Microwave dielectric heating in synthetic organic chemistry

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First described more than two decades ago, microwave-assisted organic synthesis has matured from a laboratory curiosity to an established technique that today is heavily used in both academia and industry. One of the most valuable advantages of using controlled microwave dielectric heating for chemical synthesis is the dramatic reduction in reaction times: from days and hours to minutes and seconds. As will be explained in this *tutorial review*, there are many more good reasons why organic chemists are nowadays incorporating dedicated microwave reactors into their daily work routine.

1. Introduction. Microwave theory

In an ideal world, chemical transformations occur at room temperature, reach full conversion within a few minutes, and provide quantitative isolated product yields. The reality, however, is quite different. Many synthetically relevant processes necessitate an elevated temperature regime in order to proceed, with reaction times of several hours or even days to drive a reaction to completion not being uncommon. Until recently, heating reaction mixtures on a laboratory scale was typically performed using isomantles, oil baths or hot plates applying a reflux set-up where the reaction temperature is controlled by the boiling point of the solvent. This traditional form of heating is a rather slow and inefficient method for transferring energy into a reaction mixture, since it depends on convection currents and on the thermal conductivity of the various materials that must be penetrated, and often results in the temperature of the reaction vessel being higher than that of the reaction mixture.

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In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the molecules that are present in the reaction mixture.[1,2] Microwave irradiation triggers heating by two main mechanisms—dipolar polarization and ionic conduction. Whereas the dipoles in the reaction mixture (for example the polar solvent molecules) are involved in the dipolar polarization effect, the charged particles in a sample (usually ions) are affected by ionic conduction. When irradiated at microwave frequencies, the dipoles or ions of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss.[1–3] The ability of a specific material or solvent to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent (tan δ) and in general a reaction medium with a high tan δ at the standard operating frequency of a microwave synthesis reactor (2.45 GHz) is required for good absorption and, consequently, for efficient heating (Table 1).[1–3]

For low absorbing solvents, polar additives such as ionic liquids or passive heating elements made out of strongly microwave absorbing materials can be added to otherwise low absorbing reaction mixtures in order to increase the absorbance level of the medium.[4] Since the reaction vessels employed in microwave chemistry are made out of essentially microwave transparent materials such as glass or Teflon (tan $\delta < 0.01$), only the reaction mixture—not the reaction vessel—is heated.

The use of microwave heating in organic synthesis was introduced in 1986 by the groups of Gedye and Giguere/Majetich.[5] Although many of the early pioneering experiments in microwave-assisted synthesis have been carried out in domestic microwave ovens, the trend since the year 2001 undoubtedly is to use dedicated microwave reactors specifically designed for synthetic applications (controlled microwave synthesis).[3] These instruments feature built-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of internal fiber-optic probes or external infrared sensors, and software that enables on-line temperature/pressure control by regulation of microwave power output.[2,3]

Table 1 Loss tangents (tan δ) of selected solvents (2.45 GHz, 20 °C)[a]

Solvent	tan δ	Solvent	tan δ
Ethylene glycol	1.350	1,2-Dichloroethane	0.127
Ethanol	0.941	Water	0.123
DMSO	0.825	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
1,2-Dichlorobenzene	0.280	Tetrahydrofuran	0.047
NMP	0.275	Dichloromethane	0.042
Acetic acid	0.174	Toluene	0.040
DMF	0.161	Hexane	0.020

[a] Data from ref. 3.

Since the introduction of dedicated microwave reactors suitable for sealed vessel processing in the year 2000, more than 2500 publications have described the use of such equipment for carrying out a large variety of synthetic transformations.[2,3]

Although a variety of different microwave reactors and processing options are available today,[2,3,6] more than 90% of all currently published microwave synthesis protocols involving dedicated instruments rely on the use of so-called single-mode microwave reactors in combination with sealed vessel processing. The temperature, power, and pressure profiles for a sample of microwave-heated methanol shown in Fig. 1 illustrate the operating principles of a modern dedicated microwave reactor run in temperature control mode.

As shown in Fig. 1, sealed vessel microwave processing allows reaction mixtures to be heated very rapidly to temperatures far above the boiling point of the solvent under atmospheric conditions. Such temperature profiles may in some cases be difficult—if not impossible—to reproduce under standard thermal heating. The very rapid heating and sometimes extreme temperatures observable in microwave chemistry make it apparent that, based on applying the Arrhenius law [$k = A \exp(-E_a/RT)$], transformations that require several hours when performed in a solvent at reflux temperature may reach completion in a few minutes using superheated solvents in a sealed vessel, autoclave-type, microwave reactor.[1] The rapid heating typically experienced in microwave-assisted transformations may in some instances also lead to altered product distributions compared to a conventional oil bath reflux experiment if the reaction product distribution is controlled by complex temperature-dependent kinetic profiles.[7]

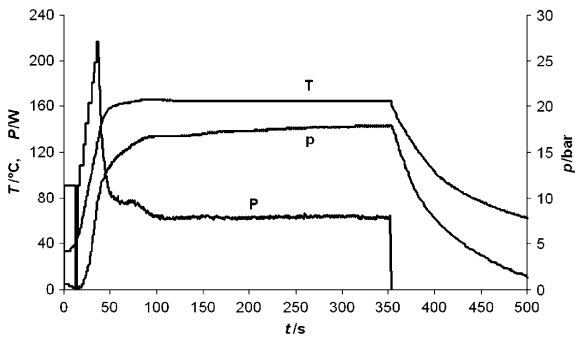


Fig. 1 Temperature (T), pressure (p), and power (P) profile for a 3 mL sample of methanol heated under sealed vessel single-mode microwave irradiation conditions to 165 °C (external infrared temperature monitoring).

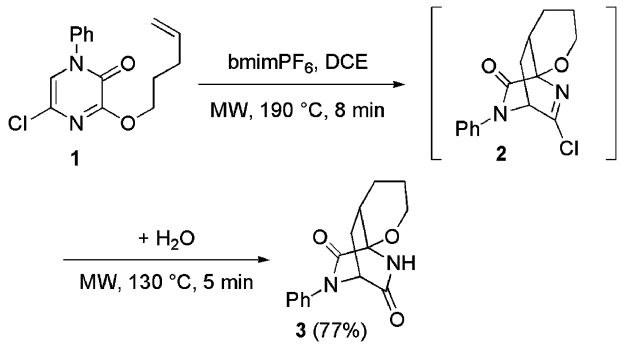
This may explain why in many cases microwave-assisted reactions performed at an optimized reaction temperature have been found to be cleaner, leading to fewer by-products compared to the conventionally heated processes carried out at the (often non-optimal) reflux temperature of the solvent.

Since the early days of microwave synthesis, the observed rate-accelerations and sometimes altered product distributions compared to oil-bath experiments have led to speculations on the existence of so-called "specific" or "non-thermal" microwave effects.[2,8] Such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart *at the same measured reaction temperature*. In the majority of published cases, however, the reasons for the observed rate enhancements and altered product distributions can probably be rationalized based on purely thermal/kinetic effects being the consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field (Fig. 1).[7,9] Despite the controversy on microwave effects, the many advantages of utilizing controlled microwave heating for synthetic purposes are nowadays undisputed and have not only been exploited in organic synthesis[2,3,6] but have also penetrated the medicinal chemistry/drug discovery field.[10] In fact, the use of microwave technology in chemistry has 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 aim of this tutorial review is to provide the reader with a basic understanding and "feeling" for the advantages of microwave technology in organic synthesis. Due to space limitations only selected examples highlighting the potential and unique capabilities of microwave-assisted organic synthesis can be given. For more extensive coverage of the subject, the reader is referred to other recent books and review articles.[2,3,6]

2. Basic concepts in microwave synthesis

2.1 Reducing reaction times: from hours to minutes

In traditional organic synthesis using reflux conditions the boiling point of the solvent controls the reaction temperature. If a high reaction temperature is required in order for a reaction to proceed, a solvent with a high boiling point must therefore be selected which may be difficult to remove during work-up and purification. In contrast, using sealed vessel microwave heating, the boiling point of the solvent is less important since the solvent can be superheated above its regular boiling point under atmospheric conditions (Fig. 1). Applying microwave chemistry, it is the dielectric properties of the solvent that need to be considered in order to maximize microwave dielectric heating effects. The effect of temperature on the rate of a reaction and the importance of choosing the proper solvent in a microwave-heated transformation is highlighted in the cycloaddition example shown in Scheme 1.[11] Under conventional reflux conditions using chlorobenzene as solvent (bp 132 °C), the intramolecular hetero-Diels–Alder reaction of alkenyl-tethered pyrazinone **1** requires *ca.* one day for completion. Since there is no need to use a high

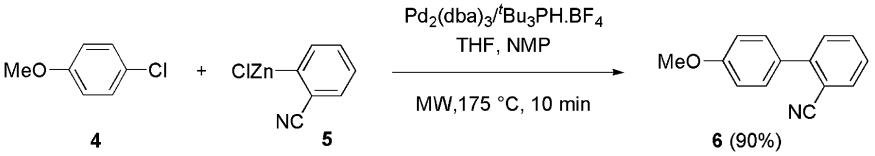


Scheme 1 Intramolecular Diels–Alder cycloaddition in ionic liquid-doped solvents.

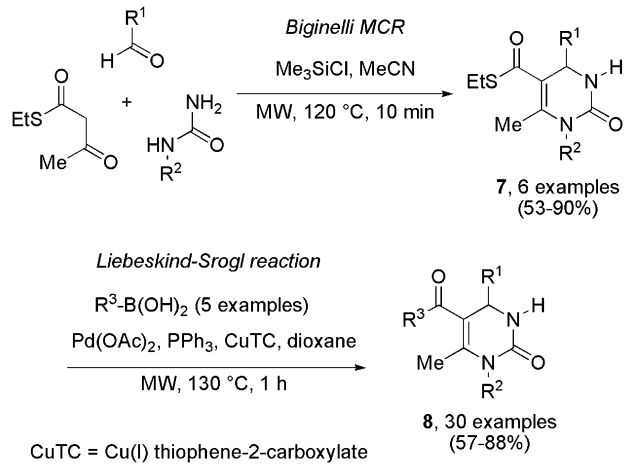
boiling solvent using a sealed vessel microwave approach, the solvent was initially changed to pure 1,2-dichloroethane (DCE, bp 83 °C). DCE is not a very strongly microwave absorbing solvent as compared to for example methanol (see Table 1) and therefore the temperature of the reaction mixture upon microwave heating could only be raised to a maximum of 170 °C, requiring several minutes to reach the ceiling temperature. Under these conditions the intramolecular hetero-Diels–Alder reaction leading to the primary cycloadduct **2** required *ca.* one hour for completion.[11] In order to further increase the reaction temperature and therefore to reduce the reaction time, the solvent system was modified by addition of a small amount of a strongly microwave absorbing ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate, bmimPF_6). Ionic liquids interact very efficiently with microwaves through the ionic conduction mechanism (see above) and are rapidly heated at rates easily exceeding 10 °C per second.[2,6] By adding a small amount of bmimPF_6 as a "doping agent", the dielectric properties of the reaction mixture were effectively tuned so that rapid heating—within less than one minute—to 190 °C became possible, leading to an internal pressure of *ca.* 11 bar in the microwave vessel. Under these conditions the cycloaddition **1** → **2** was completed within 8 min. For the required hydrolysis step **2** → **3** conventional conditions call for room temperature hydrolysis in chloroform in an open atmosphere for 18 h.[11] Using sealed vessel microwave heating the hydrolysis was achieved within 5 min by simply adding a small amount of water through the septum of the microwave vessel and resubjection of the reaction mixture to microwave heating at 130 °C. The overall reaction time for this two step process was therefore reduced from two days to 13 min (!) providing a nearly identical isolated product yield to that reported using conventional conditions.[11] This example clearly demonstrates the usefulness of "microwave flash heating" in reducing reaction times by rapidly increasing the reaction temperature to a level typically not attainable under reflux conditions.

Another example where the reaction time of a known transformation was significantly reduced using microwave heating technology is shown in Scheme 2. The Negishi cross-coupling of unactivated aryl chloride **4** with a sterically demanding *o*-cyano organozinc chloride (**5**) utilizing 2 mol% of a reactive Pd catalyst in a THF–NMP solvent mixture was reported to require 24 h at 100 °C in a sealed vessel to reach completion. Keeping the reaction conditions more or less identical, but using rapid microwave heating at a substantially higher temperature (175 °C), the reaction time for the preparation of biaryl **6** could be reduced to 10 min.[12] Since NMP is a strongly microwave absorbing solvent (Table 1), the use of an additive was not necessary in this case. A larger number of successful microwave-assisted transition metal-catalyzed C–C and C–N bond forming reactions have been reported in the recent literature.[13] It should be mentioned that under sealed vessel conditions many of these rapid transition metal-catalyzed transformations can be performed without an inert atmosphere. In addition, because of the direct heating of the reaction mixture rather than of the reaction vessel, the lifetime of the metal catalysts can sometimes be increased through the minimization of wall effects.[13]

The fact that microwave-assisted reactions are typically very fast can be additionally exploited in a variety of different ways that are either related to reaction optimization or to the production of compound libraries. In this context, the use of single-mode microwave reactors with incorporated robotic vial transfer is nowadays a very common procedure, which is typically employed when a compound series has to be prepared unattended (library synthesis), or when a range of reaction conditions need to be screened and optimized efficiently.[10,14] If reaction times are within minutes, an automated sequential microwave technique often becomes as efficient as a parallel reaction set-up if a limited number of compounds need to be prepared. In Scheme 3 the preparation of a small collection of dihydropyrimidine derivatives **7** using a Biginelli multicomponent reaction (MCR) is described.[15] Because of the short reaction times under microwave conditions compared to traditional reflux heating (here 10 min *versus* 4–6 h) more reaction parameters such as solvent/catalyst type and quantity, molar ratio of building blocks, reagent concentration and temperature can be optimized in the same time period.[14,15] This significantly speeds up the overall time required for reaction optimization, in particular when the process is combined with a statistic-based approach ("Design of Experiment") which can readily gauge interaction effects between the limiting factors of a reaction.[16] In the example shown in Scheme 3 the six dihydropyrimidine derivatives of type **7** obtained in the initial multicomponent step were subsequently cross-coupled with five boronic acids using Pd-catalyzed Liebeskind–Srogl C–C bond forming



Scheme 2 High-speed Negishi couplings using Pd catalysis.



Scheme 3 Synthesis of dihydropyrimidine compound libraries in automated sequential and parallel formats.

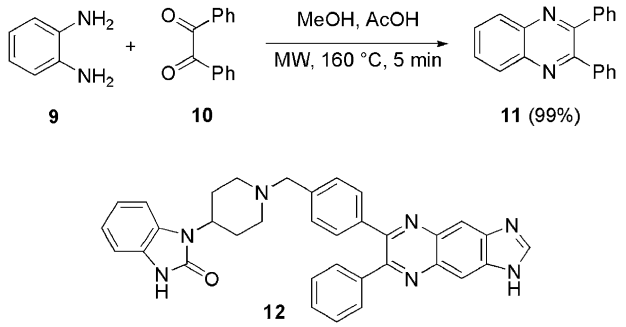
conditions.[15] This generated a library of 30 5-aroyl-dihydropyrimidines of type **8**.

In this context it should be emphasized that not all microwave-assisted reactions proceed to completion within five or ten minutes. In the case of the Liebeskind–Srogl coupling **7** → **8**, for example, a reaction time of one hour at 130 °C was required to achieve full conversion and high isolated product yields. The synthesis of a library of thirty compounds using automated sequential processing therefore needed 30 h of processing time.[15] While automated sequential microwave synthesis has been a very successful concept for the construction of small compound libraries,[10,14] this method may become impractical if one considers the generation of larger compound collections since the timesaving aspect of high-speed microwave synthesis is diminished by having to irradiate each reaction mixture individually. In case of the Liebeskind–Srogl reaction, the same dihydropyrimidine library **8** could also be synthesized in a parallel microwave fashion producing similar individual product yields in one single irradiation experiment employing a larger microwave reactor in combination with a multivessel rotor system.[15] Parallel microwave synthesis under controlled conditions can be carried out in a variety of formats, including the use of microtiter plates allowing the simultaneous processing of 200 or more individual microwave reactions.[17]

While short reaction times are generally considered as a valuable—but not essential—feature in organic chemistry, they are an indispensable requirement for the synthesis of short-lived radiolabelled (for example ^{11}C, ^{18}F) substances used in the field of positron emission tomography (PET). Several research groups have exploited high-speed microwave chemistry for the synthesis of a variety of different radiotracer materials.[2]

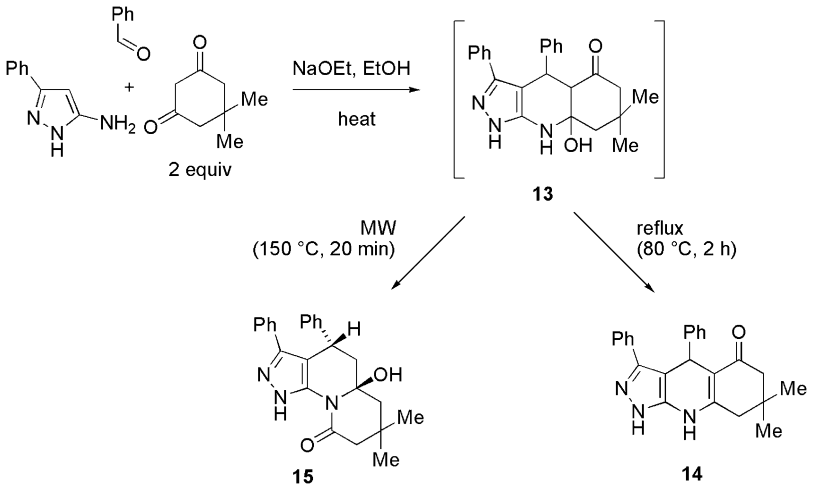
2.2 Improving yields and influencing selectivities

Microwave-assisted reactions are generally performed at substantially higher reaction temperatures as compared to conventional reflux experiments. This can lead to several different effects apart from the expected increase in reaction speed (see section 2.1). Since microwave reactions are typically performed at a carefully optimized reaction temperature for the desired reaction pathway, in many instances cleaner transformations, leading to fewer by-products compared to conventionally heated processes will be experienced.[7] Combined with the rapid heating and cooling (Fig. 1) and the minimization of wall effects due to the direct "in core" heating, these beneficial effects can be quite substantial, and cases where yields have increased dramatically are not uncommon.[2,3,6] Significantly increased yields in very short reaction times, for example, were seen in the cyclocondensation of 1,2-diamine **9** with 1,2-diketone **10** leading to quinoxaline **11** (Scheme 4).[18] Optimized reaction conditions involved sealed-vessel microwave heating of an equimolar mixture of the diamine and diketone component for 5 min at 160 °C in a 9 : 1 methanol–acetic acid solvent mixture. While the microwave protocol resulted in a quantitative isolated yield of the quinoxaline product, conventional oil-bath reflux processing under similar conditions led to moderate yields (32–85%) and required extended reaction times (2–12 h). Importantly, incorporating functionality into either of the reaction partners led to dramatic variations in reaction time and yield using conventional reflux processing. In contrast, the microwave protocol shown in Scheme 4 proved to be robust allowing the preparation of several hundred quinoxaline and related heterocyclic products in very high yields (>90%).[10,18] Based on the highly efficient microwave-assisted 2,3-diphenylquinoxaline synthesis a series of potent and selective kinase inhibitors were developed in a drug discovery project (*e.g.* lead structure **12**).[10] It should be pointed out that low to moderate yields for a specific chemical transformation may often be acceptable if only a single compound has to be synthesized. However, for the generation of a collection of several hundred compounds a general applicable and high-yielding method is typically required in order to avoid time-consuming and costly isolation and purification issues. This is precisely what makes microwave synthesis such a popular and powerful tool in the drug discovery industry, with many successful case studies having been reported.[10]



Scheme 4 Improved synthesis of 2,3-diphenylquinoxalines.

Since microwave-heated reactions are often performed in a comparatively high temperature regime, altered product distributions and selectivities as compared to a conventionally heated experiment will sometimes be experienced. In the multicomponent condensation of 5-aminopyrazoles, aromatic aldehydes and cyclic 1,3-diketones under strongly basic conditions shown in Scheme 5, a change in the reaction pathway was observed comparing the experiment carried out at the

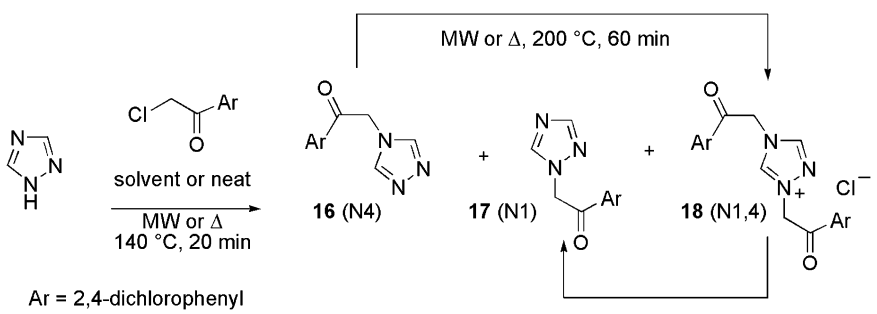


Scheme 5 Altered product distributions in multicomponent reactions.

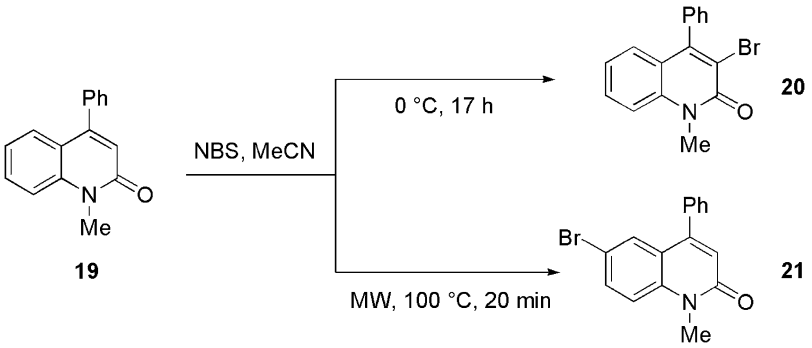
reflux temperature of the solvent (80 °C, 6 h) with the sealed-vessel microwave experiment at 150 °C.[19] While the condensation reaction at reflux temperature provided mostly the known tricyclic Hantzsch-type dihydropyridine derivative **14**, the microwave experiment performed at 150 °C favored an alternative reaction pathway that involved base-mediated ring-opening–recyclization of the cyclic 1,3-diketone moiety from the common intermediate **13**, ultimately providing pyrazolo[4,3-*c*]quinolizinone **15**.[19] This example illustrates nicely that high-temperature microwave processing can sometimes lead to unexpected products, favoring reaction pathways not seen under conventional processing at lower temperatures.

The phenacylation of 1,2,4-triazole with 2,2′,4′-trichloroacetophenone serves as an example how selectivities can be modified by temperature and also highlights the importance of proper internal temperature measurements in microwave synthesis (Scheme 6).[9] Earlier studies have suggested that the regioselectivity in the alkylation process can be influenced by the mode of heating. Employing non-polar solvents or solvent-free conditions dramatic differences between an oil bath and a microwave heated alkylation were claimed at the same monitored temperature, and therefore classified as non-thermal microwave effects.[20] For example, the alkylation at 140 °C for 20 min in xylene was reported to produce a mixture of the *N*1 (32%) (**17**), *N*4 (28%) (**16**) and *N*1,4-bisalkylated triazoles (40%) (**18**) applying conventional heating.[20] In contrast, employing single-mode microwave irradiation at the same measured temperature of 140 °C was claimed to yield exclusively the *N*1 isomer.[20] A more recent reinvestigation using efficient stirring of the reaction mixture and sensitive internal temperature monitoring has proven that the differences in selectivities observed in this alkylation are simply due to thermal effects.[9] In contrast to the previously published results nearly identical mixtures of *N*1, *N*4 and *N*1,4-bisalkylated 1,2,4-triazole products **16–18** were obtained for both heating modes at a carefully controlled internal reaction temperature of 140 °C. In contrast, performing the alkylation process at higher reaction temperatures clearly favored the formation of the *N*1-alkylated triazole **17**, both in microwave and conventionally heated experiments. After 60 min at 200 °C only the *N*1-alkylated triazole **17** was observed in the crude reaction mixture.[9] Control experiments have shown that the thermodynamically more stable *N*1 isomer **17** is formed by bimolecular rearrangement from the kinetic *N*4 isomer **16** involving the quaternary triazolium salt **18** as an intermediate. In this alkylation, the strongly microwave absorbing nature of the ionic liquid-type triazolium intermediates can lead to thermal runaways in the microwave experiments that were not detected by conventional infrared temperature monitoring technology and therefore led to a misinterpretation of results.[9]

A similar example involves the bromination of quinolinone **19** with *N*-bromosuccinimide (NBS) which at room temperature provides an 83 : 17 mixture of the 3-bromo- and 6-bromo isomers **20** and **21** within 4 h (Scheme 7).[21] An increase of the reaction temperature to 50 °C led to full consumption of the starting material **19** in a considerably shorter time period, but



Scheme 6 Thermodynamic and kinetic control in the alkylation of 1,2,4-triazole.



Scheme 7 Thermodynamic and kinetic control in the bromination of quinolones.

provided an almost equimolar ratio of bromoquinolinone isomers (**20** : **21** = 55 : 45). The same temperature dependence on the regiochemistry of bromination was also seen when the brominations were carried out under microwave conditions over a wide temperature range (60–150 °C).[21] Performing the bromination at 100 °C (microwave, 20 min) allowed the selective preparation of the 6-bromoquinolinone isomer **21**, with only trace amounts of the 3-bromo isomer **20** being formed. Apparently, the higher reaction temperatures used under microwave conditions favored the formation of the thermodynamically more stable 6-bromoquinolin-2(1*H*)-one isomer, which was supported by energy calculations on both bromoquinolinones.[21] Consequently, bromination at 0 °C (17 h) led to a 92 : 8 selectivity in favor of 3-bromo-1-methyl-4-phenylquinolin-2(1*H*)-one (**20**). Selectivities in chemical transformations are quite often influenced by the reaction temperature and therefore microwave heating clearly is a valuable tool to control these selectivities. It is perhaps instructive to note that in the bromination discussed in Scheme 7 the 3-bromoquinolone isomer **20** was the required synthetic target.[21] In this instance, microwave chemistry was therefore able to speed up an otherwise slow reaction, but ultimately led to an undesired product! It should be evident, therefore, that microwave chemistry can not be the solution for every synthetic problem and will clearly "not work" in all cases.

3. Advanced microwave processing techniques

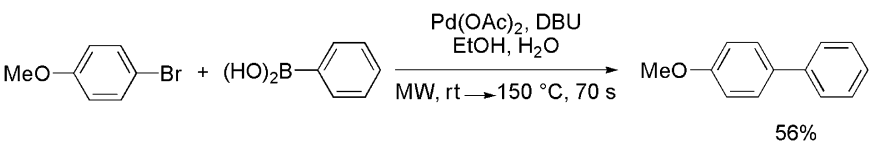
3.1 On-line reaction monitoring

One apparent disadvantage of sealed vessel microwave synthesis is that monitoring the reaction progress invariably will involve stopping the reaction allowing the superheated mixture to cool down, followed by the physical removal of the reaction vessel from the microwave reactor and subsequent standard analysis of the reaction mixture by HPLC or similar techniques. Similarly, in a closed reactor the operator is not able to visually follow the progress of the reaction as in a conventional reflux experiment. Color or viscosity changes, the formation of precipitation or the evolution of gases, the efficiency of the magnetic stirring, among other things, can therefore not easily be monitored. A recent series of publications has demonstrated that by using *in situ* Raman spectroscopy the progress of a variety of chemical transformations performed under sealed vessel microwave conditions, such as for example Suzuki cross-couplings, can be directly monitored on-line.[22] For some specific cases (Scheme 8), it has been shown that reactions are extremely fast and in fact were completed after only 70 s of microwave heating as confirmed by monitoring characteristic signals in the Raman spectrum.[22] Recent advances in single-mode microwave reactor technology do now also allow the interfacing of digital cameras into the system and therefore a visual inspection of the reaction mixture, eliminating some of the above mentioned monitoring issues.[23]

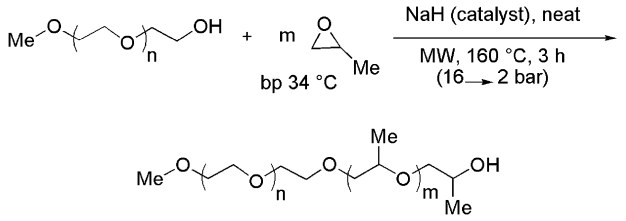
In some instances it is also possible to take advantage of the on-line pressure monitoring incorporated in modern microwave reactors. In the solvent-free anionic ring-opening polymerization of propylene oxide with polyethylene glycol monomethyl ether under basic conditions (Scheme 9), the progress of the polymerization can be conveniently followed by monitoring the reaction pressure.[24] Due to the fact that propylene oxide has a boiling point of only 34 °C, the autogenic pressure (16 bar at 160 °C) generated by this starting material at the beginning of the reaction gradually decreases with time. A pressure drop to (nearly) zero indicates full consumption of propylene oxide and thus a complete conversion.[24] Relevant information on the progress of certain types of reactions can additionally be obtained following the magnetron output power curve in temperature-controlled microwave experiments.

3.2 Open *versus* closed vessel conditions

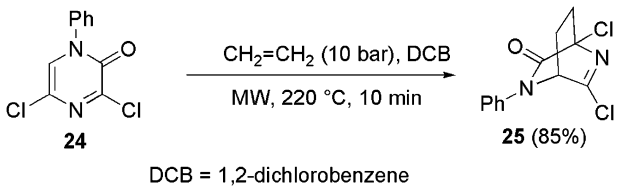
Although most microwave-assisted transformations today are carried out under sealed vessel conditions, there are a few cases where it is essential to use an open vessel set-up. Typically, in those instances one of the reaction products needs to be



Scheme 8 High-speed Suzuki cross-couplings monitored by *in situ* Raman spectroscopy.



Scheme 9 Anionic ring opening polymerization followed by on-line pressure monitoring.



Scheme 11 Diels–Alder reaction of pyrazinone **24** with ethene under pre-pressurized conditions.

removed from the reaction mixture in order to drive the equilibrium to the product. For the microwave-assisted ring-closing metathesis of diene **22**, for example, it was crucial to remove the developing ethene during the reaction in order to obtain the tricyclic product **23** in high yields (Scheme 10).[25] This was possible by passing an argon stream through the reaction solution ("gas sparging") under open vessel microwave conditions. Importantly, under standard closed-vessel microwave conditions starting material **22** was recovered almost quantitatively. Similar examples have been reported for esterification and transesterification reactions, sometimes involving preparative distillations in combination with open vessel microwave conditions.[26]

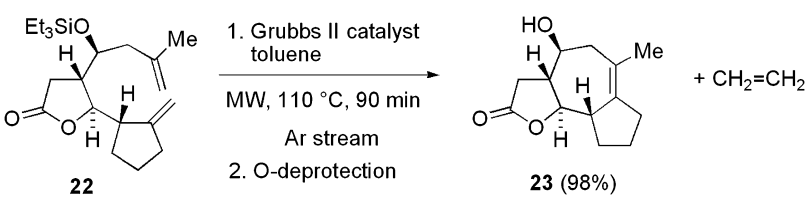
3.3 Gaseous reagents

In other cases, it can be essential to pre-pressurize a reaction vessel with a reactive gas for carrying out a microwave-assisted transformation. Although standard microwave reactors do normally not allow carrying out of autoclave reactions, equipment is now available that makes it possible to pre-pressurize the reaction vessel in a microwave reactor with reactive gases (ethylene, hydrogen, carbon monoxide, *etc*.) up to a pressure of *ca*. 20 bar prior to microwave irradiation.[6] Using conventional conditions, the Diels–Alder cycloaddition of pyrazinone heterodiene **24** with ethene to the corresponding bicyclic cycloadduct **25** has to be carried out in an autoclave at 110 °C for 12 h applying an ethene pressure of 25 bar (Scheme 11). Under standard high-temperature microwave conditions without pre-pressurization the temperature in the cycloaddition could not be increased above 190 °C (140 min) due to a competing retro-Diels–Alder fragmentation.[11] A further reduction in reaction time by increasing the reaction temperature was only possible by performing the cycloaddition in a dedicated microwave reactor after pre-pressurization of the reaction vessel with 10 bar of ethene. Under these autoclave conditions the reaction equilibrium was shifted to the cycloadduct side and a 85% product yield could be obtained within 10 min at 220 °C.[27] Microwave reactors of this type that can withstand high temperatures and pressures (300 °C, 80 bar) are particularly suitable for performing chemistry in high temperature water in the so-called near-critical region,[28] or working with supercritical solvents.[29]

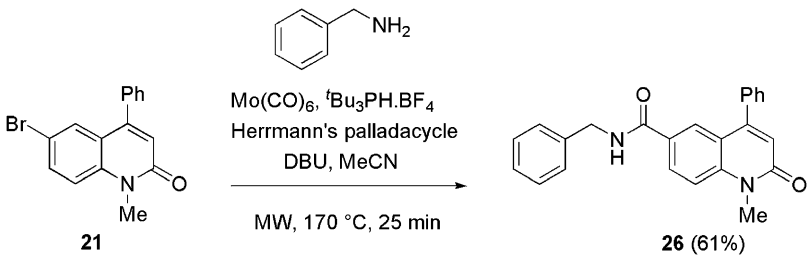
Instead of employing gaseous reagents where special equipment is necessary, an often more convenient technique is to utilize solid reagents that liberate the required gas, for example carbon monoxide, during the heating. In combination with standard sealed vessel microwave processing a partial pressure of the respective gas will be generated in the reaction tube, allowing the gas to participate in the reaction. One of these solid reagents is $Mo(CO)_6$ which is known to liberate carbon monoxide smoothly at higher temperatures. The Larhed group has developed and extensively employed $Mo(CO)_6$ as solid carbon monoxide source for a diverse range of Pd-catalyzed carbonylations (such as alkoxy- and aminocarbonylations) under microwave conditions.[30] An example of an aminocarbonylation using 6-bromoquinolone **21** as substrate is shown in Scheme 12. Employing benzylamine as amine reagent and Herrmann's palladacycle (5 mol%) in combination with Fu's salt [$(^t Bu)_3PH{\cdot}BF_4$] as a catalyst system, the anticipated quinoline-6-carboxamide **26** was obtained in 61% isolated yield after microwave heating at 170 °C for 25 min.[21]

3.4 Passive heating elements

The necessity of adjusting the dielectric properties of a reaction mixture so that efficient absorption of microwave energy and conversion into heat can take place has already been discussed above. In the cycloaddition example shown in Scheme 1 an ionic liquid was utilized as doping agent in order to raise the tan δ value of the reaction mixture (Table 1).[11] While ionic liquids have proven very valuable in modifying the dielectric properties of a low microwave-absorbing reaction medium,[2,4,6] their use is not without limitations as sometimes the ionic liquid is not temperature stable or may be incompatible with certain reaction types or sensitive functional groups. In these instances the use of so-called passive heating elements (PHE) is recommended.[4] Passive heating elements are non-invasive heating aids in the form of cylinders or stir bars made out of strongly microwave absorbing materials (for example silicon carbide or graphite-doped Teflon) that can be added to the microwave reaction vessel when low-absorbing reaction mixtures are employed. For the microwave-assisted aza-



Scheme 10 Ring-closing metathesis with concurrent removal of ethylene by gas sparging.



Scheme 12 Carbonylation chemistry using a solid source of carbon monoxide in combination with sealed vessel microwave heating.

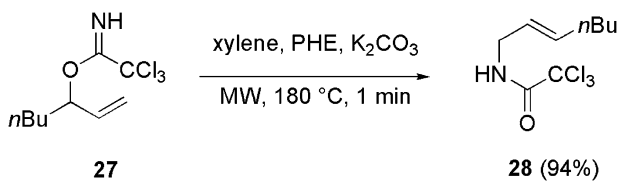
Claisen rearrangement of allylic imidate **27** to the corresponding amide **28** (Overman rearrangement) in *o*-xylene at 180 °C the use of a passive heating element was essential (Scheme 13).[31] In the absence of the PHE the low-absorbing reaction medium could not be efficiently heated to 180 °C applying microwave irradiation. Using a graphite-based PHE in combination with microwave irradiation, the Overman rearrangement **27** → **28** proceeded smoothly and the observed product yields and reaction times at 180 °C (94% in 1 min) compared very favorably with previous reports using the same solvent under conventional reflux conditions at 140 °C (2.5 h, 74% yield).[31]

3.5 Scale-up in batch and continuous flow mode

It has to be noted that with very few exceptions most examples of microwave-assisted syntheses published till date were performed on a less than 1 g scale (typically 1–5 mL reaction volume). This is in part a consequence of the popularity of the above-mentioned single-mode microwave reactors that allow processing of small reaction volumes under sealed vessel conditions. Keeping in mind some of the physical limitations of microwave dielectric heating (in particular the limited penetration depth),[1,2] continuous flow techniques where the reaction mixture is passed through a microwave-transparent flow cell positioned inside a suitable microwave reactor are gaining importance.[32] The previously optimized reaction time under batch microwave conditions now needs to be related to a ''residence time'' (the time for which the sample stays in the microwave-heated cell) at a specific flow rate. Recent advances in continuous flow processing already allow the production of kg quantities of material per day in prototype instruments.[33] Other hyphenated techniques include the combination of microwave and ultrasound processing,[34] as well as for example microwave-assisted photochemistry and electrochemistry applications.[2]

4. Selected synthetic applications

At the time of writing *ca.* 2500 references on controlled microwave-assisted organic synthesis published since 2001



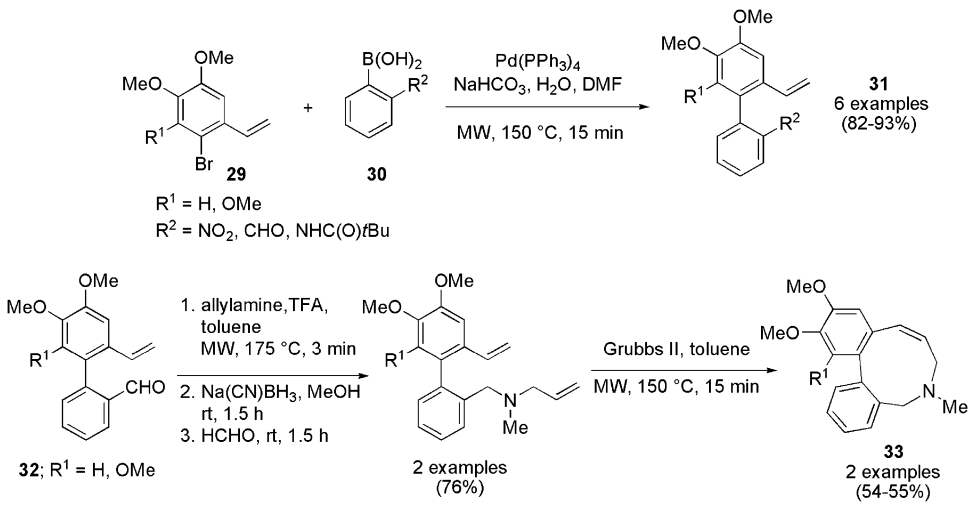
Scheme 13 Use of passive heating elements (PHE) in microwave chemistry.

can be found in the literature. The steadily growing number of articles on microwave synthesis confirm the notion that essentially any type of chemical transformation that requires heat can be carried out under microwave conditions. This does not necessarily imply that dramatic rate-enhancements compared to a classical, thermal process can be achieved in all cases, but the simple convenience of using microwave technology makes this non-classical heating method almost a ''must have'' tool in modern synthetic chemistry. In the past, microwave conditions were often used only when all other options to perform a particular reaction have failed, or when exceedingly long reaction times or high temperatures were required to complete a reaction. This practice is now 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. In this section a selection of some recently published applications are discussed with an emphasis on multistep microwave procedures.

Microwave-assisted Suzuki reactions can be performed in many different ways and have been incorporated into a variety of challenging synthetic projects.[13] The group of Van der Eycken, for example, has reported on the synthesis of *N*-shifted and ring-expanded buflavine alkaloid analogs combining microwave-assisted Suzuki couplings with ring-closing metathesis (Scheme 14).[35] Key steps toward ring-expanded buflavine analogs **33** involved initial Suzuki coupling (15 min) of highly electron rich aryl halides **29** with *ortho*-substituted boronic acids **30** followed by ring closing metathesis for the medium-sized ring construction. For the preparation of the nine-membered ring buflavine scaffolds **33**, a microwave-assisted reductive amination step (3 min) was first performed on the biaryl aldehydes **32** followed by metathesis using Grubbs second-generation catalyst (15 min).[35]

Microwave-assisted transition metal-catalyzed couplings have also been reported involving heterogeneous catalysts. In recent years the Lipshutz group has extensively studied the use of readily prepared nickel-in-charcoal (Ni/C) in carbon–carbon and carbon–heteroatom bond forming reactions.[36] In combination with microwave heating a variety of Ni-catalyzed transformations such as Negishi and Suzuki cross-couplings, as well as aminations, could be accelerated from a few hours to minutes using controlled microwave irradiation compared to conventional heating, resulting in excellent product yields (Scheme 15).[36]

A common misperception about microwave synthesis is that due to the high reaction temperatures that are often employed, this technology could not be applied to more sensitive transformations, such as for example asymmetric reactions or the



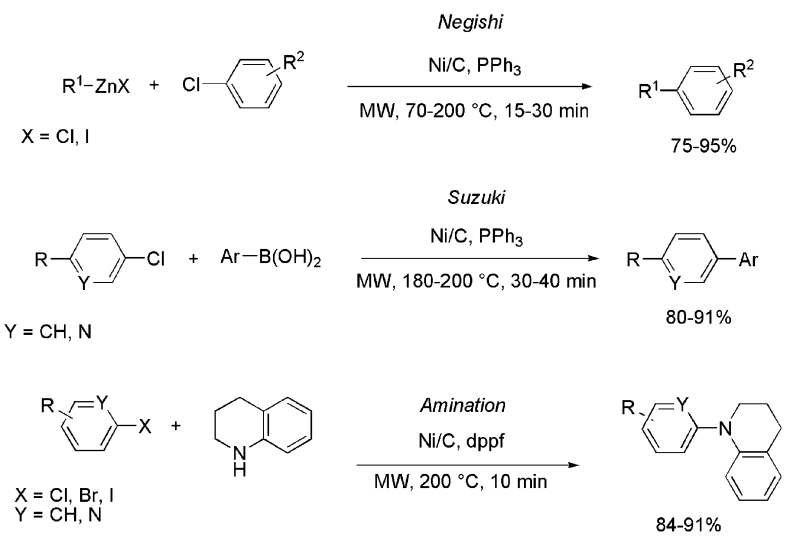
Scheme 14 Suzuki cross-coupling in combination with ring-closing metathesis for the construction of buflavine alkaloid analogs.

preparation of complex natural products possessing labile stereocenters. While comparatively few enantioselective processes under microwave conditions have been reported in the past, this number is steadily increasing.

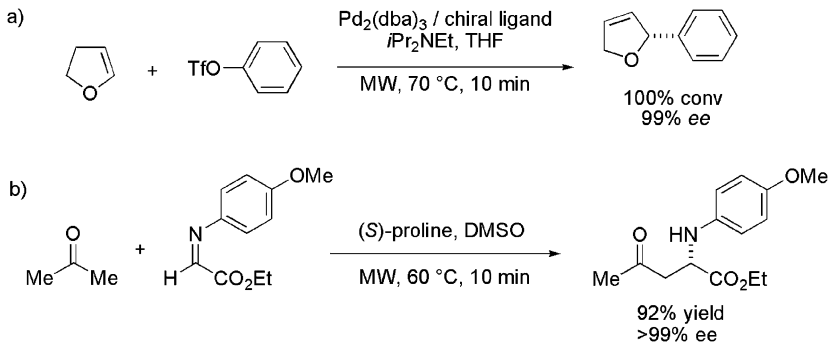
A case in point are asymmetric Heck reactions based on chiral sugar-based phosphite–oxazoline ligands.[37] Performing, for example, the Heck reaction of 2,3-dihydrofuran with phenyl triflate employing a sugar-derived ligand in combination with a Pd catalyst provided the corresponding coupled products in excellent conversion, regio- (up to 98%) and enantioselectivities (Scheme 16a). Compared to conventional heating at 50 °C (where excellent conversions, regio- and enantioselectivities were also obtained) applying microwave heating at 70 °C accelerated the reactions from up to 15 h to only 10 min.[37] Similarly, asymmetric Mannich reactions like the one shown in Scheme 16b using (*S*)-proline as chiral organocatalyst could be performed very effectively within 10 min at 60 °C using microwave heating.[38] Isolated product yields and enantioselectivities were in fact slightly higher than those reported for the corresponding reaction at room temperature lasting for 2 h.[38]

Microwave chemistry can easily be combined with other enabling technologies such as solid-phase organic synthesis, the use of polymer-supported reagents, catalyst/scavengers, or fluorous-type reactions.[2,3,6] Scheme 17 provides an example for the multi-step solid-phase synthesis of Imatinib (Gleevec), a marketed anticancer drug, reported by Carotti and coworkers.[39] By applying microwave heating in five steps of the synthesis (preparation of linker **34**, nucleophilic substitution, reduction of the nitro group, formation of guanidine and final cyclization) the overall process could be significantly accelerated. Key steps in the synthesis were the guanylation of aniline **35** where a higher yield and purity of product **36** was obtained under microwave irradiation, and the final cyclization to resin bound Imatinib where the reaction time was reduced from 20 h to 50 min using microwave heating.

Microwave heating technology has also been applied to solid-phase peptide synthesis using dedicated automated microwave peptide synthesizers.[2,6,40] Typically, the use of controlled microwave heating to *ca.* 60 °C for both the required coupling and Fmoc-deprotection cycles allows a reduction in



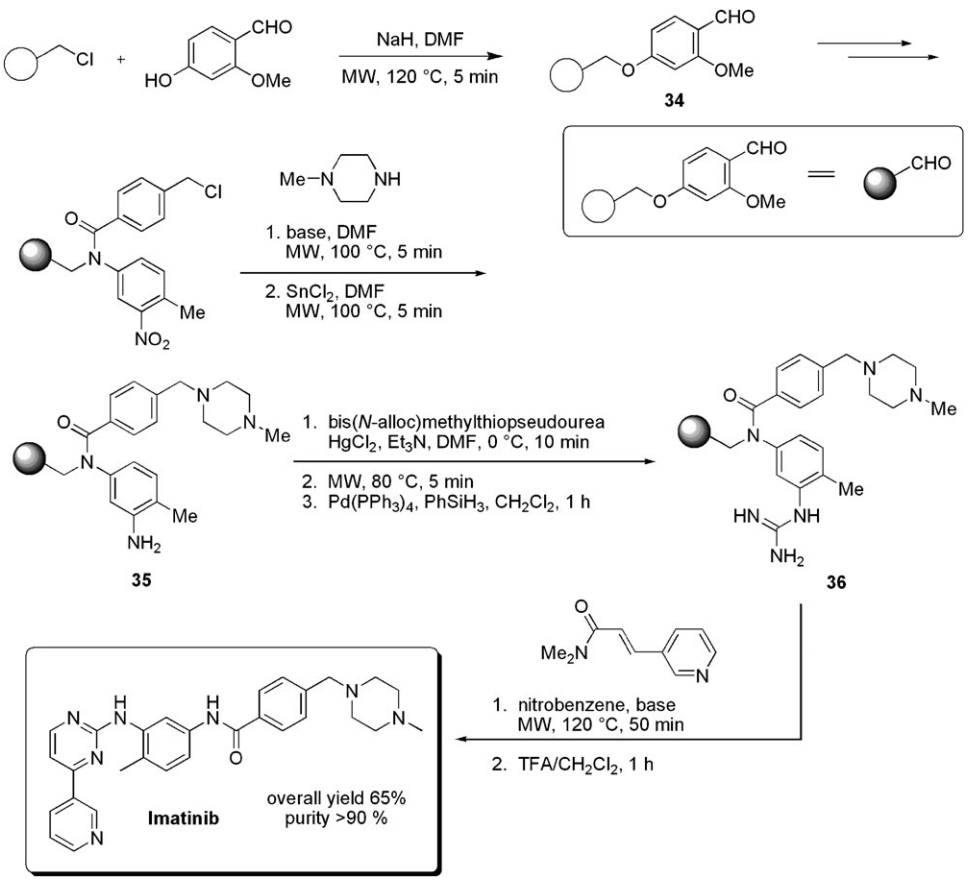
Scheme 15 C–C and C–N bond formation using a heterogeneous nickel catalyst.



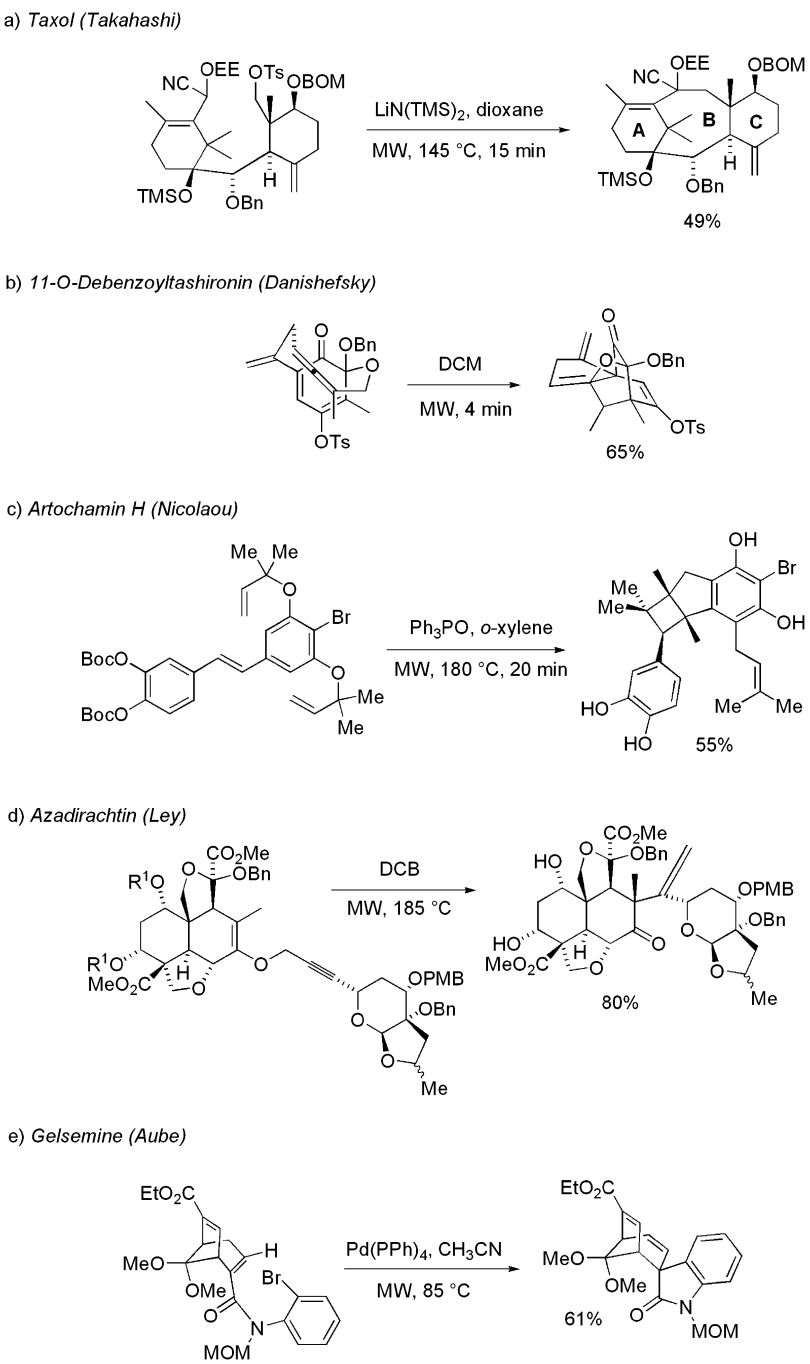
Scheme 16 Asymmetric Heck and Mannich reactions using chiral transition-metal catalysts or organocatalysts.

reaction time for those steps to a few minutes without leading to racemization of the amino acids.[40] Peptides can therefore be synthesized in a fraction of the time normally experienced in room temperature peptide synthesis.[41] Even more important, difficult to prepare longer peptide sequences can be synthesized in a much higher degree of purity using microwave heating as compared to the standard room temperature approach. As reported by Papini and coworkers,[42] the hydrophobic glycopeptide CSF114(Glc) consisting of 21 amino acid units could be synthesized in 46% isolated yield and 72% HPLC purity using an automated microwave peptide synthesizer, which compared very favorably with a mere 10% isolated yield and less than 20% peptide purity employing conventional room temperature peptide synthesis. The positive impact of microwave heating on the coupling and deprotection steps in peptide synthesis in terms of higher purities and enhanced reaction times have been ascribed to a reduction in chain aggregation.[40]

Along with recent applications of microwave heating for more delicate transformations such as asymmetric synthesis and peptide couplings, the use of microwave technology for the total synthesis of complex natural products is also increasing. Scheme 18 provides a summary of recently published synthetic approaches toward complex natural products where one of the synthetic steps has been performed by microwave heating.[43] It appears that in the examples highlighted in Scheme 18 microwave heating was used perhaps as the "last resort" to obtain a meaningful conversion in a reasonable timeframe for one



Scheme 17 Multi-step solid-phase synthesis of Imatinib.



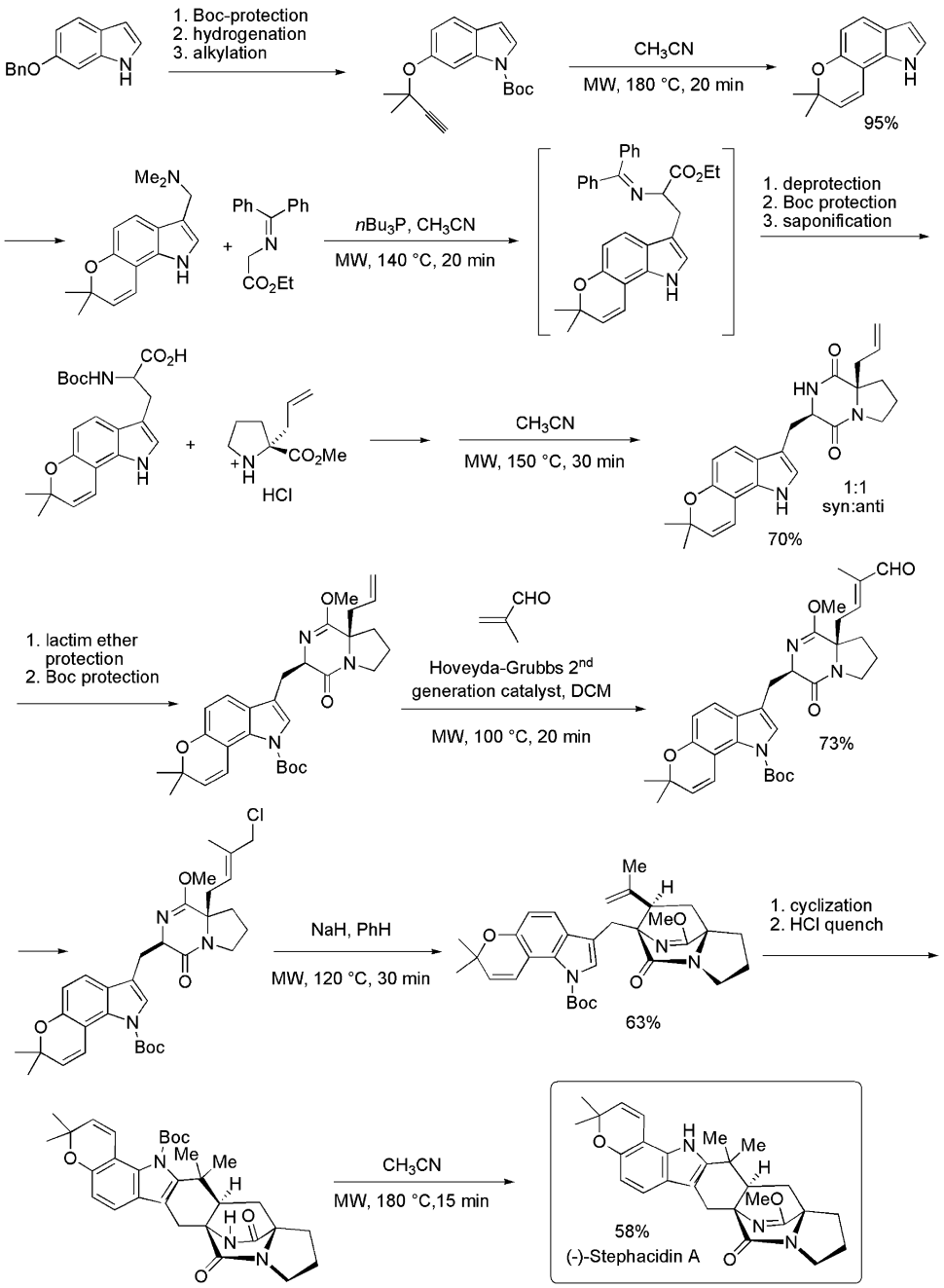
Scheme 18 Examples of microwave heating steps in natural product synthesis.[43]

difficult transformation in a long sequence of steps, and not as the "first choice" for carrying out organic synthesis.

In contrast to the "single use" of microwave heating in multistep natural product synthesis shown in Scheme 18, Williams and coworkers have recently described the 17 step asymmetric total synthesis of the fungal metabolite (−)-stephacidin A in overall 6% yield.[44] Out of the 17 steps, six reaction steps made use of single-mode sealed vessel microwave heating (Scheme 19). The authors comment that the use of microwave technology has helped in reducing reaction times from hours to minutes for most transformations and has also increased the yields of several key transformations.[44] This example gives hope that microwave chemistry will in the future be used more often as the "first choice" for carrying out synthetic transformations requiring heat.

5. Conclusions and outlook

Although important questions relating to the existence of "special microwave effects",[8,9] the scalability[33] and overall energy efficiency[45] of microwave-heated processes remain unresolved, there is little doubt that microwave-assisted organic



Scheme 19 Total synthesis of (−)-stephacidin A using microwave technology.

synthesis will become a standard technology in most synthetic laboratories in a few years' time. The many advantages of this enabling technology—highlighted in this brief introductory review—are nowadays not only exploited in organic and medicinal chemistry but are also being used in polymer synthesis,[46] material sciences,[47] nanotechnology[48] and biochemical processes.[40] One of the major drawbacks of this relatively new technology is 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. This fact has severely limited the penetration of microwave synthesis in academic laboratories around the world. It can only be hoped that this situation will change over the next several years and less expensive equipment will become available.

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