1
Microwave Synthesis – An Introduction

While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, oil bath or hot plate as a source of applying heat to a chemical reaction. In the past few years, heating chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. Since the first published reports on the use of microwave irradiation to carry out organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986 [1], more than 3500 articles have been published in this fast moving and exciting field, today generally referred to as microwave-assisted organic synthesis (MAOS) [2, 3]. In many of the published examples, microwave heating has been shown to dramatically reduce reaction times, increase product yields and enhance product purities by reducing unwanted side reactions compared to conventional heating methods. The advantages of this enabling technology have, more recently, also been exploited in the context of multistep total synthesis [4] and medicinal chemistry/drug discovery [5], and have additionally penetrated related fields such as polymer synthesis [6], material sciences [7], nanotechnology [8] and biochemical processes [9]. The use of microwave irradiation in chemistry has thus become such a popular technique in the scientific community that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. The statement that, in principle, any chemical reaction that requires heat can be performed under microwave conditions has today been generally accepted as a fact by the scientific community.

The short reaction times provided by microwave synthesis make it ideal for rapid reaction scouting and optimization of reaction conditions, allowing very rapid progress through the "hypotheses–experiment–results" iterations, resulting in more decision points per unit time. In order to fully benefit from microwave synthesis one has to be prepared to fail in order to succeed. While failure could cost a few minutes, success would gain many hours or even days. The speed at which multiple variations of reaction conditions can be performed allows a morning discussion of "What should we try?" to become an after lunch discussion of "What were the results?" Not

Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments, and Protocols
C. Oliver Kappe, Doris Dallinger, and S. Shaun Murphree

ISBN: 978-3-527-32097-4

surprisingly, therefore, many scientists, both in academia and in industry, have turned to microwave synthesis as a frontline methodology for their projects.

Arguably, the breakthrough in the field of MAOS on its way from laboratory curiosity to standard practice started in the pharmaceutical industry around the year 2000. Medicinal chemists were among the first to fully realize the true power of this enabling technology. Microwave synthesis has since been shown to be an invaluable tool for medicinal chemistry and drug discovery applications since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds [5]. Many reaction parameters can therefore be evaluated in a few hours to optimize the desired chemistry. Compound libraries can then be rapidly synthesized in either a parallel or (automated) sequential format using microwave technology [5]. In addition, microwave synthesis often allows the discovery of novel reaction pathways, which serve to expand "chemical space" in general, and "biologically-relevant, medicinal chemistry space", in particular.

In the early days of microwave synthesis, experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements [1]. Kitchen microwave ovens are not designed for the rigors of laboratory usage: acids and solvents corrode the interiors quickly and there are no safety controls. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed vessel conditions. In the 1990s several groups started to experiment with solvent-free microwave chemistry (so-called dry-media reactions), which eliminated the danger of explosions [10]. Here, the reagents were pre-adsorbed onto either a more or less microwave transparent inorganic support (i.e., silica, alumina or clay) or a strongly absorbing one (i.e., graphite), that additionally may have been doped with a catalyst or reagent. Particularly in the beginning of MAOS, the solvent-free approach was very popular since it allowed the safe use of domestic microwave ovens and standard open vessel technology. While a large number of interesting transformations using dry-media reactions have been published in the literature [10], technical difficulties relating to non-uniform heating, mixing, and the precise determination of the reaction temperature remained unsolved, in particular when scale-up issues needed to be addressed.

Alternatively, microwave-assisted synthesis was, in the past, often carried out using standard organic solvents under open vessel conditions. If solvents are heated by microwave irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the reaction temperature that can be achieved. In order to nonetheless achieve high reaction rates, high-boiling microwave absorbing solvents were frequently used in open-vessel microwave synthesis [11]. However, the use of these solvents presented serious challenges during product isolation and recycling of solvent. In addition, the risks associated with the flammability of organic solvents in a microwave field and the lack of available dedicated microwave reactors allowing adequate temperature and pressure control were major concerns. The initial slow uptake of microwave technology in the late 1980s and 1990s has often been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating.

In particular, the use of kitchen microwave ovens in combination with non-reliable temperature monitoring devices led to considerable confusion in the microwave chemistry community in the late 1990s and has given MAOS a bad reputation and the stigma of a "black box" science. The majority of organic chemists at that time were not taking microwave chemistry seriously and the discussion and irritation around the topic of "microwave effects" has probably contributed to this situation [12]. Historically, since the early days of microwave synthesis, the observed rate-accelerations and sometimes altered product distributions compared to oil-bath experiments led to speculation on the existence of so-called "specific" or "non-thermal" microwave effects [13]. Such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart at the same apparent temperature. Reviewing the present literature it appears that today most scientists agree that, in the majority of cases, the reason for the observed rate enhancements is a purely thermal/kinetic effect, that is, a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field, although clearly effects that are caused by the uniqueness of the microwave dielectric heating mechanism ("specific microwave effects") must also be considered. While for the chemist in industry this discussion may seem futile, the debate on "microwave effects" is undoubtedly going to continue for many years in the academic world. Because of the recent availability of modern dedicated microwave reactors with on-line accurate monitoring of both temperature and pressure, some of the initial confusion on microwave effects has subsided. This can also be attributed, to some extent, to the fact that microwave synthesis today is mostly carried out in solution phase using organic solvents, where the temperature of the reaction mixture can generally be adequately monitored.

Controlled MAOS in sealed vessels using standard solvents – a technique pioneered by Strauss in the mid 1990s [14] – has thus celebrated a steady comeback since the year 2000 and today clearly is the method of choice for performing microwave-assisted reactions. This is evident from surveying the recently published literature in the area of microwave-assisted organic synthesis (Figure 1.1). In addition to the primary and patent literature, many review articles [3–19], several books [2], special issues of journals [20], feature articles [21], online databases [22], information on the world-wide-web [23], and educational publications [24, 25] provide extensive coverage of the subject. Among the about 850 original publications that appeared in 2007 describing microwave-assisted reactions under controlled conditions, a careful analysis demonstrates that in about 90% of all cases sealed vessel processing (autoclave technology) in dedicated single-mode microwave instruments has been employed. A recent survey has, however, found that as many as 30% of all published MAOS papers still employ kitchen microwave ovens [26], a practice banned by most of the respected scientific journals today. For example, the American Chemical Society (ACS) organic chemistry journals will typically not consider manuscripts describing the use of kitchen microwave ovens or the absence of a reaction temperature, as specified in the relevant publication guidelines [27].

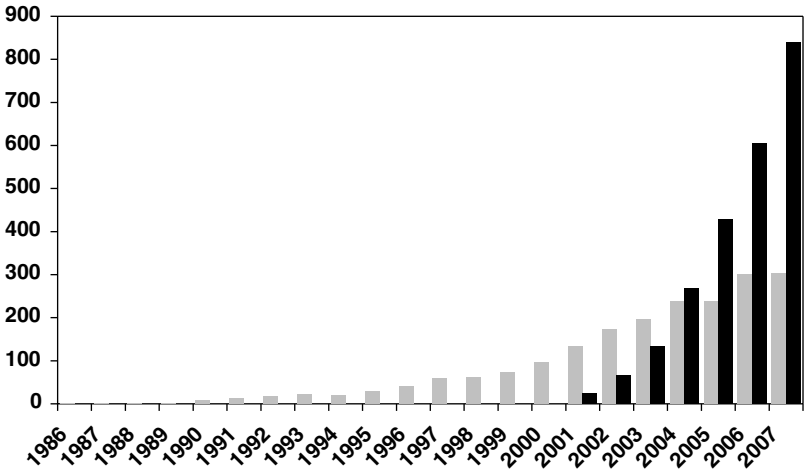

Figure 1.1 Publications on microwave-assisted organic synthesis (1986–2007). Gray bars: Number of articles involving MAOS for seven selected synthetic organic chemistry journals (*J. Org. Chem., Org. Lett., Tetrahedron, Tetrahedron Lett., Synth. Commun., Synthesis, Synlett*. SciFinder Scholar keyword search on "microwave"). The black bars represent the number of publications (2001–2007) reporting MAOS experiments in dedicated reactors with adequate process control (about 50 journals, full text search: microwave). Only those articles dealing with synthetic organic chemistry were selected.

Recent innovations in microwave reactor technology now allow controlled parallel and automated sequential processing under sealed vessel conditions, and the use of continuous or stop-flow reactors for scale-up purposes. In addition, dedicated vessels for solid-phase synthesis, for performing transformations using pre-pressurized conditions and for a variety of other special applications, have been developed. Today there are four major instrument vendors that produce microwave instrumentation dedicated to organic synthesis. All these instruments offer temperature and pressure sensors, built-in magnetic stirring, power control, software operation and sophisticated safety controls. The number of users of dedicated microwave reactors is therefore growing at a rapid rate and it appears only to be a question of time until most laboratories will be equipped with suitable microwave instrumentation.

In the past, microwave chemistry was often used only when all other options to perform a particular reaction had failed, or when exceedingly long reaction times or high temperatures were required to complete a reaction. This practice is now slowly changing and, due to the growing availability of microwave reactors in many laboratories, routine synthetic transformations are now also being carried out by microwave heating. One of the major drawbacks of this relatively new technology remains the equipment cost. While prices for dedicated microwave reactors for organic synthesis have come down considerably since their first introduction in the late 1990s, the current price range for microwave reactors is still many times higher

than that of conventional heating equipment. As with any new technology, the current situation is bound to change over the next several years and less expensive equipment should become available. By then, microwave reactors will have truly become the "Bunsen burners of the twenty first century" and will be standard equipment in every chemical laboratory.

References

1 Gedye, R., Smith, F., Westaway, K., Ali, H., Baldisera, L., Laberge, L. and Rousell, J. (1986) *Tetrahedron Letters*, **27**, 279–282; Giguere, R.J., Bray, T.L., Duncan, S.M. and Majetich, G. (1986) *Tetrahedron Letters*, **27**, 4945–4948.

2 Loupy, A.(ed.) (2002) *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim; Hayes, B.L. (2002) *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC; Lidström, P. and Tierney, J.P.(eds) (2005) *Microwave-Assisted Organic Synthesis*, Blackwell Publishing, Oxford; Kappe, C.O. and Stadler, A. (2005) *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim; Loupy, A.(ed.) (2006) *Microwaves in Organic Synthesis*, 2nd edn, Wiley-VCH, Weinheim; Larhed, M. and Olofsson, K.(eds) (2006) *Microwave Methods in Organic Synthesis*, Springer, Berlin; Van der Eycken, E. and Kappe, C.O.(eds) (2006) *Microwave-Assisted Synthesis of Heterocycles*, Springer, Berlin.

3 Abramovitch, R.A. (1991) *Organic Preparations and Procedures International*, **23**, 685–711; Caddick, S. (1995) *Tetrahedron*, **51**, 10403–10432; Lidström, P., Tierney, J., Wathey, B. and Westman, J. (2001) *Tetrahedron*, **57**, 9225–9283; Kappe, C.O. (2004) *Angewandte Chemie-International Edition*, **43**, 6250–6284; Hayes, B.L. (2004) *Aldrichimica Acta*, **37**, 66–77; Ondruschka, B. and Bonrath, W. (2006) *Chimia*, **60**, 326–329; Kappe, C.O. (2006) *Chimia*, **60**, 308–312; Kappe, C.O. (2008) *Chemical Society Reviews*, **37**, 1127–1139.

4 Baxendale, I.R., Ley, S.V., Nessi, M. and Piutti, C. (2002) *Tetrahedron*, **58**, 6285–6304; Artman, D.D., Grubbs, A.W. and Williams, R.M. (2007) *Journal of the American Chemical Society*, **129**, 6336–6342; Appukkuttan, P. and Van der Eycken, E. (2006) *Topics in Current Chemistry*, **266**, 1–47.

5 Krstenansky, J.L. and Cotterill, I. (2000) *Current Opinion in Drug Discovery & Development*, **4**, 454–461; Larhed, M. and Hallberg, A. (2001) *Drug Discovery Today*, **6**, 406–416; Wathey, B., Tierney, J., Lidström, P. and Westman, J. (2002) *Drug Discovery Today*, **7**, 373–380; Wilson, N.S. and Roth, G.P. (2002) *Current Opinion in Drug Discovery & Development*, **5**, 620–629; Dzierba, C.D. and Combs, A.P. (2002) in *Annual Reports in Medicinal Chemistry* (ed. A.M. Doherty), Academic Press, New York, Vol. 37, pp. 247–256; Al-Obeidi, F., Austin, R.E., Okonya, J.F. and Bond, D.R.S. (2003) *Mini-Reviews in Medicinal Chemistry*, **3**, 449–460; Ersmark, K., Larhed, M. and Wannberg, J. (2004) *Current Opinion in Drug Discovery & Development*, **7**, 417–427; Shipe, W.D., Wolkenberg, S.E. and Lindsley, C.W. (2005) *Drug Discovery Today: Technologies*, **2**, 155–161; Kappe, C.O. and Dallinger, D. (2006) *Nature Reviews Drug Discovery*, **5**, 51–64; Mavandadi, F. and Pilotti, A. (2006) *Drug Discovery Today*, **11**, 165–174; Wannberg, J., Ersmark, K. and Larhed, M. (2006) *Topics in Current Chemistry*, **266**, 167–198; Chighine, A., Sechi, G. and Bradley, M. (2007) *Drug Discovery Today*, **12**, 459–464; Larhed, M., Wannberg, J. and Hallberg, A. (2007) *The QSAR & Combinatorial Science*,

26, 51–68; Alcázar, J., Diels, G. and Schoentjes, B. (2007) *Mini-Reviews in Medicinal Chemistry*, **7**, 345–369; Shipe, W.D., Yang, F., Zhao, Z., Wolkenberg, S.E., Nolt, M.B. and Lindsley, C.W. (2006) *Heterocycles*, **70**, 655–689.

6 Bogdal, D., Penczek, P., Pielichowski, J. and Prociak, A. (2003) *Advances in Polymer Science*, **163**, 193–263; Wiesbrock, F., Hoogenboom, R. and Schubert, U.S. (2004) *Macromolecular Rapid Communications*, **25**, 1739–1764; Hoogenboom, R. and Schubert, U.S. (2007) *Macromolecular Rapid Communications*, **28**, 368–386; Bogdal, D. and Prociak, A. (2007) *Microwave-Enhanced Polymer Chemistry and Technology*, Blackwell Publishing, Oxford; Zhang, C., Liao, L. and Gong, S. (2007) *Green Chemistry*, **9**, 303–314; Sinwell, S. and Ritter, H. (2007) *Australian Journal of Chemistry*, **60**, 729–743.

7 Barlow, S. and Marder, S.R. (2003) *Advanced Functional Materials*, **13**, 517–518; Zhu, Y.-J., Wang, W.W., Qi, R.-J. and Hu, X.-L. (2004) *Angewandte Chemie-International Edition*, **43**, 1410–1414; Perelaer, J., de Gans, B.-J. and Schubert, U.S. (2006) *Advanced Materials*, **18**, 2101–2104; Jhung, S.H., Jin, T., Hwang, Y.K. and Chang, J.-S. (2007) *Chemistry – A European Journal*, **13**, 4410–4417; Millos, C.J., Whittaker, A.G. and Brechin, E.K. (2007) *Polyhedron*, **26**, 1927–1933.

8 Tsuji, M., Hashimoto, M., Nishizawa, Y., Kubokawa, M. and Tsuji, T. (2005) *Chemistry – A European Journal*, **11**, 440–452; Tompsett, G.A., Conner, W.C. and Yngvesson, K.S. (2006) *ChemPhysChem*, **7**, 296–319; Langa, F. and de la Cruz, P. (2007) *Combinatorial Chemistry & High Throughput Screening*, **10**, 766–782.

9 Collins, J.M. and Leadbeater, N.E. (2007) *Organic and Biomolecular Chemistry*, **5**, 1141–1150; Lill, J.R., Ingle, E.S., Liu, P.S., Pham, V. and Sandoval, W.N. (2007) *Mass Spectrometry Reviews*, **26**, 657–671; Sandoval, W.N., Pham, V., Ingle, E.S., Liu, P.S. and Lill, J.R. (2007) *Combinatorial Chemistry & High Throughput Screening*, **10**, 751–765; Rejasse, B., Lamare, S., Legoy, M.-D. and Besson, T. (2007) *Journal of Enzyme Inhibition and Medicinal Chemistry*, **22**, 518–526.

10 Loupy, A., Petit, A., Hamelin, J., Texier-Boullet, F., Jacquault, P. and Mathé, D. (1998) *Synthesis*, 1213–1234; Varma, R.S. (1999) *Green Chemistry*, **1**, 43–55; Kidawi, M. (2001) *Pure and Applied Chemistry*, **73**, 147–151; Varma, R.S. (2001) *Pure and Applied Chemistry*, **73**, 193–198; Varma, R.S. (2002) *Tetrahedron*, **58**, 1235–1255; Varma, R.S. (2002) *Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation*, Kavitha Printers, Bangalore; Varma, R.S. and Ju, Y. (2006) in *Microwaves in Organic Synthesis*, 2nd edn (ed. A. Loupy), Wiley-VCH, Weinheim, pp. 362–415 (Chapter 8); Besson, T., Thiéry, V. and Dubac, J. (2006) in *Microwaves in Organic Synthesis*, 2nd edn (ed. A. Loupy), Wiley-VCH, Weinheim, pp. 416–455 (Chapter 9).

11 Bose, A.K., Banik, B.K., Lavlinskaia, N., Jayaraman, M. and Manhas, M.S. (1997) *Chemtech*, **27**, 18–24; Bose, A.K., Manhas, M.S., Ganguly, S.N., Sharma, A.H. and Banik, B.K. (2002) *Synthesis*, 1578–1591.

12 Kuhnert, N. (2002) *Angewandte Chemie-International Edition*, **41**, 1863–1866; Strauss, C.R. (2002) *Angewandte Chemie-International Edition*, **41**, 3589–3591.

13 Perreux, L. and Loupy, A. (2001) *Tetrahedron*, **57**, 9199–9223; Perreux, L. and Loupy, A. (2002) in *Microwaves in Organic Synthesis* (ed. A. Loupy), Wiley-VCH, Weinheim, pp. 61–114 (Chapter 3); de La Hoz, A., Diaz-Ortiz, A. and Moreno, A. (2004) *Current Organic Chemistry*, **8**, 903–918; Perreux, L. and Loupy, A. (2006) in *Microwaves in Organic Synthesis*, 2nd edn (ed. A. Loupy), Wiley-VCH, Weinheim, pp. 134–218 (Chapter 4); Loupy, A. and Varma, R.S. (2006) *Chimica Oggi-Chemistry Today*, **24** (3), 36–39; de La Hoz, A., Díaz-Ortiz, A. and Moreno, A. (2005) *Chemical Society Reviews*, **34**,

164–178; de La Hoz, A., Díaz-Ortiz, A. and Moreno, A. (2005) *Advances in Organic Synthesis*, **1**, 119–171; de La Hoz, A., Díaz-Ortiz, A. and Moreno, A. (2006) in *Microwaves in Organic Synthesis*, 2nd edn (ed. A. Loupy), Wiley-VCH, Weinheim, pp. 219–277 (Chapter 5).

14 Strauss, C.R. and Trainor, R.W. (1995) *Australian Journal of Chemistry*, **48**, 1665–1692; Strauss, C.R. (1999) *Australian Journal of Chemistry*, **52**, 83–96; Strauss, C.R. (2002) in *Microwaves in Organic Synthesis* (ed. A. Loupy), Wiley-VCH, Weinheim, pp. 35–60 (Chapter 2); Roberts, B.A. and Strauss, C.R. (2005) *Accounts of Chemical Research*, **38**, 653–661.

15 For more technical reviews, see: Nüchter, M., Müller, U., Ondruschka, B., Tied, A. and Lautenschläger, W. (2003) *Chemical Engineering & Technology*, **26**, 1207–1216; Nüchter, M., Ondruschka, B., Bonrath, W. and Gum, A. (2004) *Green Chemistry*, **6**, 128–141; Nüchter, M., Ondruschka, B., Weiß, D., Bonrath, W. and Gum, A. (2005) *Chemical Engineering & Technology*, **28**, 871–881; Kremsner, J.M., Stadler, A. and Kappe, C.O. (2006) *Topics in Current Chemistry*, **266**, 233–278; Kirschning, A., Solodenko, W. and Mennecke, K. (2006) *Chemistry – A European Journal*, **12**, 5972–5990; Stankiewicz, A. (2006) *Chemical Engineering Research & Design*, **84**, 511–521; Schwalbe, T. and Simons, K. (2006) *Chimica Oggi-Chemistry Today*, **24** (3), 56–61; Baxendale, I.R. and Pitts, M.R. (2006) *Chimica Oggi-Chemistry Today*, **24** (3), 41–45; Leveque, J.-M. and Cravotto, G. (2006) *Chimia*, **60**, 313–320; Glasnov, T.N. and Kappe, C.O. (2007) *Macromolecular Rapid Communications*, **28**, 395–410; Cravotto, G. and Cintas, P. (2007) *Chemistry – A European Journal*, **13**, 1902–1909; Petricci, E. and Taddei, M. (2007) *Chimica Oggi-Chemistry Today*, **25**, 40–45; Matloobi, M. and Kappe, C.O. (2007) *Chimica Oggi-Chemistry Today*, **25**, 26–31; Kappe, C.O. and Matloobi, M. (2007) *Combinatorial Chemistry & High Throughput Screening*, **10**, 735–750; Baxendale, I.R., Hayward, J.J. and Ley, S.L. (2007) *Combinatorial Chemistry & High Throughput Screening*, **10**, 802–836.

16 **Organic synthesis:** de la Hoz, A., Díaz-Ortiz, A., Moreno, A. and Langa, F. (2000) *European Journal of Organic Chemistry*, 3659–3673; Larhed, M., Moberg, C. and Hallberg, A. (2002) *Accounts of Chemical Research*, **35**, 717–727; Corsaro, A., Chiacchio, U., Pistara, V. and Romeo, G. (2004) *Current Organic Chemistry*, **8**, 511–538; Xu, Y. and Guo, Q.-X. (2004) *Heterocycles*, **63**, 903–974; Romanova, N.N., Gravis, A.G. and Zyk, N.V. (2005) *Russian Chemical Reviews*, **74**, 969–1013; de la Hoz, A., Díaz-Ortiz, A. and Moreno, A. (2005) *Advances in Organic Synthesis*, **1**, 119–171; Rakhmankulov, D.L., Shavshukova, S.Yu. and Latypova, F.N. (2005) *Chemistry of Heterocyclic Compounds*, **41**, 951–961; Kuznetsov, D.V., Raev, V.A., Kuranov, G.L., Arapov, O.V. and Kostikov, R.R. (2005) *Russian Journal of Organic Chemistry*, **41**, 1719–1749; Molteni, V. and Ellis, D.A. (2005) *Current Organic Synthesis*, **2**, 333–375; Leadbeater, N.E. (2005) *Chemical Communications*, **23**, 2881–2902;Bougrin, K., Loupy, A. and Soufiaoui, M. (2005) *Journal of Photochemistry and Photobiology C: Photochemistry Reviews*, **6**, 139–167; Strauss, C.R. and Varma, R.S. (2006) *Topics in Current Chemistry*, **266**, 199–231; Nilsson, P., Olofsson, K. and Larhed, M. (2006) *Topics in Current Chemistry*, **266**, 103–144; Suna, E. and Mutule, I. (2006) *Topics in Current Chemistry*, **266**, 49–101; Zhang, W. (2006) *Topics in Current Chemistry*, **266**, 145–166; Dallinger, D. and Kappe, C.O. (2007) *Chemical Reviews*, **107**, 2563–2591; Appukkuttan, P. and Van der Eycken, E. (2008) *European Journal of Organic Chemistry*, 1133–1155; Coquerel, Y. and Rodriguez, J. (2008) *European Journal of Organic Chemistry*, 1125–1132; Polshettiwar, V. and Varma, R.S. (2008) *Accounts of Chemical Research*, **41**, 629–639.

17 **Radiochemistry:** Elander, N., Jones, J.R., Lu, S.-Y. and Stone-Elander, S. (2000)

Chemical Society Reviews, **29**, 239–250; Stone-Elander, S. and Elander, N. (2002) *Journal of Labelled Compounds & Radiopharmaceu-ticals*, **45**, 715–746; Stone-Elander, S., Elander, N., Thorell, J.-O. and Fredriksson, A. (2007) *Ernst Schering Research Foundation Workshop*, **62**, pp. 243–269.

18 **Combinatorial chemistry**: Kappe, C.O. (2002) *Current Opinion in Chemical Biology*, **6**, 314–320; Lew, A., Krutznik, P.O., Hart, M.E. and Chamberlin, A.R. (2002) *Journal of Combinatorial Chemistry*, **4**, 95–105; Lidström, P., Westman, J. and Lewis, A. (2002) *Combinatorial Chemistry & High Throughput Screening*, **5**, 441–458; Blackwell, H.E. (2003) *Organic and Biomolecular Chemistry*, **1**, 1251–1255; Swamy, K.M.K., Yeh, W.-B., Lin, M.-J. and Sun, C.-M. (2003) *Current Medicinal Chemistry*, **10**, 2403–2423; Desai, B. and Kappe, C.O. (2004) *Topics in Current Chemistry*, **242**, 177–208; Santagada, V., Frecentese, F., Perissutti, E., Favretto, L. and Caliendo, G. (2004) *The QSAR & Combinatorial Science*, **23**, 919–944; Bhattacharyya, S. (2005) *Molecular Diversity*, **9**, 253–257; Lange, T. and Lindell, S. (2005) *Combinatorial Chemistry & High Throughput Screening*, **8**, 595–606; Martinez-Palou, R. (2006) *Molecular Diversity*, **10**, 435–462.

19 **Dielectric heating:** Gabriel, C., Gabriel, S., Grant, E.H., Halstead, B.S. and Mingos, D.M.P. (1998) *Chemical Society Reviews*, **27**, 213–224; Mingos, D.M.P. and Baghurst, D.R. (1991) *Chemical Society Reviews*, **20**, 1–47; Leadbeater, N.E., Torenius, H.M. and Tye, H. (2004) *Combinatorial Chemistry & High Throughput Screening*, **7**, 511–528; Habermann, J., Ponzi, S. and Ley, S.V. (2005) *Mini-Reviews in Organic Chemistry*, **2**, 125–137.

20 Kappe, C.O.(ed.) (2003) Microwaves in Combinatorial and High-Throughput Synthesis (a special issue). *Molecular Diversity*, **7**, 95–307; Van der Eycken, E. and Van der Eycken, J.(eds) (2004) Microwaves in Combinatorial and High-Throughput Synthesis, (a special issue). *The QSAR & Combinatorial Science*, **23** (10), 823–986; Leadbeater, N.E.(ed.) (2006) Microwave-Assisted Synthesis (a special issue). *Tetrahedron*, **62** (19), 4623–4732; de la Hoz, A. and Díaz-Ortiz, A.(eds) (2007) The Use of Microwaves in High Throughput Synthesis (a special issue). *Combinatorial Chemistry and High Throughput Screening*, **10** (9/10), 773–934.

21 Stinson, S. (1996) *Chemical & Engineering News*, **74**, 45–46; Dagani, R. (1997) *Chemical & Engineering News*, **75**, 26–33; Whittaker, G. (1998) *New Scientist*, **2123**, 34; Cresswell, S.L. and Haswell, S.J. (1999) *Chemistry & Industry*, 621–624; Edwards, P. (2001) *Drug Discovery Today*, **6**, 614; Cresswell, S.L. and Haswell, S.J. (2001) *Journal of Chemical Education*, **78**, 900–904; Dutton, G. (2002) *Genetic Engineering News*, **22**, 13–17;Watkins, K.J. (2002) *Chemical & Engineering News*, **80** (6), 17–18; Adam, D. (2003) *Nature*, **421**, 571–572; Leadbeater, N.E. (2004) *Chemistry World*, **1**, 38–41; Minkel, J.R. (2004) *Drug Discovery & Development*, **7**(3), 47–52; Marx, V. (2004) *Chemical & Engineering News*, **82** (50), 14–19; Yarnell, A. (2007) *Chemical & Engineering News*, **85** (21), 32–33.

22 Biotage Pathfinder Database (http://www.biotagepathfinder.com); Microwave-Assisted Organic Synthesis Database (http://www.mwchemdb.com); Microwave Chemistry Literature Highlights (http://www.organic-chemistry.org/Highlights/microwave.shtm).

23 Websites on microwave synthesis: http://www.maos.net; http://microwavesynthesis.net.

24 Katritzky, A.R., Cai, C., Collins, M.D., Scriven, E.F.V., Singh, S.K. and Barnhardt, E.K. (2006) *Journal of Chemical Education*, **83**, 634–636; Murphree, S.S. and Kappe, C.O. (2008) *Journal of Chemical Education*, **85**, in press.

25 McGowan, C. and Leadbeater, N.E. (2006) *Clean, Fast Organic Chemistry: Microwave-*

Assisted Laboratory Experiments, CEM Publishing, Matthews, NC; Bogdal, D. (2005) *Microwave-assisted Organic Synthesis One Hundred Reaction Procedures*, Elsevier, Oxford.

26 Moseley, J.D., Lenden, P., Thomson, A.D. and Gilday, J.P. (2007) *Tetrahedron Letters*, **48**, 6084–6087 (Ref. 13).

27 *Journal of Organic Chemistry*, 73, 2008 Issue 1.