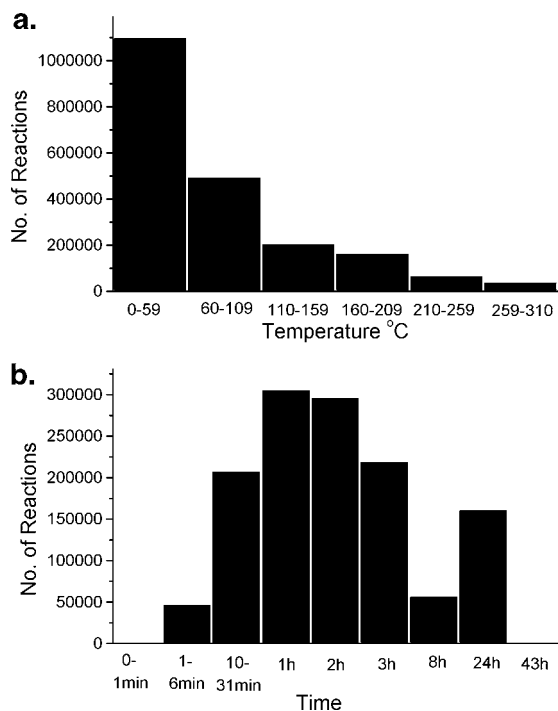
Since about 2000, various commercial microwave reactors have appeared.<sup>23</sup> Some, based on patents embodied by the CMR and MBR, were manufactured under license. Commercial batch systems now are produced in Europe, Asia, and North America. They operate typically on scales from around 1 mL to 2 L and may employ multimodal cavities as with the CMR and MBR or monomodal cavities for so-called "focused"<sup>3a</sup> microwaves. The modality though has little influence on reactions conducted above the multimilligram scale in appropriately designed systems.

Scheme 8. High-Throughput Solvent-Free Hantzsch Synthesis (Equation Not Balanced)<sup>24a</sup>Scheme 9. MW-Assisted Heck, Suzuki, and Stille Coupling (Equation Not Balanced)<sup>25</sup>

Dielectric properties of materials change with temperature and chemical composition.<sup>4b</sup> Depending upon the nature of the reaction, diminution of starting materials and formation of products could lead to an increase or a decrease in microwave susceptibility.<sup>14a</sup> Consequently, as reactions progress, frequent tuning of either multi- or monomodal cavities is necessary to ensure maximal absorption of the input energy. In computer-managed units, this function is usually automated.

With commercial systems, microwave reactions may be performed with or without magnetic stirring in vessels of glass, ceramic, or polymeric materials. Reactions may or may not be externally air-cooled. Cooling may be direct, by the cold finger. Reactors may have the capability for "simultaneous heating and cooling" as advocated by one manufacturer or for concurrent heating and cooling as we originally termed it.<sup>14a</sup> Temperatures may be measured remotely by infrared pyrometer rather than intimately by optic fiber thermometer<sup>10</sup> or by grounded thermocouple.<sup>12</sup>

Notwithstanding relatively minor technical variations,<sup>14a</sup> the features, operation, and timing of release of these systems attest to their origins; computer-driven and robotically automated microwave reactors adopting the concepts and principles<sup>10,12</sup> underpinning the MBR and CMR have become commonplace in organic chemical laboratories. They are employed extensively in chemical discovery, where successive reactions can be performed rapidly in parallel or sequentially (Scheme 8).<sup>24</sup> Work by other groups has afforded metal-catalyzed processes including Heck, Suzuki, and Stille reactions (Scheme 9).<sup>25</sup> Such reactions typically can be completed within minutes by microwave "flash heating"<sup>26</sup> in pressurized systems, sometimes with high regio- and enantioselectivities.<sup>27</sup> Numerous other applications have been reported.<sup>28</sup> With one manufacturer claiming that about 10 000 reactions



**FIGURE 3.** (a and b) Distribution of temperature (a) and time (b) for published reactions.<sup>29</sup>

per week are performed in its systems alone, microwave chemistry in closed vessels has dramatically influenced approaches to synthesis.

As discussed in the next section, a significant but rather gratifying predicament has emerged as a consequence of these developments.

### Technology for Establishing Alternative Reaction Conditions and for Predetermining Yields or Conversions

For more than two million organic chemical reactions reported over the past one and a half centuries,<sup>29</sup> approximately 80% were conducted below 110 °C and reaction times for the majority were 1–4 h. Fewer than 20% were completed within 30 min (parts a and b of Figure 3). These statistics reflect the huge contribution of traditional methods in organic synthesis, typically involving solvents boiling no higher than toluene. However, chemists accustomed to traditional methods now pose questions such as: "If my reaction takes 5 h in refluxing EtOH and the yield is 33%, could I obtain a 90% yield at 170 °C and, if so, in what time?" Without altering other parameters, the desired new conditions involve alternative temperatures, times, and yields. Kinetics studies may be conducted, but they would require extensive and laborious experimentation.

Although a model predicting reaction kinetics and yields under classical and microwave heating has been reported for specific reactions,<sup>30a</sup> we sought a generic technology to enable known conditions for virtually *any* thermal reaction to be translated readily and directly into improved protocols, without the need for extensive empirical studies regarding kinetics and/or optimization.

Given the diversity of individual reactions, orders of reaction, and rates, it appeared unlikely that desired conditions could be obtained confidently through only one specific calculation; therefore, an iterative, interactive approach was pursued.<sup>30b</sup>

First, the reaction surfaces were mapped for two unrelated processes, a transesterification and an intramolecular ring closure. Temperatures of 0 °C and above, times from minutes to months, and concentrations of catalyst varying by up to 2 orders of magnitude were employed. Algorithms derived manually from the empirical data were incorporated into an interactive software program. Time, temperature, and yield or conversion were treated as equally weighted parameters that could be traded against one another. From one set of experimental data for a reaction, conditions could be calculated for any time (between 0.1 and 10<sup>5</sup> min) and temperature (between 0 and 270 °C) to afford any nominated yield or conversion between 5 and 100%.<sup>30b</sup>

The hypothetical case above concerned experimentally obtained parameters (78 °C, 5 h, and 33% yield) and theoretical data involving two of three desired parameters (170 °C and 90% yield). The time, calculated by the program, would complete the theoretical data set and enable the conditions to be attempted. With the developed methodology, an iteration (i.e., experimental testing of the calculation) would be conducted with the estimated conditions (170 °C at the calculated time). The yield may be lower, higher, or 90% as calculated. When necessary, experimental results from the first iteration can be employed as reference data for a second calculation and iteration, as shown in Table 1. A graphical representation of the interactive, iterative process for entry 1 in Table 1 is shown in Figure 4.

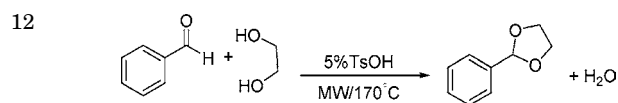
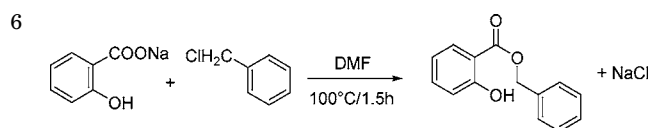
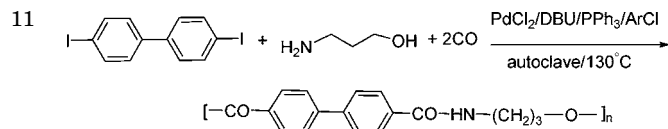
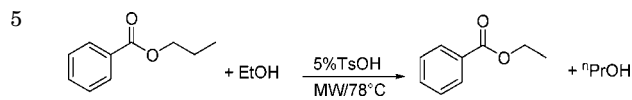
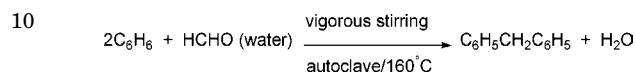
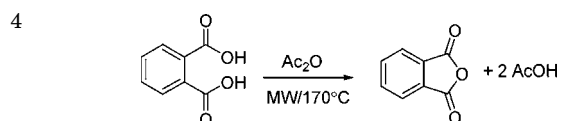
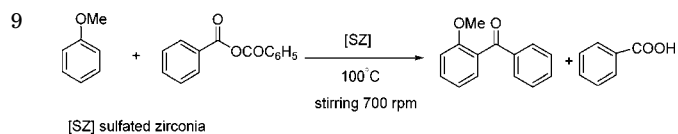
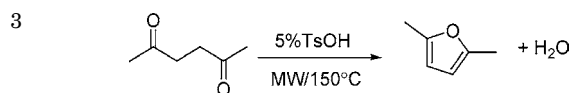
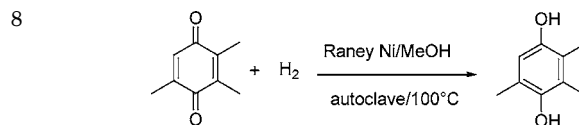
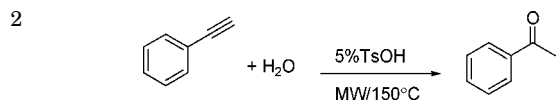
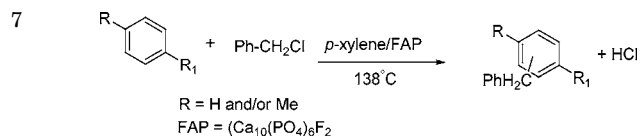
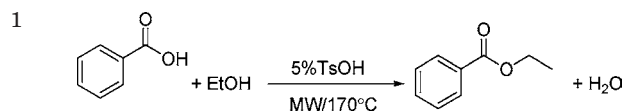
Table 1 contains random examples from a total sample set of >50 individual reactions and 300 translations of conditions. The correlation coefficient between the predicted and experimentally obtained yields for the first iteration was 0.75. After the second iteration, however, it rose to 0.97, with an even spread of data points above and below the line of best fit (Figure 5). A satisfactory result usually was obtained within two iterations, and a third iteration was not frequently required. The technology proved to be robust, versatile, and effective for a broad range of unrelated reactions. Possible alternative pathways to different products at higher temperature rarely interfered. Obvious potential applications were in chemical discovery, where rapid throughput and optimization are vital in minimizing the time to market. Half-lives of initiators were determined for free-radical reactions under different conditions, and extents of degradation of compounds in the environment could be estimated. Significantly, the technology also enabled early recognition of optimal conditions or the establishment of equilibria even when yields or conversions were not quantitative.

Conditions were optimized for many reactions and reaction types (Table 1). The software was successfully applied to many literature reactions performed by others, under various conditions, not necessarily involving mi-

**Table 1. Examples of Estimated Conditions for Specific Conversions, the Corresponding Experimental Results, and Reaction Type**

entry <sup>a</sup>	reference data (temperature, conversion, and time <sup>b</sup> )	translated conditions	desired conversion (%)	first iteration (%)	second iteration (%)	reaction type
1 <sup>c</sup>	86 °C, 60%, 73 min <sup>d</sup> 170 °C, 98%, 4.9 min <sup>f</sup>	170 °C, 4.9 min	90	98 <sup>e</sup>		esterification
2 <sup>c</sup>	130 °C, 20%, 21 min <sup>d</sup>	150 °C, 98 min	90	93 <sup>e</sup>	91 <sup>g</sup>	addition
3 <sup>c</sup>	78 °C, 20%, 18 min <sup>d</sup>	150 °C, 4.0 min	80	82 <sup>e</sup>		cyclization
4 <sup>c</sup>	140 °C, 57%, 10.0 min <sup>d</sup> 170 °C, 70%, 8.0 min <sup>f</sup>	170 °C, 8.0 min	90	70 <sup>e</sup>		
5 <sup>c</sup>	150 °C, 91%, 71 min <sup>d</sup>	170 °C, 15 min	90		84 <sup>g</sup>	anhydride formation
6 <sup>31</sup>	150 °C, 91%, 71 min <sup>d</sup> 90 °C, 35%, 14.5 min <sup>d</sup> 110 °C, 83%, 16 min <sup>f</sup>	78 °C, 1740 min 110 °C, 16 min 110 °C, 21 min	91 90 90	90 <sup>e</sup> 83 <sup>e</sup>	90 <sup>g</sup>	transesterification esterification
7 <sup>32</sup>	138 °C, 20%, 132 min <sup>d</sup>	138 °C, 936 min	80	80 <sup>e</sup>		Friedel–Crafts alkylation
8 <sup>34</sup>	100 °C, 20%, 6.0 min <sup>d</sup>	100 °C, 68 min	90	91 <sup>e</sup>		hydrogenation
9 <sup>33</sup>	100 °C, 20%, 1.3 min <sup>d</sup>	100 °C, 14.0 min	90	91 <sup>e</sup>		Friedel–Crafts acylation
10 <sup>35</sup>	160 °C, 40%, 12.0 min <sup>d</sup> 160 °C, 84%, 62 min <sup>f</sup>	160 °C, 62 min 160 °C, 99 min	95 95	84 <sup>e</sup>	95 <sup>g</sup>	condensation
11 <sup>36</sup>	90 °C, 20%, 2.0 min <sup>d</sup> 130 °C, 67%, 4.0 min <sup>f</sup>	130 °C, 4.0 min 130 °C, 8.0 min	90 90	67 <sup>e</sup>	89 <sup>g</sup>	carbonylation-polycondensation
12 <sup>c</sup>	120 °C, 32%, 30 min <sup>d</sup>	170 °C, 24 min	90	90 <sup>e</sup>		dioxolane synthesis

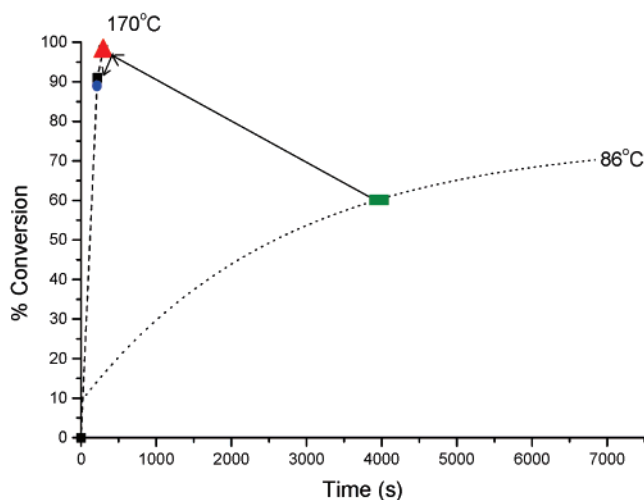
<sup>a</sup> The 12 reaction schemes shown below the table correspond with the 12 entries, respectively. <sup>b</sup> Times <15 min are quoted to one decimal place, and times >15 min are quoted to the nearest minute. <sup>c</sup> Reported for the first time. <sup>d</sup> Experimental data upon which a calculation was made. <sup>e</sup> Experimental outcome of calculated conditions (first iteration). <sup>f</sup> Experimental result from first iteration now employed as reference data for refinement (second iteration), where applicable. <sup>g</sup> Experimental outcome for second iteration, where applicable.



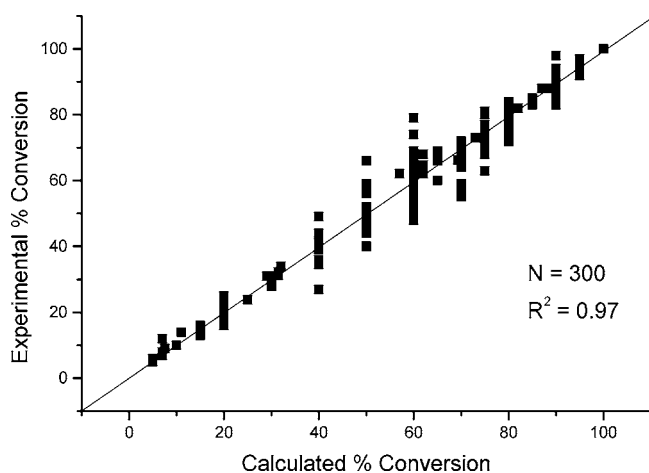
crowaves. Reactions were conducted in the presence of solvent (organic or inorganic) or solvent free, when applicable. They included homogeneous and heterogeneous systems and were catalyzed by acid, base, and metals (in solution or suspension), auto-catalyzed, uncatalyzed, and stirred at different rates. Transformations included esterification,<sup>10,11,31</sup> transesterification, amidation, imidation, etherification,<sup>16</sup> cyclization, addition, hydrolysis

of esters and amides, lactonization, ring cleavage, O-alkylation,<sup>32</sup> acylation,<sup>33</sup> hydrogenation,<sup>34</sup> condensation,<sup>35</sup> carbonylation,<sup>36</sup> and acetalization.

Proof of concept was demonstrated. This was rewarding, because the technology appeared to be counterintuitive and was instigated and developed in response to what we alone had perceived to be a highly complex and rapidly emerging problem. Already, the ability to calculate



**FIGURE 4.** Graphical representation of entry 1 in Table 1. (Green rectangle) Reference conditions: 86 °C, reaction time of 73 min, and 60% conversion (actual data point lying on a hypothetical or experimentally derived curve). (Blue circle) Desired conditions: 170 °C and 90% conversion; calculated time required, 4.9 min. (Red triangle) First iteration, 170 °C for 4.9 min gave 98% conversion. (Black square) Second iteration, 170 °C for 3.6 min gave 91% conversion.



**FIGURE 5.** Plot of anticipated (calculated) versus experimentally determined conversions based on calculated conditions for 300 reactions (second iteration).

desired conditions for anticipated yields has enhanced efficient utilization of microwave reactors, conventionally heated autoclaves, and laboratory glassware in our laboratories.

## Concluding Remarks

Through their capability for rapid, direct syntheses by the generation and control of higher temperatures, the MBR and CMR were the first major departure from traditional hardware for preparative organic chemistry. Now, other innovations such as combinatorial systems for parallel synthesis have appeared. Although most of those developments are beyond the present scope, the rate of advancement in analytical techniques no longer outstrips that for practical methods.

In our laboratory, the microwave reactors became core elements of a broad strategy toward environmentally benign organic chemistry,<sup>14b</sup> which since the 1990s, has become known as green chemistry.<sup>37</sup> Although not always so when we began, the highest priorities for the chemical industry now are process and product safety and the environment.<sup>14b</sup> Significant current issues for the industry include reducing stockpiles of chemicals and restricting the transportation of potentially hazardous substances. In that regard, miniaturization of chemical plant is advantageous, but ideally, capacity should not be adversely affected by it. The small reactors envisaged for such means of production preferably would be versatile, self-contained, readily relocatable within a chemical facility, desirably automated, and remotely operated. Capacity for throughput would need to be high, with short turn-around times brought about by rapid start-up, shut-down, and ready cleaning.

The MBR and CMR possess most if not all of the desired attributes. They have already found widespread use on the laboratory scale, particularly for drug discovery. Industrial units capable of carrying out microwave reactions on the tonne scale and operating as discussed above are now contemplated. The technology is amenable to scale-out through the application of several small systems in parallel or to scale-up with a lower number of larger systems. The range of available alternatives suggests that huge plants may not be required.<sup>23</sup>

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