Synthetic Methods

Controlled Microwave Heating in Modern Organic Synthesis

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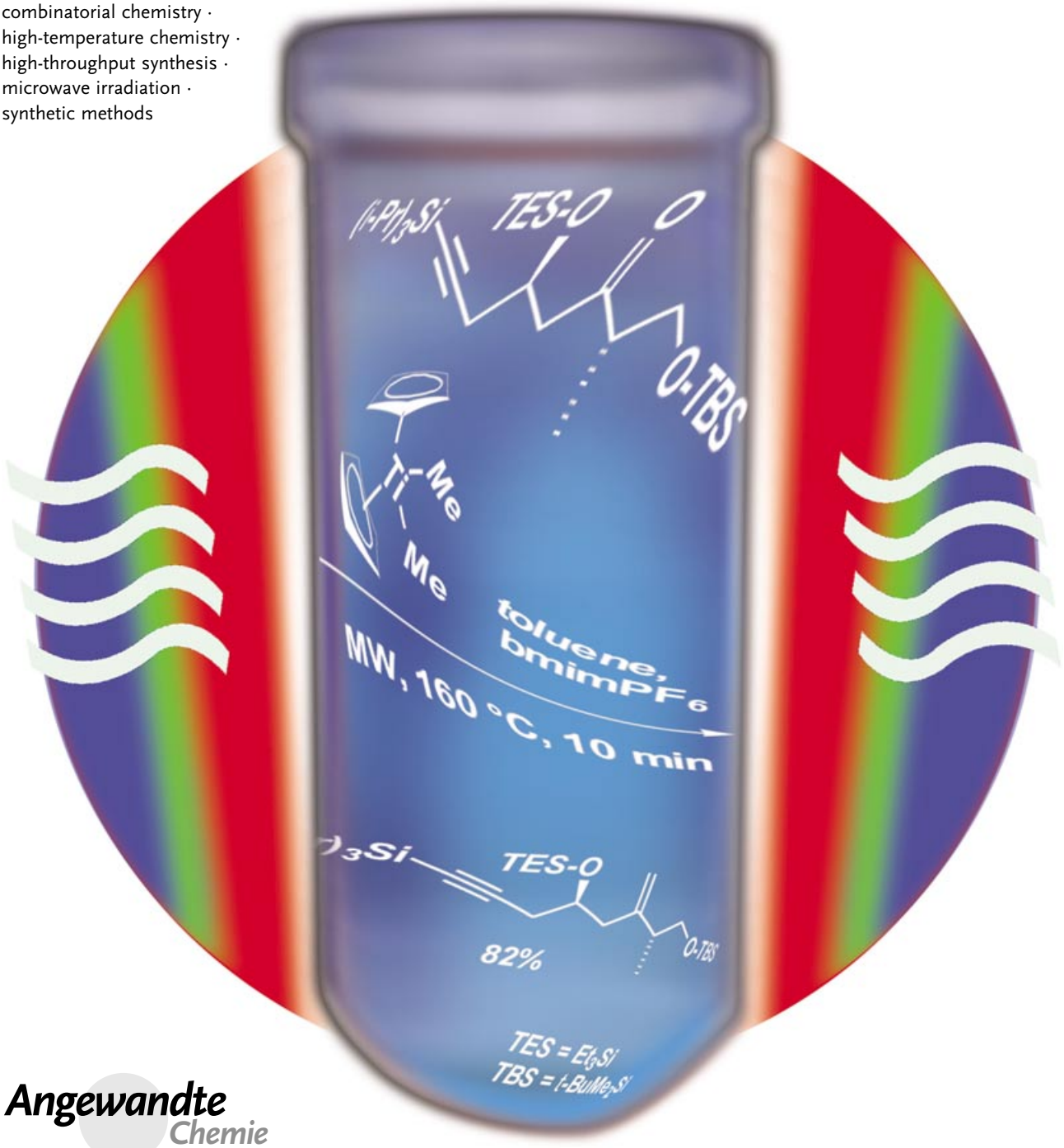
combinatorial chemistry · high-temperature chemistry · high-throughput synthesis · microwave irradiation · synthetic methods



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Although 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 The Bunsen burner was later superseded by the isomantle, oil bath, or hot plate as a source for applying heat to a chemical reaction. In the past few years, heating and driving chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. This nonclassical heating technique is slowly moving from a laboratory curiosity to an established technique that is heavily used in both academia and industry. The efficiency of "microwave flash heating" in dramatically reducing reaction times (from days and hours to minutes and seconds) is just one of the many advantages. This Review highlights recent applications of controlled microwave heating in modern organic synthesis, and discusses some of the underlying phenomena and issues involved.

From the Contents

1. Introduction

High-speed synthesis with microwaves has attracted a considerable amount of attention in recent years.[1] More than 2000 articles have been published in the area of microwave-assisted organic synthesis (MAOS) since the first reports on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986.[2,3] The initial slow uptake of the technology in the late 1980s and early 1990s has been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available systems for adequate temperature and pressure controls were major concerns.

Although most of the early pioneering experiments in MAOS were performed in domestic, sometimes modified, kitchen microwave ovens, the current trend is to use dedicated instruments which have only become available in the last few years for chemical synthesis. The number of publications related to MAOS has therefore increased dramatically since the late 1990s to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity. A large number of review articles[4–13] and several books[14–16] provide extensive coverage of the subject. The aim of this Review is to highlight some of the most recent applications and trends in microwave synthesis, and to discuss the impact and future potential of this technology.

1.1. Microwave Theory

Microwave irradiation is electromagnetic irradiation in the frequency range of 0.3 to 300 GHz. All domestic "kitchen" microwave ovens and all dedicated microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz (which corresponds to a wavelength of 12.24 cm) to avoid interference with telecommunication and cellular phone frequencies. The energy of the microwave photon in this frequency region (0.0016 eV) is too low to break chemical bonds and is also lower than the energy of Brownian motion. It is therefore clear that microwaves cannot induce chemical reactions.[17–19]

Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. The electric component[20] of an electromagnetic field causes heating by two main mechanisms: dipolar polarization and ionic conduction. Irradiation of the sample at microwave frequencies results in the dipoles or ions aligning 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. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely.[18,19]

The heating characteristics of a particular material (for example, a solvent) under microwave irradiation conditions

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are dependent on its dielectric properties. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called loss factor tanδ. This loss factor is expressed as the quotient $\tan\delta = \varepsilon''/\varepsilon'$, where ε'' is the dielectric loss, which is indicative of the efficiency with which electromagnetic radiation is converted into heat, and ε' is the dielectric constant describing the ability of molecules to be polarized by the electric field. A reaction medium with a high tanδ value is required for efficient absorption and, consequently, for rapid heating. The loss factors for some common organic solvents are summarized in Table 1. In general, solvents can be classified as high ($\tan\delta > 0.5$), medium (tanδ 0.1–0.5), and low microwave absorbing ($\tan\delta < 0.1$).

Table 1: Loss factors (tanδ) of different solvents.[a]

Solvent	tanδ	Solvent	tanδ
ethylene glycol	1.350	DMF	0.161
ethanol	0.941	1,2-dichloroethane	0.127
DMSO	0.825	water	0.123
2-propanol	0.799	chlorobenzene	0.101
formic acid	0.722	chloroform	0.091
methanol	0.659	acetonitrile	0.062
nitrobenzene	0.589	ethyl acetate	0.059
1-butanol	0.571	acetone	0.054
2-butanol	0.447	tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	dichloromethane	0.042
NMP	0.275	toluene	0.040
acetic acid	0.174	hexane	0.020

[a] Data from ref. [15]; 2.45 GHz, 20 °C.

Other common solvents without a permanent dipole moment such as carbon tetrachloride, benzene, and dioxane are more or less microwave transparent. It has to be emphasized that a low tanδ value does not preclude a particular solvent from being used in a microwave-heated reaction. Since either the substrates or some of the reagents/catalysts are likely to be polar, the overall dielectric properties of the reaction medium will in most cases allow sufficient heating by microwaves (see Section 1.2). Furthermore, polar additives such as ionic liquids, for example, can be added to otherwise low-absorbing reaction mixtures to increase the absorbance level of the medium (see Section 2.2.1).

C. Oliver Kappe received his doctoral degree from the Karl-Franzens-University in Graz (Austria), where he worked with Prof. G. Kollenz on cycloaddition and rearrangements of acylketenes. After postdoctoral research work with Prof. C. Wentrup at the University of Queensland (Australia) and Prof. A. Padwa at Emory University (US), he moved back to the University of Graz where he obtained his Habilitation (1998) and is currently associate Professor. In 2003 he spent a sabattical period at the Scripps Research Institute in La Jolla (US) with Prof. K. B. Sharpless. His research interests include microwave-enhanced synthesis, combinatorial chemistry, and multicomponent reactions.

Traditionally, organic synthesis is carried out by conductive heating with an external heat source (for example, an oil bath). This is a comparatively slow and inefficient method for transferring energy into the system, since it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. In contrast, microwave irradiation produces efficient internal heating (in-core volumetric heating) by direct coupling of microwave energy with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture. Since the reaction vessels employed are typically made out of (nearly) microwave-transparent materials, such as borosilicate glass, quartz, or teflon, an inverted temperature gradient results compared to conventional thermal heating (Figure 1). The very efficient internal heat transfer results in minimized wall effects (no hot vessel surface) which may lead to the observation of so-called specific microwave effects (see Section 1.2), for example, in the context of diminished catalyst deactivation.

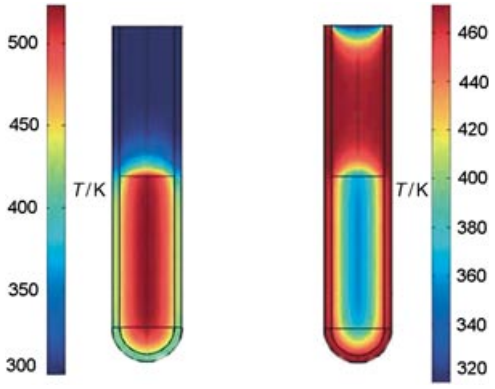


Figure 1. Inverted temperature gradients in microwave versus oil-bath heating: Difference in the temperature profiles (finite element modeling) after 1 min of microwave irradiation (left) and treatment in an oil-bath (right). Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating) whereas in the oil-heated tube, the reaction mixture in contact with the vessel wall is heated first.[38]

1.2. Microwave Effects

Since the early days of microwave synthesis, the observed rate accelerations and sometimes altered product distributions compared to oil-bath experiments have led to speculation on the existence of so-called "specific" or "non-thermal" microwave effects.[21–23] Historically, such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart carried out at the same apparent temperature. 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. As shown in Figure 2, a high microwave absorbing solvent such as methanol ($\tan\delta = 0.659$) can be rapidly superheated to

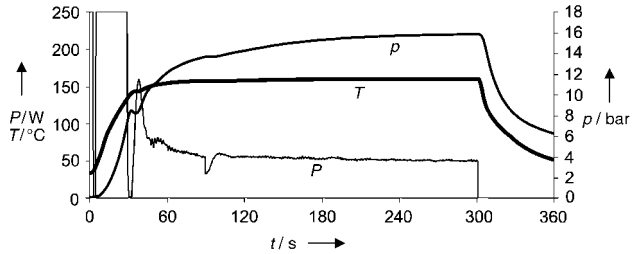


Figure 2. Temperature (T), pressure (p), and power (P) profile for a sample of methanol (3 mL) heated under sealed-vessel microwave irradiation conditions (single-mode heating, 250 W, 0–30 s), temperature control using the feedback from IR thermography (40–300 s), and active gas-jet cooling (300–360 s). The maximum pressure in the reaction vessel was ca. 16 bar. After the set temperature of 160 °C is reached, the power regulates itself down to ca. 50 W.

temperatures $>100\,^{\circ}C$ above its boiling point when irradiated under microwave conditions in a sealed vessel. The rapid increase in temperature can be even more pronounced for media with extreme loss factors, such as ionic liquids (see Section 2.2.1), where temperature jumps of 200 °C within a few seconds are not uncommon. Naturally, such temperature profiles are very difficult if not impossible to reproduce by standard thermal heating. Therefore, comparisons with conventionally heated processes are inherently troublesome.

Dramatic rate enhancements between reactions performed at room temperature or under standard oil-bath conditions (heating under reflux) and high-temperature microwave-heated processes have frequently been observed. As Baghurst and Mingos have pointed out on the basis of simply applying the Arrhenius law $[k = A\exp(-E_a/RT)]$, a transformation that requires 68 days to reach 90 % conversion at 27 °C, will show the same degree of conversion within 1.61 seconds (!) when performed at 227 °C (Table 2).[18] The very rapid heating and extreme temperatures observable in microwave chemistry means that many of the reported rate enhancements can be rationalized by simple thermal/kinetic effects.

Table 2: Relationship between temperature and time for a typical first-order reaction.[a]

T [°C]	k [s^{-1}]	t (90% conversion)
27	1.55×10^{-7}	68 days
77	4.76×10^{-5}	13.4 h
127	3.49×10^{-3}	11.4 min
177	9.86×10^{-2}	23.4 s
227	1.43	1.61 s

[a] Data from ref. [18]; $A = 4\times10^{10}$ $mol^{-1}\,s^{-1}$, $E_a = 100$ $kJ\,mol^{-1}$.

In addition to the above mentioned thermal/kinetic effects, microwave effects that are caused by the uniqueness of the microwave dielectric heating mechanisms (see Section 1.1) must also be considered. These effects should be termed "specific microwave effects" and shall be defined as accelerations that can not be achieved or duplicated by conventional heating, but essentially are still thermal effects. In this category fall, for example 1) the superheating effect of solvents at atmospheric pressure,[24] 2) the selective heating of, for example, strongly microwave absorbing heterogeneous catalysts or reagents in a less polar reaction medium,[25–27] 3) the formation of "molecular radiators" by direct coupling of microwave energy to specific reagents in homogeneous solution (microscopic hotspots),[26] and 4) the elimination of wall effects caused by inverted temperature gradients (Figure 1).[28] It should be emphasized that rate enhancements falling under this category are essentially still a result of a thermal effect (that is, a change in temperature compared to heating by standard convection methods), although it may be difficult to experimentally determine the exact reaction temperature.

Some authors have suggested the possibility of "non-thermal microwave effects" (also referred to as athermal effects). These should be classified as accelerations that can not be rationalized by either purely thermal/kinetic or specific microwave effects. Nonthermal effects essentially result from a direct interaction of the electric field with specific molecules in the reaction medium. It has been argued that the presence of an electric field leads to orientation effects of dipolar molecules and hence changes the pre-exponential factor A or the activation energy (entropy term) in the Arrhenius equation.[21,22] A similar effect should be observed for polar reaction mechanisms, where the polarity is increased going from the ground state to the transition state, thus resulting in an enhancement of reactivity by lowering the activation energy.[22] Microwave effects are the subject of considerable current debate and controversy,[21–23] and it is evident that extensive research efforts will be necessary to truly understand these and related phenomena.[29] Since the issue of microwave effects is not the primary focus of this Review, the interested reader is referred to more detailed surveys and essays covering this topic.[21–23]

1.3. Processing Techniques

Frequently used processing techniques employed in microwave-assisted organic synthesis involve solventless ("dry-media") procedures where the reagents are preadsorbed onto either a more or less microwave transparent (silica, alumina, or clay)[32] or strongly absorbing (graphite)[33] inorganic support, which can additionally be doped with a catalyst or reagent. The solvent-free approach was very popular particularly in the early days of MAOS since it allowed the safe use of domestic household microwave ovens and standard open-vessel technology. Although a large number of interesting transformations with "dry-media" reactions have been published in the literature,[32] technical difficulties relating to non-uniform heating, mixing, and the precise determination of the reaction temperature remain unsolved, in particular when scale-up issues need to be addressed. In addition, phase-transfer catalysis (PTC) has also been widely employed as a processing technique in MAOS.[34]

Alternatively, microwave-assisted synthesis can be carried out in standard organic solvents either under open- or sealed-vessel conditions. If solvents are heated by microwave

irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent (as in an oil-bath experiment) typically limits the reaction temperature that can be achieved. In the absence of any specific or nonthermal microwave effects (such as the superheating effect at atmospheric pressure which has been reported to be up to 40 °C)[24] the expected rate enhancements would be comparatively small. To nonetheless achieve high reaction rates, high-boiling microwave-absorbing solvents such as DMSO, *N*-methyl-2-pyrrolidone (NMP), 1,2-dichlorobenzene (DCB), or ethylene glycol (see Table 1) have been frequently used in open-vessel microwave synthesis.[6] However, the use of these solvents presents serious challenges during product isolation. The recent availability of modern microwave reactors with on-line monitoring of both temperature and pressure has meant that MAOS in sealed vessels—a technique pioneered by Strauss in the mid 1990s[35]—has been celebrating a comeback in recent years. This is clearly evident from surveying the recently published literature in the area of MAOS (see Section 2), and it appears that the combination of rapid dielectric heating by microwaves with sealed-vessel technology (autoclaves) will most likely be the method of choice for performing MAOS in the future.

1.4. Equipment

Although many of the early pioneering experiments in microwave-assisted organic synthesis were carried out in domestic microwave ovens, the current trend is undoubtedly to use dedicated instruments for chemical synthesis. In a domestic microwave oven the irradiation power is generally controlled by on/off cycles of the magnetron (pulsed irradiation), and it is typically not possible to monitor the reaction temperature in a reliable way. This disadvantage, combined with the inhomogeneous field produced by the low-cost magnetrons and the lack of safety controls, means that the use of such equipment can not be recommended. In contrast, all of today's commercially available dedicated microwave reactors for synthesis[36–38] feature built-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of fiber-optic probes or IR sensors, and software that enables on-line temperature/pressure control by regulation of microwave power output (Figure 2).

Two different philosophies with respect to microwave reactor design are currently emerging: multimode and monomode (also referred to as single-mode) reactors.[17] In the so-called multimode instruments (conceptually similar to a domestic oven), the microwaves that enter the cavity are reflected by the walls and the load over the typically large cavity. In most instruments a mode stirrer ensures that the field distribution is as homogeneous as possible. In the much smaller monomode cavities, the electromagnetic irradiation is directed through an accurately designed rectangular or circular wave guide onto the reaction vessel mounted at a fixed distance from the radiation source, thus creating a standing wave. The key difference between the two types of reactor systems is that whereas in multimode cavities several reaction vessels can be irradiated simultaneously in multi-vessel rotors (parallel synthesis), in monomode systems only one vessel can be irradiated at the time. In the latter case high throughput can be achieved by integrated robotics that move individual reaction vessels in and out of the microwave cavity. Most instrument companies offer a variety of diverse reactor platforms with different degrees of sophistication with respect to automation, database capabilities, safety features, temperature and pressure monitoring, and vessel design. Importantly, single-mode reactors processing comparatively small volumes also have a built-in cooling feature that allows for rapid cooling of the reaction mixture with compressed air after completion of the irradiation period (see Figure 2). The dedicated single-mode instruments available today can process volumes ranging from 0.2 to about 50 mL under sealed-vessel conditions (250 °C, ca. 20 bar), and somewhat higher volumes (ca. 150 mL) under open-vessel reflux conditions. In the much larger multimode instruments several liters can be processed under both open- and closed-vessel conditions. Continuous-flow reactors are nowadays available for both single- and multimode cavities that allow the preparation of kilograms of materials by using microwave technology (see Section 2.10).[36–38]

2. Literature Survey

2.1. Scope and Organization of the Review

This Review highlights recent applications of controlled microwave heating technology in organic synthesis. The term "controlled" here refers to the use of a dedicated microwave reactor for synthetic chemistry purposes (single- or multimode). Therefore, the exact reaction temperature during the irradiation process has been adequately determined in the original literature source. Although the aim of this Review is not primarily to speculate about the existence or non-existence of microwave effects (see Section 1.2), the results of adequate control experiments or comparison studies with conventionally heated transformations will sometimes be presented. The reader should not draw any definitive conclusions about the involvement or non-involvement of "microwave effects" from those experimental results, because of the inherent difficulties in conducting such experiments (see above). In terms of processing techniques (Section 1.3), preference is given to transformations in solution under sealed-vessel conditions, since this reflects the recent trend in the literature, and these transformations are in principle scalable in either batch or continuous-flow modes. Sealed-vessel microwave technology was employed unless otherwise specifically noted. Most of the examples have been taken between 2002 and 2003. Earlier examples of controlled MAOS are limited and can be found in previous review articles and books.[4–16]

2.2. Transition-Metal-Catalyzed C–C Bond Formations

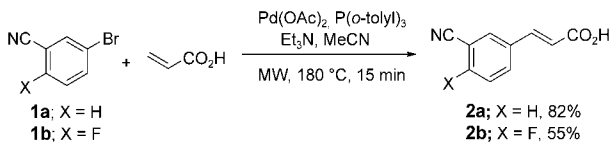
Homogeneous transition-metal-catalyzed reactions represent one of the most important and best studied reaction

types in MAOS. Transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions typically need hours or days to reach completion with traditional heating under reflux conditions and often require an inert atmosphere. The research groups of Hallberg, Larhed, and others have demonstrated over the past few years that the rate of many of those transformations can be enhanced significantly by employing microwave heating under sealed-vessel conditions ("microwave flash heating"), in most cases without an inert atmosphere.[10] The use of metal catalysts in conjunction with microwaves may have significant advantages over traditional heating methods, since the inverted temperature gradients under microwave conditions (Figure 1) may lead to an increased lifetime of the catalyst through elimination of wall effects.[28,39]

2.2.1. Heck Reactions

The Heck reaction, a palladium-catalyzed vinylic substitution, is typically conducted with alkenes and organohalides or pseudohalides as reactants. Numerous elegant synthetic transformations based on C–C bond-forming Heck reactions have been developed both in classical organic synthesis and natural product chemistry.[40] Solution-phase Heck reactions were carried out successfully by MAOS as early as 1996, thereby reducing reaction times from several hours under conventional reflux conditions to sometimes less than five minutes.[41] These early examples of microwave-assisted Heck reactions have been extensively reviewed by Larhed and will not be discussed herein.[10]

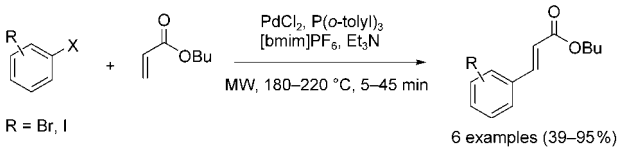
Scheme 1 shows a recent example of a standard Heck reaction involving aryl bromides **1** and acrylic acid to furnish



Scheme 1. Examples of Heck Reactions carried out on a 2 and 80 mmol scale.

the corresponding cinnamic acids **2**.[42] Optimization of the reaction conditions under small-scale (2 mmol) single-mode microwave conditions led to a protocol that employed MeCN as the solvent, 1 mol% $Pd(OAc)_2/P(o\text{-tolyl})_3$ as the catalyst system, and triethylamine as the base. The reaction time was 15 minutes at a reaction temperature of 180 °C. Interestingly, the authors have discovered that the rather expensive homogeneous catalyst system can be replaced by 5% Pd/C (< 0.1 mol% concentration of Pd catalyst) without the need to change any of the other reaction parameters.[42] The yields for cinnamic acid derivative **2a** were very similar when either homogeneous or heterogeneous Pd catalysts were used in the Heck reaction. In the same article[42] the authors also demonstrate that it is possible to directly scale-up the 2-mmol Heck reaction to 80 mmol (ca. 120 mL total reaction volume) by switching from a single-mode to a larger multimode microwave cavity (see also Section 2.10). Importantly, the optimized small-scale reaction conditions could be directly used for the larger scale reaction, thus giving rise to very similar product yields.

In 2002 Larhed and co-workers reported microwave-promoted Heck arylations in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6; Scheme 2).[43] Among the variety of possible "green" solvent

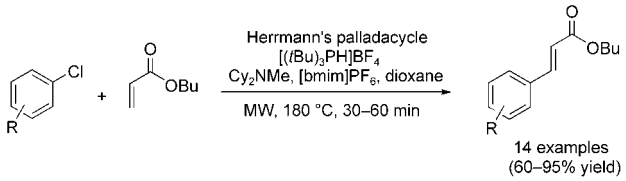


Scheme 2. Heck reactions in ionic liquids.

alternatives for catalytic and other reactions, nonvolatile room-temperature ionic liquids have attracted a considerable amount of attention in recent years.[44] Ionic liquids interact very efficiently with microwaves through the ionic conduction mechanism (see Section 1.1) and are rapidly heated at rates easily exceeding 10 °C s^{-1} without any significant pressure build-up. Therefore, safety problems arising from over-pressurization of heated sealed reaction vessels can be minimized.[45,46] In the Heck reactions shown in Scheme 2, 4 mol% of $PdCl_2/P(o\text{-tolyl})_3$ was used. Full conversions were achieved within 5 (X = I) and 20 minutes (X = Br). Transformations that were performed without the phosphane ligand required 45 minutes. A key feature of this catalyst/ionic liquid system is the recyclability: the phosphane-free system $PdCl_2$/[bmim]PF_6 was recyclable at least five times. After each cycle, the volatile product was directly isolated in high yield by rapid distillation under reduced pressure.[43]

The concept of performing microwave synthesis in room-temperature ionic liquids has been applied to 1,3-dipolar cycloaddition reactions,[47] catalytic transfer hydrogenations,[48] ring-closing metathesis,[49] and the conversion of alcohols into alkyl halides.[50] As an alternative to the use of the rather expensive ionic liquids as solvents, several research groups have used ionic liquids as "doping agents" for microwave heating of otherwise nonpolar solvents such as hexane, toluene, THF, or dioxane. This technique, first introduced by Ley et al. in 2001 (see Section 2.9.4),[51] is becoming increasingly popular, as demonstrated by the many recently published examples.[52–60] Systematic studies on temperature profiles and the thermal stability of ionic liquids under microwave irradiation conditions by Leadbeater and Torenius[52,53] have shown that addition of a small amount of an ionic liquid (0.1 mmol mL^{-1} solvent) suffices to obtain dramatic changes in the heating profiles by changing the overall dielectric properties (namely, tanδ) of the reaction medium.

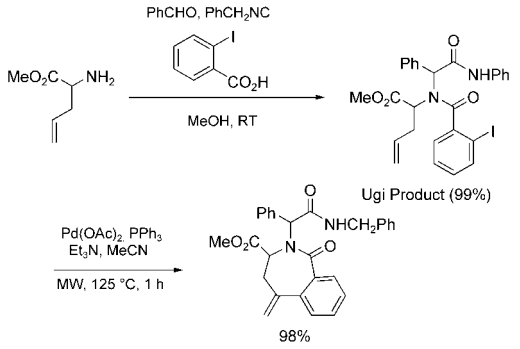
Larhed and co-workers have exploited the combination of [bmim]PF_6 and dioxane in the Heck coupling of both electron-rich and electron-poor aryl chlorides with butyl acrylate (Scheme 3).[56] Transition-metal-catalyzed carbon–carbon bond-forming reactions involving unreactive aryl chlorides have represented a synthetic challenge for a long time. Only recently, as a result of advances in the develop-



Scheme 3. Heck reactions of aryl chlorides with air-stable phosphonium salts as ligand precursors. Electron-rich and electron-poor aryl chlorides are equally suitable substrates.

ment of highly active catalyst/ligand systems, have those transformations been accessible.[61] For the Heck coupling shown in Scheme 3, the air-stable but highly reactive $[(t\mathrm{Bu})_3\mathrm{PH}]\mathrm{BF}_4$ phosphonium salt described by Netherton and Fu[62] was employed as a ligand precursor using the palladacycle *trans*-di(μ-acetato)bis[*o*-di-*o*-tolylphosphanyl)-benzyl]dipalladium(II)[63] developed by Herrmann et al. as the palladium precatalyst. Depending on the reactivity of the aryl chloride, 1.5–10 mol% of Pd catalyst (3–20% of ligand), 1.5 equivalents of Cy_2NMe as a base, and 1.0 equivalent of $[bmim]PF_6$ in dioxane were irradiated at 180 °C under sealed-vessel conditions (no inert gas atmosphere) with the aryl chloride and butyl acrylate for 30–60 min. The desired cinnamic esters were obtained in moderate to excellent yields under these optimized conditions (Scheme 3).[56]

A synthetically useful application of an intramolecular microwave-assisted Heck reaction was described by Gracias et al. (Scheme 4).[64] In their approach toward the synthesis of



Scheme 4. Sequential Ugi reactions and Heck cyclizations for the synthesis of seven-membered N-heterocycles.

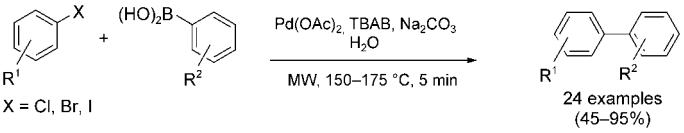
seven-membered N-heterocycles, the initial product of an Ugi four-component reaction was subjected to an intramolecular Heck cyclization using 5 mol% $Pd(OAc)_2/PPh_3$ as the catalytic system. Microwave irradiation at 125 °C in acetonitrile for 1 h provided 98% yield of the product shown in Scheme 4. A number of related sequential Ugi reaction/Heck cyclizations were reported in the original publication, also involving aryl bromides instead of iodides.

A very recent addition to the already powerful spectrum of microwave Heck chemistry is the development of a general procedure for carrying out oxidative Heck couplings, that is, the Pd^{II}-catalyzed carbon–carbon coupling of aryl boronic acids with alkenes using $Cu(OAc)_2$ as a reoxidant (100–170 °C, 5–30 min).[65]

2.2.2. *Suzuki Reactions*

The Suzuki reaction (the palladium-catalyzed cross-coupling of aryl halides with boronic acids) is arguably one of the most versatile and at the same time also one of the most often used cross-coupling reactions in modern organic synthesis.[66,67] Carrying out high-speed Suzuki reactions under controlled microwave conditions can be considered almost a routine synthetic procedure today, given the enormous literature precedent for this transformation.[10] Recent examples include the use of the Suzuki protocol for the high-speed modification of various heterocyclic scaffolds of pharmacological or biological interest.[68–74]

A significant advance in Suzuki chemistry has been the observation that Suzuki couplings can be readily carried out using water as the solvent in conjunction with microwave heating.[75–79] Water, being cheap, readily available, nontoxic, and nonflammable, has clear advantages as a solvent for use in organic synthesis. With its comparatively high loss factor (tanδ) of 0.123 (see Table 1), water is also a potentially very useful solvent for microwave-mediated synthesis, especially in the high-temperature region accessible by using sealed vessel technology. Leadbeater and Marco have recently described very rapid, ligand-free palladium-catalyzed aqueous Suzuki couplings of aryl halides with aryl boronic acids (Scheme 5).[75] Key to the success of this method was the



Scheme 5. Ligand-free Suzuki reactions with TBAB as an additive.

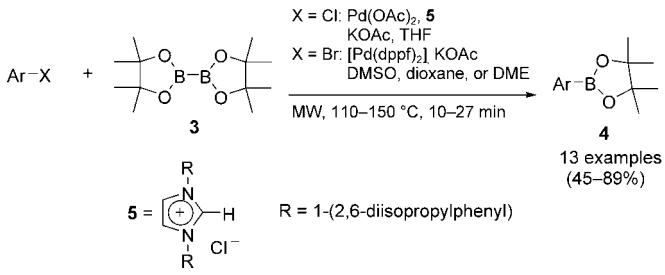
use of 1.0 equivalents of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst. The role of the ammonium salt is to facilitate the solubility of the organic substrates and to activate the boronic acid by formation of $[R_4N]^+[ArB(OH)_3)]^-$. A wide variety of aryl bromides and iodides were successfully coupled with aryl boronic acids by using controlled microwave heating at 150 °C for 5 minutes with only 0.4 mol% of $Pd(OAc)_2$ as catalyst (Scheme 5).[75] Aryl chlorides also reacted but required higher temperatures (175 °C).

The same Suzuki couplings could also be performed under microwave-heated open-vessel reflux conditions (110 °C, 10 min) on a tenfold scale and gave nearly identical yields to the closed-vessel reactions.[76,77] Importantly, nearly the same yields were also obtained when the Suzuki reactions were carried out in a preheated oil bath (150 °C) instead of using microwave heating, clearly indicating the absence of any specific or nonthermal microwave effects (see Section 1.2).[76]

The same authors have reported another modification in which, surprisingly, it was also possible to carry out the Suzuki reactions depicted in Scheme 5 in the absence of the palladium catalyst![78,79] These transition-metal-free aqueous Suzuki-type couplings again utilized 1.0 equivalent of TBAB

as an additive, 3.8 equivalents of Na_2CO_3 as a base, and 1.3 equivalents of the corresponding boronic acid (150 °C, 5 min). High yields were obtained with aryl bromides and iodides whereas aryl chlorides proved unreactive under the conditions used. The reaction is also limited to electron-poor or electron-neutral boronic acids. While the exact mechanism of this unusual transformation remains unknown, one possibility would be a radical pathway where the reaction medium, water, provides an enhanced π-stacking interaction as a result of the hydrophobic effect.[67]

The large number of boronic acids that are commercially available makes the Suzuki reaction and related types of coupling chemistry highly attractive in the context of high-throughput synthesis and derivatization. In addition, boronic acids are air and moisture stable, of relatively low toxicity, and the boron-derived by-products can easily be removed from the reaction mixture. Therefore, it is not surprising that efficient and rapid microwave-assisted protocols have been developed for their preparation. In 2002 Fürstner and Seidel outlined the synthesis of pinacol aryl boronates from aryl chlorides bearing electron-withdrawing groups and commercially available bis(pinacol)borane (**3**), using a palladium catalyst formed in situ from $Pd(OAc)_2$ and imidazolium chloride **5** (Scheme 6, X = Cl).[80] The very reactive N-

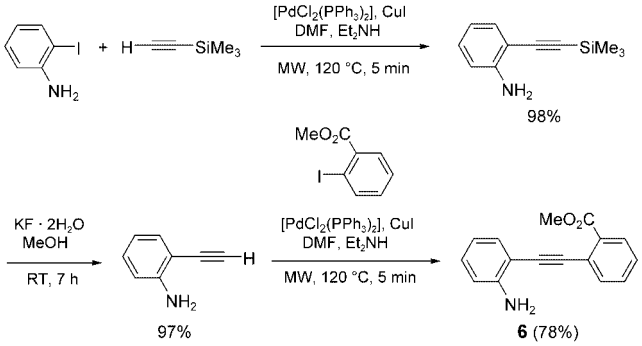


Scheme 6. Palladium-catalyzed formation of aryl boronates from electron-rich and electron-poor (hetero)aryl halides.

heterocyclic carbene (NHC) ligand (6–12 mol %) allowed this transformation to proceed to completion within 10–20 minutes at 110 °C in THF by using microwave irradiation in sealed vessels. The conventionally heated process (reflux THF (ca. 65 °C), argon atmosphere) gave comparable yields, but required 4–6 h to reach completion. Dehaen and co-workers subsequently disclosed a complementary approach in which electron-rich aryl bromides were used as substrates (Scheme 6, X = Br) and 3 mol % $[Pd(dppf)Cl_2]$ (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene) was used as the catalyst.[81] A somewhat higher reaction temperature (125–150 °C) was employed to produce a variety of different aryl boronates in good to excellent yields.[81] High-speed microwave-assisted trifluoromethanesulfonation (triflation) reactions of phenols with *N*-phenyltrifluorosulfonimide (120 °C, 6 min) have also been reported in the literature.[82]

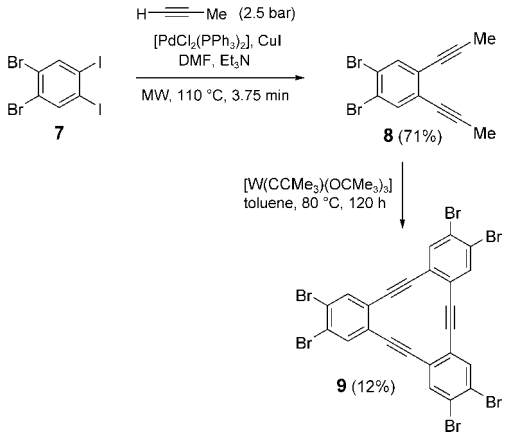
2.2.3. *Sonogashira Reactions*

The Sonogashira reaction (palladium/copper-catalyzed coupling of terminal acetylenes with aryl and vinyl halides) enjoys considerable popularity as a reliable and general method for the preparation of unsymmetrical alkynes.[83] General protocols for microwave-assisted Sonogashira reactions under controlled conditions were first reported in 2001 by Erdélyi and Gogoll.[84] Typical reaction conditions for the coupling of aryl iodides, bromides, chlorides, and triflates involve DMF as the solvent, diethylamine as the base, and $[PdCl_2(PPh_3)_2]$ (2–5 mol %) as the catalyst with CuI (5 mol %) as an additive.[84] Gogoll and co-workers later utilized these protocols in a rapid domino Sonogashira sequence to synthesize amino ester **6** (Scheme 7).[85]



Scheme 7. Domino Sonogashira sequence for the synthesis of bis(aryl)acetylenes.

Essentially the same experimental protocol was employed by Vollhardt and co-workers to synthesize *o*-dipropynylated arene **8**, which served as the precursor to tribenzocyclyne **9** through an alkyne metathesis reaction (Scheme 8).[86] In this



Scheme 8. Double Sonogashira reactions under propyne pressure.

case the Sonogashira reaction was carried out in a pre-pressurized (ca. 2.5 atm of propyne) sealed microwave vessel. Double Sonogashira coupling of the dibromodiiodobenzene **7** was completed within 3.75 minutes at 110 °C. It is worth mentioning that the authors have not carried out the corresponding tungsten-mediated alkyne metathesis chemistry under microwave conditions to shorten the exceedingly long reaction times and perhaps to improve the low yield (see

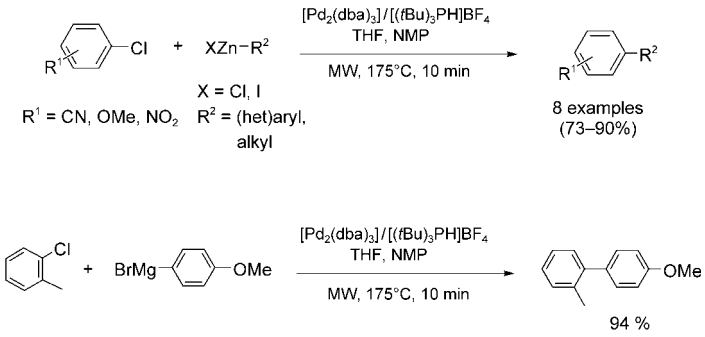
Scheme 16 for a microwave-assisted alkyne metathesis reaction). Additional examples of microwave-assisted Sonogashira couplings in the derivatization of pyrazinones[70] and pyrimidine[87] scaffolds have been reported.

As with the Suzuki reaction, there have been two recent independent reports by the groups of Leadbeater and Van der Eycken[88] that have shown that it is also possible to perform transition-metal-free Sonogashira couplings. Again, these methods rely on the use of microwave-heated water as the solvent, a phase-transfer catalyst (TBAB or polyethylene glycol), and a base (NaOH or Na_2CO_3). So far these metal-free procedures have been successful for aryl bromides and iodides, and typical reaction conditions involve heating to about 170 °C for 5–25 minutes. A recent report by He and Wu describes a copper-catalyzed (palladium-free) Sonogashira-type cross-coupling reaction.[89]

2.2.4. Stille, Negishi, and Kumada Reactions

Microwave-assisted Stille reactions involving organotin reagents as coupling partners were reviewed in 2002.[10] Until recently, very little work was published on Negishi (organozinc reagents) and Kumada (organomagnesium reagents) cross-coupling reactions under microwave conditions. There are two examples in the peer-reviewed literature describing Negishi cross-coupling reactions of activated aryl bromides[90] and heteroaryl chlorides[91] with organozinc halides.

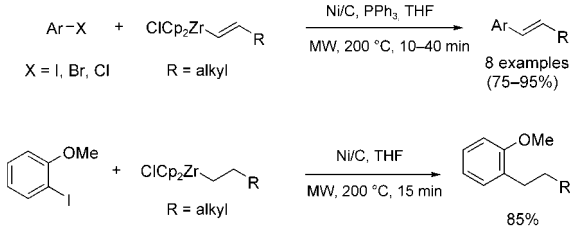
A general procedure describing high-speed microwave-assisted Negishi and Kumada couplings of unactivated aryl chlorides was recently reported (Scheme 9).[92] This procedure



Scheme 9. Negishi and Kumada cross-coupling reactions.

uses 0.015–2.5 mol % of $[Pd_2(dba)_3]$ as a palladium source and the air-stable $[(t\mathrm{Bu})_3\mathrm{PH}]\mathrm{BF}_4$ phosphonium salt (see Scheme 3) as ligand precursor. Successful couplings were observed for both aryl organozinc chlorides and iodides. By using this methodology it was also possible to successfully couple aryl chlorides with alkyl zinc reagents such as *n*-butylzinc chloride very rapidly without the need for an inert atmosphere. The optimized conditions involved the use of sealed-vessel microwave irradiation at 175 °C for 10 minutes. Grignard reactions were also carried out successfully by applying the same reaction conditions (Scheme 9). In the same article the authors also describe microwave-assisted methods for the preparation of the corresponding organozinc and magnesium compounds.[92]

In addition to the classical Negishi cross-coupling in which organozinc reagents are utilized, the "zirconium version" involving the coupling of zirconocenes with aryl halides has also been described by using sealed-vessel microwave technology. Lipshutz and Frieman have reported the rapid coupling of both vinyl and alkyl zirconocenes (prepared in situ by hydrozirconation of alkynes or alkenes, respectively), with aryl iodides, bromides, and chlorides (Scheme 10).[93] While aryl iodides required only 5 mol % Ni/C as a ligand-free heterogeneous catalytic system, the presence of triphenylphosphane as a ligand was necessary to successfully couple aryl bromides (10 mol %) and chlorides (20 mol % ligand). Full conversion was achieved under those conditions within 10–40 min at 200 °C using THF as the solvent.



Scheme 10. Nickel-catalyzed cross-coupling of alkenyl and alkyl zirconocenes with aryl halides.

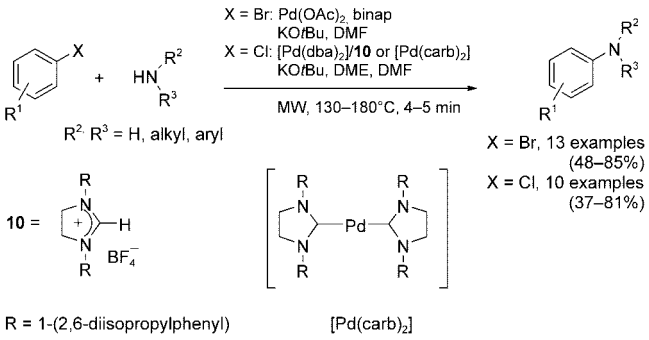
2.3. Transition-Metal-Catalyzed Carbon–Heteroatom Bond Formation

2.3.1. Buchwald–Hartwig Reactions

The research groups of Buchwald[94] and Hartwig[95] have developed a large variety of useful palladium-mediated methods for C–O and C–N bond formation. These arylations have been enormously popular in recent years. A vast amount of published material is available describing a wide range of palladium-catalyzed methods, ligands, solvents, temperatures, and substrates which has led to a broad spectrum of tunable reaction conditions that allows access to most target molecules that incorporate an aryl amine motif.

In 2002 Alterman and co-workers described the first high-speed Buchwald–Hartwig aminations by controlled microwave heating (Scheme 11).[96] The best results were obtained in DMF as the solvent without an inert atmosphere by employing 5 mol % of $Pd(OAc)_2$ as precatalyst and 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap) as the ligand. The procedure proved to be quite general and provided moderate to high yields for both electron-rich and electron-poor aryl bromides. Caddick and co-workers were also able to extend this rapid amination protocol to electron-rich aryl chlorides by utilizing more reactive discrete Pd–N-heterocyclic carbene (NHC) complexes or in situ generated palladium/imidazolium salt complexes (1 mol %, Scheme 11).[97]

Independent investigations by Maes and co-workers have described the use of 2-(dicyclohexylphosphanyl)biphenyl as a



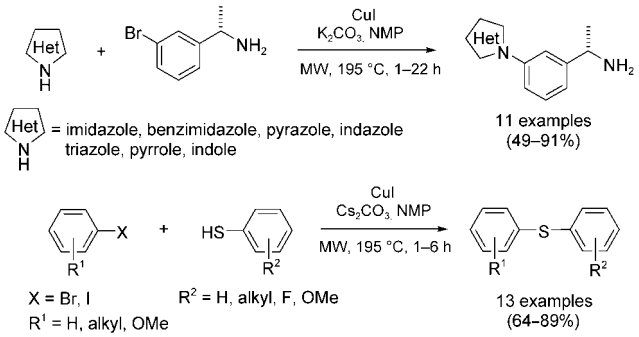
Scheme 11. Buchwald–Hartwig amination reactions.

ligand for the successful and rapid Buchwald–Hartwig coupling of (hetero)aryl chlorides with amines under microwave conditions (0.5–2 mol% Pd catalyst).[98] Microwave-assisted palladium-catalyzed aminations have been reported on a number of different substrates, including bromoquinolines,[99] aryl triflates,[100] intramolecular aminations for the synthesis of benzimidazoles,[101] and the coupling of aryl chlorides with sulfonamides.[102]

Direct palladium- or nickel-catalyzed carbon–phosphorous couplings of aryl iodides, bromides, and triflates with diphenylposphane in the presence of a base such as KOAc or diazobicyclo[2.2.2]octane (DABCO) are also reported to result in the rapid formation of triarylphosphanes.[103]

2.3.2. *Ullmann Condensation Reactions*

A recent survey of the literature on the Ullmann and related condensation reactions has highlighted the growing importance and popularity of copper-mediated C–N, C–O, and C–S bond-forming protocols.[104] Scheme 12 shows two

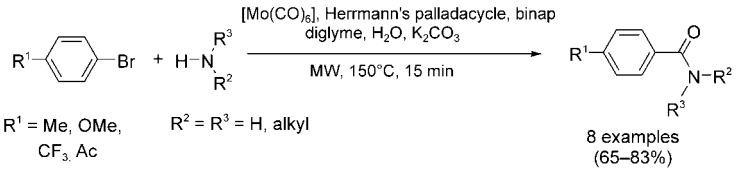


Scheme 12. Ullmann-type carbon–nitrogen and carbon–sulfur bond formations.

examples of microwave-assisted Ullmann-type condensations from researchers at Bristol–Myers Squibb. In the first example, (*S*)-1-(3-bromophenyl)ethylamine was coupled with eleven heteroarenes containing N-H groups in the presence of 10 mol% CuI and 2.0 equivalents of K_2CO_3 base.[105,106] The comparatively high reaction temperature (195 °C) and the long reaction times are noteworthy. For the coupling of 3,5-dimethylpyrazole, for example, microwave heating for 22 h was required to afford a 49% yield of the isolated product! The average reaction times were 2–3 h. In the second example, similar conditions were chosen to react mainly aromatic thiols with aryl bromides and iodides to afford aryl sulfides.[107] The same authors have also described the synthesis of diaryl ethers by copper-catalyzed arylation of phenols with aryl halides.[108]

2.4. *Transition-Metal-Catalyzed Carbonylation Reactions*

Larhed and co-workers took advantage of the rapid and controlled heating made possible by microwave irradiation of solvents under sealed-vessel conditions and reported a number of valuable palladium-catalyzed carbonylation reactions (Scheme 13).[109–113] The key feature of all those proto-

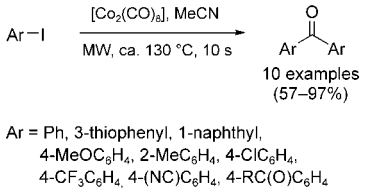


Scheme 13. Palladium-catalyzed aminocarbonylations. Diglyme = diethyleneglycol dimethylether.

cols is the use of molybdenum hexacarbonyl as a solid precursor of carbon monoxide, which is required in carbonylation chemistry. $[Mo(CO)_6]$ liberates enough CO in situ at 150 °C, for example, that rapid aminocarbonylation reactions take place (at 210 °C, CO is liberated instantaneously). The initially reported conditions used a combination of the palladacycle developed by Herrmann and co-workers (7.4 mol% Pd) and binap as the catalytic system in a diglyme/water mixture and provided the desired secondary and tertiary amides in high yield (Scheme 13).[109] As in many other cases, an inert atmosphere was not required.

Subsequent improvements in the experimental protocol allowed the use of sterically and electronically more-demanding amines (for example, anilines, unprotected amino acids), whereby DBU was used as the base and THF as the solvent for both aryl bromides and iodides.[110] Simple modifications of the general strategy outlined in Scheme 13 enabled the corresponding carboxylic acids[109] and esters[111] to be obtained instead of the amides. Further modifications by Alterman and co-workers have resulted in the use of DMF as a source of CO[112] and the use of formamide as a combined source of NH_3 and CO.[113] The latter method is useful for the preparation of primary aromatic amides from aryl bromides. In both cases, strong bases and temperatures around 180 °C (7–20 min) have to be used to mediate the reaction.

A somewhat related process is the cobalt-mediated synthesis of symmetrical benzophenones from aryl iodides and $[Co_2(CO)_8]$ (Scheme 14).[114] Here, $[Co_2(CO)_8]$ is used as a combined activator of the aryl iodide and as CO source. A variety of aryl iodides with different steric and electronic properties underwent the carbonylative coupling in excellent yields when acetonitrile was employed as the solvent. Remarkably, six seconds of microwave irradiation were in



Scheme 14. $[Co_2(CO)_8]$-mediated synthesis of symmetric diaryl ketones.

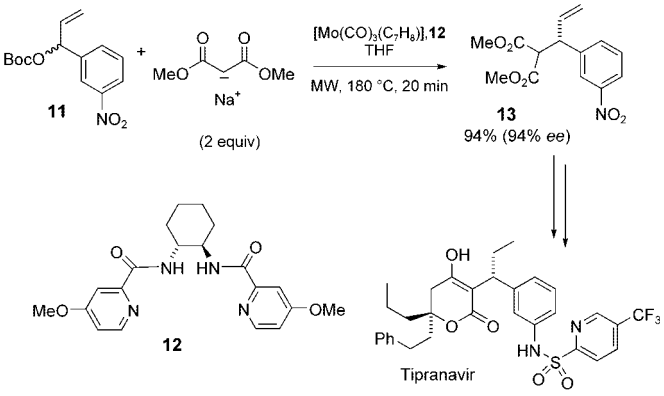
several cases sufficient to achieve full conversion! The use of an inert atmosphere, bases, or other additives were unnecessary. No conversion occurred in the absence of heating, regardless of the reaction time. However, equally high yields could also be achieved by heating the reaction mixture in an oil bath for two minutes.

2.5. Asymmetric Allylic Alkylations

A frequent criticism of microwave synthesis has been that the typically high reaction temperatures will invariably lead to reduced selectivities. This is perhaps the reason why comparatively few enantioselective processes driven by microwave heating have been reported in the literature. For a reaction to occur with high enantioselectivity there must be a large enough difference in the activation energy for the processes leading to the two enantiomers. The higher the reaction temperature, the larger the difference in energy required to achieve high selectivity. Despite these limitations, a number of very impressive enantioselective reactions involving chiral transition-metal complexes have been described. The research groups of Moberg, Hallberg, and Larhed reported on microwave-mediated palladium-[115,116] and molybdenum-catalyzed[117–119] asymmetric allylic alkylation reactions involving neutral carbon, nitrogen, and oxygen nucelophiles in 2000. Both processes were carried out under non-inert conditions and yielded the desired products in high chemical yield and with typical *ee* values of $>98\,\%$.

More recently, Trost and Andersen have applied this concept in their approach to the orally bioavailable HIV inhibitor tipranavir (Scheme 15).[120] Synthesis of the key chiral intermediate **13** was achieved by asymmetric allylic alkylation starting from carbonate **11**. A 94% yield of the product was achieved by employing 10 mol% of the molybdenum precatalyst and 15 mol% of the chiral ligand **12** with 2.0 equivalents of sodium dimethylmalonate as the additive. The reaction was carried out under sealed-vessel microwave heating at 180 °C for 20 minutes. Thermal heating under reflux conditions (67 °C) required 24 h and produced the same chemical yield of intermediate **13**, albeit in slightly higher enantiomeric purity (96% *ee*).

A similar pathway involving a microwave-driven molybdenum-catalyzed asymmetric allylic alkylation (160 °C, 6 min, THF) as the key step was elaborated by Moberg and coworkers for the preparation of the muscle relaxant (*R*)-baclofen.[121] Other enantioselective reactions performed by microwave heating include asymmetric Heck reactions[122] and ruthenium-catalyzed asymmetric hydrogen transfer processes.[123]



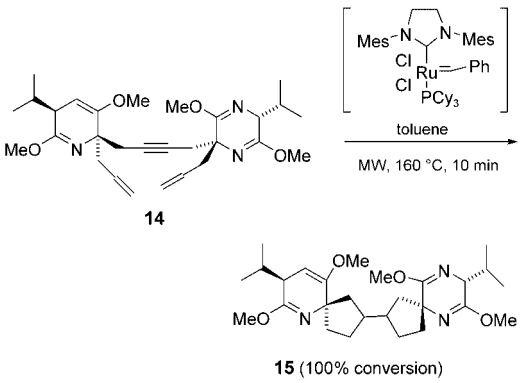
Scheme 15. Molybdenum-catalyzed asymmetric allylic alkylation in the total synthesis of the HIV inhibitor tipranavir. Boc = *tert*-butyloxycarbonyl.

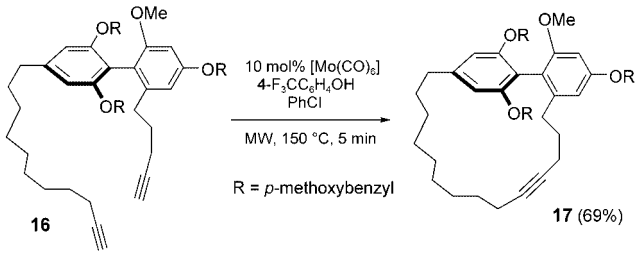
2.6. Other Transition-Metal-Mediated Processes

In recent years the olefin metathesis reaction has attracted widespread attention as a versatile carbon–carbon bond-forming method.[124] Among the numerous different metathesis methods, ring-closing metathesis (RCM) has emerged as a very powerful method for the construction of small, medium, and macrocyclic ring systems.[124] In general, metathesis reactions are carried out at room or at slightly elevated temperatures (for example, at 40 °C in refluxing CH_2Cl_2), sometimes requiring several hours of reaction time to achieve full conversion. With microwaves, otherwise sluggish RCM protocols have been reported to be completed within minutes or even seconds.[49,55,71,125–128] In 2003, for example, Efskind and Undheim reported the domino RCM of dienyne **14** with a Grubbs type II catalyst (Scheme 16).[127] While the thermal process (toluene, 85 °C) required multiple addition of fresh catalyst (3×10 mol%) over a period of 9 h to furnish a 92% yield of product **15**, microwave irradiation for 10 min at 160 °C (5 mol% catalyst, toluene) led to full conversion. The authors ascribe the dramatic rate enhancement to the rapid and uniform heating of the reaction mixture and increased catalyst lifetime by the elimination of wall effects.[127]

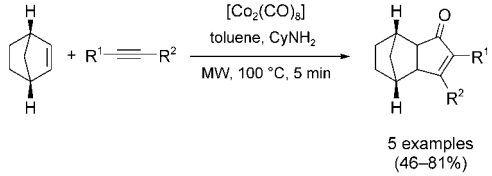
An interesting ring-closing alkyne metathesis reaction (RCAM) was recently reported by Fürstner et al. (Scheme 16).[128] Treatment of diyne **16** with 10 mol% of the catalyst prepared in situ from $[Mo(CO)_6]$ and 4-trifluoromethylphenol at 150 °C for 5 minutes led to a 69% yield of cycloalkyne **17**, which was further manipulated into a naturally occurring DNA cleaving agent of the turriane family. Conventional heating under reflux conditions in chlorobenzene for 4 h produced a 83% yield of product under otherwise identical conditions.

The [2+2+1] cycloaddition of an alkene, an alkyne, and carbon monoxide is often the method of choice for the preparation of complex cyclopentenones.[129] Groth and coworkers have demonstrated that such Pauson–Khand reactions can be carried out very efficiently with microwave heating (Scheme 17);[130] 20 mol% of $[Co_2(CO)_8]$ was suffi-





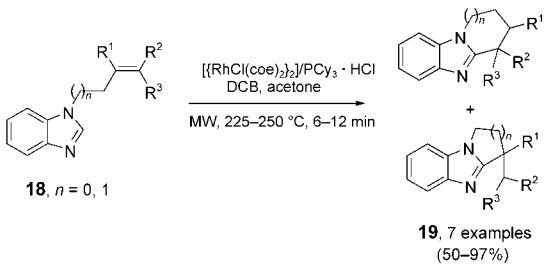
Scheme 16. Ring-closing metathesis reactions of dienynes and alkynes.



Scheme 17. Pauson–Khand [2+2+1] cycloadditions.

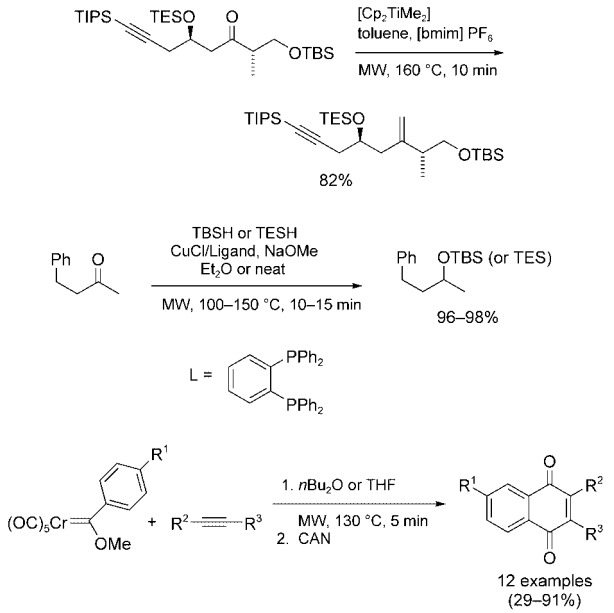
cient to drive all of the studied Pauson–Khand reactions to completion under sealed-vessel conditions, without the need for additional carbon monoxide. Under the carefully optimized reaction conditions utilizing 1.2 equivalents of cyclohexylamine as an additive in toluene, microwave heating for 5 minutes at 100 °C provided good yields of the desired cycloadducts.[130] Similar results were published independently by Evans and co-workers.[131]

Another important reaction principle in modern organic synthesis is C–H bond activation.[132] Bergman, Ellman, and co-workers have introduced a protocol that allows otherwise extremely sluggish inter- and intramolecular rhodium-catalyzed C–H bond activation to occur efficiently under microwave heating conditions. In their investigations, they found that heating the olefin-tethered benzimidazoles **18** in a mixture of 1,2-dichlorobenzene and acetone in the presence of 2.5–5 mol% $[\{RhCl(coe)_2\}_2]$ (coe = cyclooctene) and 5–10 mol% $PCy_3 \cdot HCl$ provided the desired tricyclic heterocyles **19** in moderate to excellent yields (Scheme 18).[133] Microwave heating to 225–250 °C for 6–12 min proved to be the optimum conditions. The solvents were not degassed or dried before use, but air was excluded by purging the reaction vessel with nitrogen.



Scheme 18. Intramolecular coupling of a benzimidazole ring with an alkene group under C–H activation.

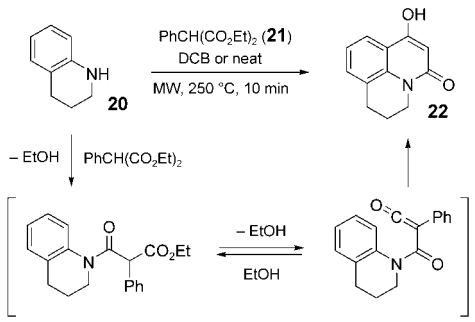
Other microwave-assisted reactions involving metal catalysts or metal-based reagents are shown in Scheme 19.[60,134,135]



Scheme 19. Petasis olefination,[60] hydrosilylation of ketones,[134] and Dötz benzannulation.[135] CAN = cerium ammonium nitrate, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl.

2.7. Heterocycle Synthesis

The formation of heterocyclic rings by cyclocondensation reactions is typically a process well-suited for microwave technology. Many of these condensation reactions require high temperatures and conventional reaction conditions very often involve heating the reactants in an oil, metal, or sand bath for many hours or even days. One representative example is the formation of 4-hydroxy-1*H*-quinolin-2-ones of type **22** from anilines and malonic esters (Scheme 20). The corresponding conventional, thermal protocol involves heating the two components in equimolar amounts in an oil bath at 220–300 °C for several hours (without solvent),[136] whereas similar high yields can be obtained by microwave heating at 250 °C for 10 minutes.[137] Here it was essential to use open-vessel technology, since the two equivalents of the volatile by-product ethanol that formed under normal (atmospheric pressure) conditions were simply distilled off and therefore



Scheme 20. Formation of 4-hydroxy-1*H*-quinolin-2-one **22** from aniline **20** and malonic ester **21**.

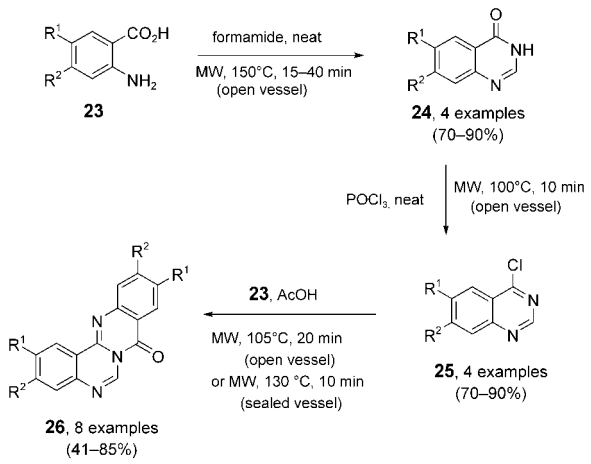
removed from the equilibrium (Scheme 20).[136] Preventing removal of ethanol from the reaction mixture, by using a standard closed-vessel microwave system, leads to significantly lower yields (Table 3). These experiments highlight the importance of choosing appropriate experimental conditions when using microwave heating technology. In the present example, scale-up of the synthesis shown in Scheme 20 would clearly only be feasible by using open-vessel technology.[138]

Table 3: Yields for **22** on microwave heating under closed- and open-vessel conditions (Scheme 20).[a,b]

x [mmol][c]	Solvent [mL]	Yield [%]	*p* [bar]
1	2	76	3.6
2	2	67	5.3
4	2	60	7.4
1	0.5	91	2.0
2	–	92	[d]
4	–	90	[d]

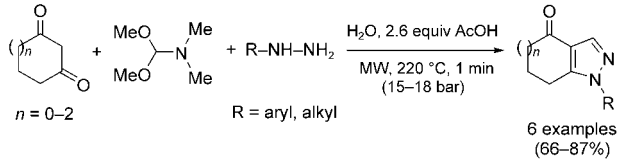
[a] Data from ref. [137]. [b] Microwave heating (250 °C, 10 min) in dichlorobenzene or without solvent. [c] Reaction quantity. [d] Open vessel.

A related cyclocondensation was recently described by Besson and co-workers in the context of synthesizing 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones by Niementowski condensation reactions (Scheme 21).[139] In the first step of this multistep sequence, anthranilic acid derivatives **23** were condensed with formamide (5.0 equiv) under open-vessel microwave conditions (Niementowski condensation).[140] Subsequent chlorination with excess $POCl_3$, again using open-vessel conditions, produced the anticipated 4-chloroquinazoline derivatives **25**, which were subsequently condensed with **23** in acetic acid to produce the tetracyclic target structures **26**. The final condensation reactions were completed within 20 minutes at reflux (ca. 105 °C) under open-vessel conditions, but not surprisingly could also be performed more rapidly by using sealed-vessel heating at 130 °C. The reaction depicted in Scheme 21 is one of the growing number of examples where not only one, often conventionally difficult to execute transformation has been carried out by microwave synthesis, but several steps in a sequence have been performed by microwave dielectric heating.



Scheme 21. Formation of 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **26** by Niementowski condensation.

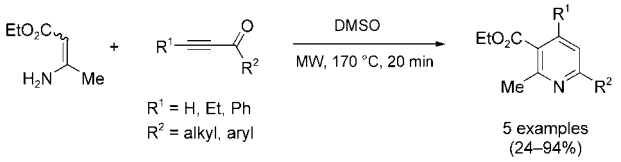
Molteni et al. have described the three-component, one-pot synthesis of fused pyrazoles by treating cyclic 1,3-diketones with dimethylformamide dimethylacetal (DMFDMA) and a suitable bidentate nucleophile such as a hydrazine derivative (Scheme 22).[141] The reaction proceeds with initial formation of an enaminoketone as the key intermediate from the 1,3-diketone and DMFDMA precursors, followed by a tandem addition-elimination/cyclodehydration step. Remarkably, the authors were able to perform the multicomponent condensation by heating all three building blocks together with a small amount of acetic acid (2.6 equiv) in water at 220 °C for 1 minute! Upon cooling the reaction, the desired products crystallized directly and were isolated in high purity by simple filtration. Although most of the starting materials are actually insoluble in water at room temperature, at 220 °C water behaves similar to an organic solvent and is therefore able to dissolve many organic materials that are otherwise not soluble in such a polar solvent. It should be emphasized that high-temperature water chemistry at near-critical conditions (ca. 275 °C, 60 bar) has received considerable attention in recent years,[142] and that sealed-vessel microwave heating technology appears to be an ideal tool to rapidly attain this environment.[5,143] Molteni et al. have successfully used other bidentate nucleophiles such as amidines and hydroxylamine for the synthesis of related heterocycles.[141] Numerous reports of the use of DMFDMA as a building block for the rapid synthesis of a large variety of heterocyclic ring systems by MAOS have also appeared.[144–147]



Scheme 22. Three-component condensation of fused pyrazoles in water.

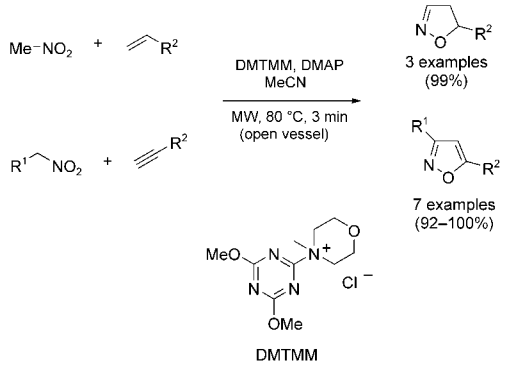
The Bohlmann–Rahtz synthesis of trisubstituted pyridines from β-aminocrotonates and an ethynyl ketone has found application in the preparation of a variety of heterocycles

containing this structural motif.[148] Bagley et al. have developed a microwave-assisted modification of this heteroannulation method, which is best conducted in DMSO at 170 °C for 20 minutes, and provides the desired pyridine derivatives in 24–94 % yield (Scheme 23).[149] A related protocol involving a tandem oxidation/heteroannulation of propargylic alcohols was described by the same authors.[150]



Scheme 23. Bohlmann–Rahtz synthesis of trisubstituted pyridines.

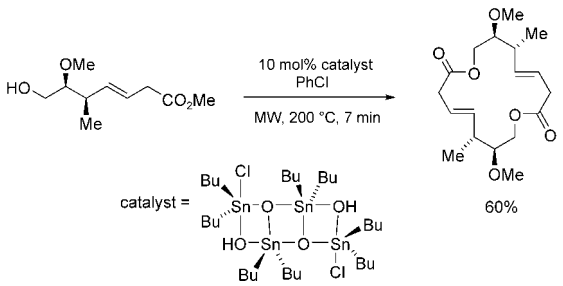
Cycloaddition reactions are clearly very important for the construction of heterocycles, and numerous examples of heterocycle synthesis by controlled microwave heating have been described. For example, nitro alkenes are converted in situ into nitrile oxides by 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) and 4-dimethylaminopyridine (DMAP, Scheme 24).[151] The generated



Scheme 24. Nitrile oxide cycloaddition reactions.

1,3-dipoles undergo cycloaddition with the double or triple bond of an alkene or acetylene dipolarophile (5.0 equiv), respectively, to furnish 4,5-dihydroisoxazoles or isoxazoles. Open-vessel conditions were used and full conversion with very high yields of products was achieved within 3 minutes at 80 °C.

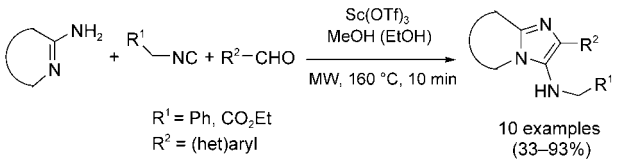
An unusual class of heterocycles are polyketide-derived macrodiolide natural products. The research groups of Porco and Panek have recently shown that stereochemically well-defined macrodiolides can be obtained by cyclodimerization of nonracemic chiral hydroxy esters (Scheme 25).[152] Preliminary experiments involving microwave irradiation demonstrated that exposing dilute solutions of the hydroxy ester (0.02 M) in chlorobenzene to sealed-vessel microwave irradiation conditions (200 °C, 7 min) in the presence of a distannoxane transesterification catalyst led to a 60 % yield of the 16-membered macrodiolide heterocycle. Conventional



Scheme 25. Formation of macrodiolides by cyclodimerization with a distannoxane catalyst.

reflux conditions (ca. 135 °C) in the same solvent (0.01 M of hydroxy ester) provided a 75 % yield after 48 h.

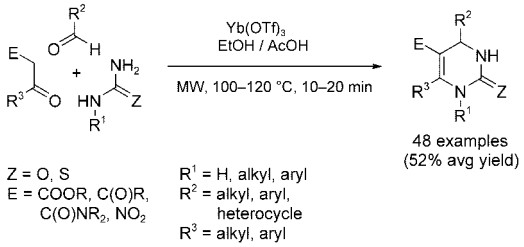
Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses.[153] The Ugi four-component condensation in which an amine, an aldehyde or ketone, a carboxylic acid, and an isocyanide combine to yield an α-acylaminoamide is particularly interesting because of the wide range of products obtainable through variation of the starting materials.[154] The reaction of heterocyclic amidines with aldehydes and isocyanides in the presence of 5 mol % $Sc(OTf)_3$ as a catalyst in an Ugi-type three-component condensation (Scheme 26) generally



Scheme 26. Ugi-type three-component condensation.

requires extended reaction times of up to 72 h at room temperature for the generation of the desired fused 3-aminoimidazoles.[155] Tye and co-workers have demonstrated that this process can be speeded up significantly by performing the reaction under sealed-vessel microwave conditions.[156] A reaction time of 10 min at 160 °C in methanol (in some cases ethanol was employed) produced similar yields of products than the same process at room temperature, but at a fraction of the time.

Another important MCR is the Biginelli synthesis of dihydropyrimidines by the acid-catalyzed condensation of aldehydes, CH-acidic carbonyl components, and urea-type building blocks (Scheme 27).[157] Under conventional conditions this MCR typically requires several hours of heating under reflux conditions (ca. 80 °C) in a solvent such as ethanol. The ideal microwave heating conditions with respect to solvent, catalyst type/concentration, irradiation time, and temperature were rapidly optimized by using the condensation of benzaldehyde, ethyl acetoacetate, and urea as a model reaction.[158] Figure 3 shows the time/temperature optimization profile for the standard Biginelli reaction using 10 mol %



Scheme 27. Biginelli synthesis of dihydropyrimidines through a three-component reaction. Tf = trifluoromethanesulfonyl.

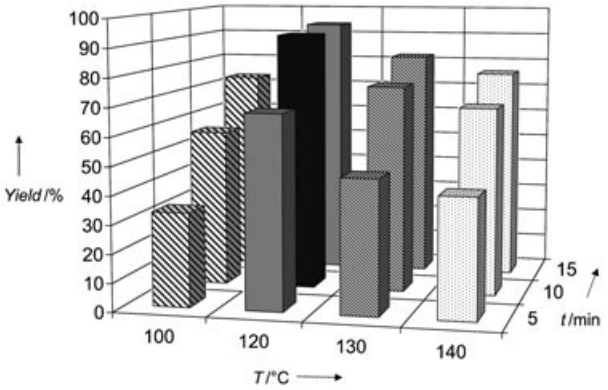


Figure 3. Rapid optimization of reaction time and temperature for the Biginelli condensation of ethyl acetoacetate, benzaldehyde, and urea (Scheme 27) in AcOH/EtOH (3:1) with 10 mol% $Yb(OTf)_3$ as a catalyst. The optimal conditions (marked in black: 120 °C, 10 min) affords the product in 92% yield.

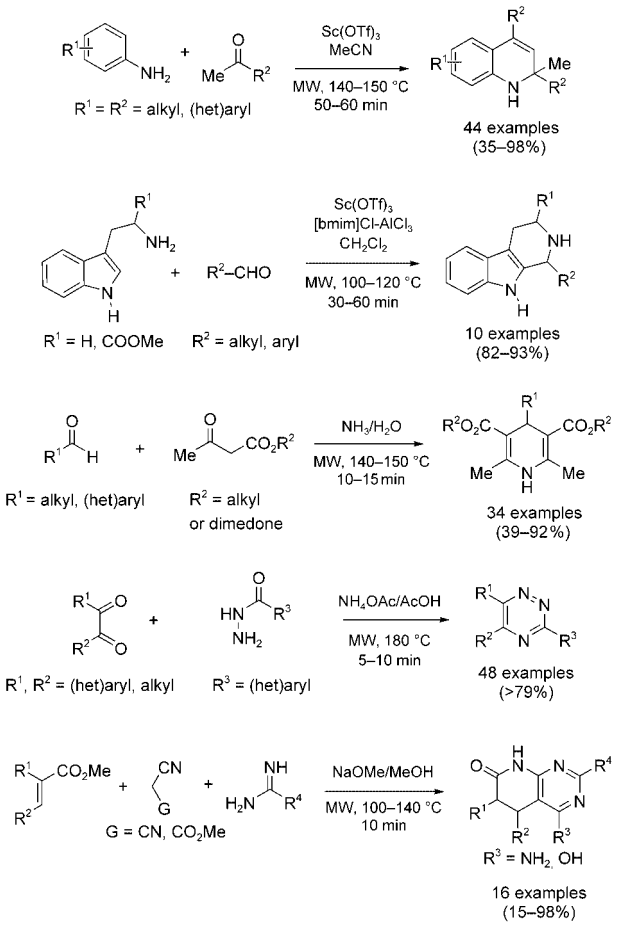
ytterbium triflate in a acetic acid/ethanol (3:1). An optimum yield of 92% of isolated dihydropyrimidine ($R^1 = H$, $Z = O$, $R^2 = Ph$, $E = CO_2Et$, $R^3 = Me$) was obtained by heating the mixture of reactants at 120 °C for 10 minutes. The fact that a temperature only marginally higher than the optimal reaction temperature leads to a significantly decreased yield for this transformation[159] underscores the importance of using controlled microwave irradiation conditions with adequate temperature control.

Figure 3 illustrates one of the key advantages of high-speed microwave synthesis, namely the rapid optimization capabilities that are particularly useful if microwave heating is coupled with automation.[158] Recent work by researchers from Arqule and Pfizer has demonstrated how the overall process can be further improved if rapid testing and tuning of reaction conditions involving microwave heating is coupled with statistical experimental design.[160] This is a particularly valuable method if a large number of reaction parameters needs to be considered.

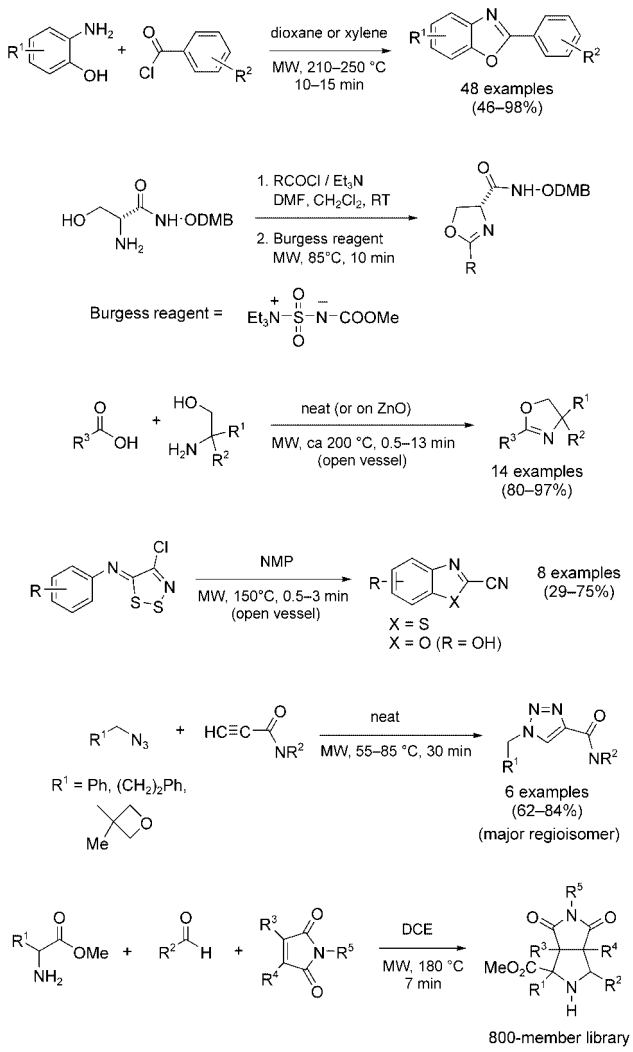
The above-mentioned robotics are also useful for preparing compound libraries through automated sequential microwave synthesis. A diverse set of 17 CH-acidic carbonyl compounds, 25 aldehydes, and 8 urea/thioureas was used for the preparation of a dihydropyrimidine library under the optimized conditions for the Biginelli reaction displayed in Scheme 27. Out of the full set of 3400 possible dihydropyrimidine derivatives, a representative subset of 48 analogues was prepared within 12 h by automated addition of building blocks and subsequent sequential microwave irradiation of each reaction vessel in a single-mode microwave reactor equipped with suitable robotics.[158]

In a conceptually different approach, Nüchter, Ondruschka et al. presented the parallel generation of a 36-member library of Biginelli dihydropyrimidines in a suitable multivessel rotor placed inside a dedicated multimode microwave reactor.[161,162] Given the fact that modern multimode microwave reactors can operate with specifically designed 96-well plates under sealed-vessel conditions, the parallel approach offers a considerable higher throughput than the automated sequential technique, albeit at the cost of having less control over the reaction parameters for each individual vessel/well. One additional limitation of the parallel approach is that all reaction vessels during library production are exposed to the same irradiation conditions in terms of reaction time and microwave power, thus not allowing specific needs of individual building blocks to be addressed by varying the time or temperature.

A range of other heterocyclic ring systems synthesized by microwave-assisted cyclocondensation or cycloaddition protocols is shown in Schemes 28 and 29.



Scheme 28. Skraup synthesis of dihydroquinolines,[163] Pictet–Spengler reaction,[57] Hantzsch–MCR synthesis of dihydropyridines,[164] triazine synthesis,[165] and Victory reaction.[166]



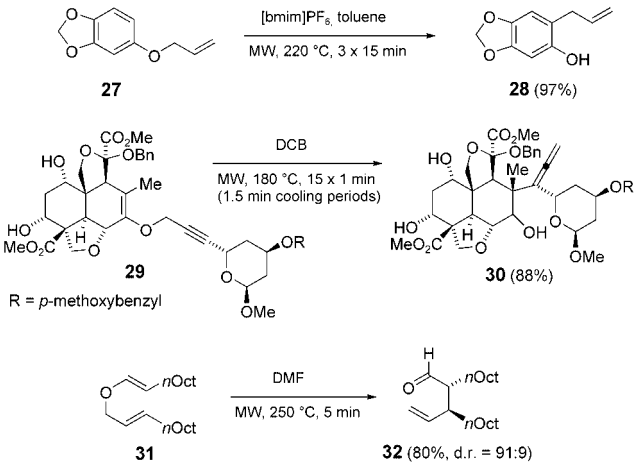
Scheme 29. Synthesis of benzoxazoles,[167] oxazolidines,[168,169] and benzothiazoles,[170] 1,3-dipolar cycloaddition reaction to form triazoles,[171] and [3+2] cycloadditions of azomethine ylides and maleimide.[172] DCE = 1,2-dichloroethane, DMB = 2,4-dimethoxybenzyl.

2.8. Miscellaneous Solution-Phase Organic Transformations

Since MAOS is becoming an increasingly popular tool for a steadily growing number of researchers, both in academia and industry, it becomes evident that, in principle, all chemical transformations requiring heat can be carried out under microwave conditions. The following literature survey of organic chemical transformations carried out in the solution phase by microwave heating is therefore limited to selected examples that highlight particularly interesting reactions or applications.

2.8.1. Rearrangements

Ley and co-workers have described the microwave-assisted Claisen rearrangement of allyl ether **27** in their synthesis of the natural product carpanone (Scheme 30).[173] A 97% yield of the rearranged product **28** could be obtained by three successive 15-minute irradiations at 220°C using



Scheme 30. Examples of Claisen rearrangements. Bn = benzyl.

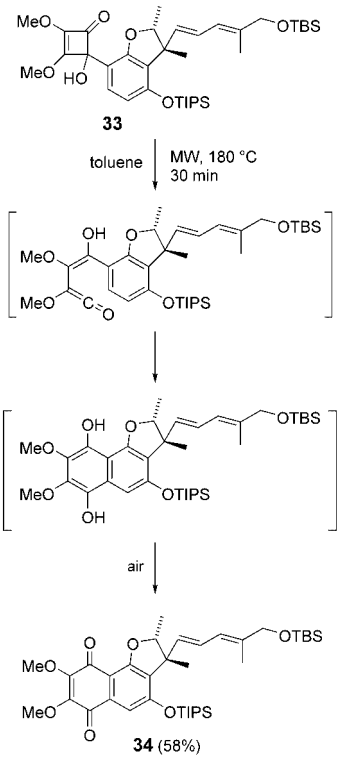
toluene doped with the ionic liquid [bmim]PF_6 as the solvent. Interestingly, one single irradiation of 45 minutes at the same temperature gave a somewhat lower yield (86%).

A related Claisen rearrangement, albeit on a much more complex substrate was reported by the same research group, again under "pulsed" microwave irradiation conditions. Heating a solution of the propargylic enol ether **29** in dichlorobenzene at 180°C for 15 minutes resulted in a 71% yield of the desired allene **30** as a single diastereomer, which was further elaborated into the skeleton of the triterpenoid natural product azadirachtin.[174] An 88% yield of product was obtained by applying 15 pulses irradiation of 1 minute duration. No rationalization for the increased yields in these "pulsed versus continuous irradiation" experiments can be given at present. Nordmann and Buchwald recently reported the diastereoselective Claisen rearrangement of allyl vinyl ether **31** to aldehyde **32**.[175] The product was obtained in 80% yield with a diastereomeric ratio of 91:9 by microwave heating at 250°C for 5 minutes in DMF. Conventional heating at 120°C for 24 hours provided somewhat higher yields and selectivities (90% yield, d.r. = 94:6).

In their search for synthetic routes to analogues of the furaquinocin antibiotics, Trost et al. have utilized a microwave-assisted squaric acid/vinylketene rearrangement to synthesize dimethoxynaphthoquinone **34**, a protected analogue of furaquinocin E (Scheme 31).[176] Since the conventional rearrangement conditions successfully applied in a closely related series of transformations (toluene, 110°C) led to incomplete conversion, the reaction was attempted by microwave heating at 180°C; this afforded an acceptable yield of **34** (58%) after oxidation to the naphthoquinone.

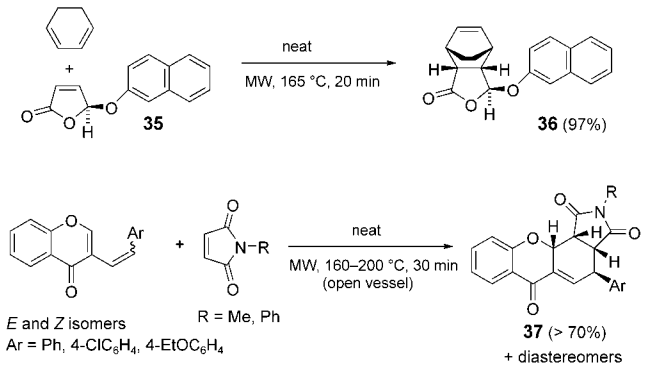
2.8.2. Cycloaddition Reactions

Cycloaddition reactions were among the first transformations to be studied by using microwave heating technology,[3,7] and numerous examples have been summarized in previous review articles and book chapters.[4–16] Conventional cycloaddition reactions require, in many cases, the use of harsh conditions such as high temperatures and long reaction times, but they can be performed with great success with the aid of



Scheme 31. Rearrangement of a squaric acid derivative to a vinylketene, which further reacts to form the tricyclic product **34**.

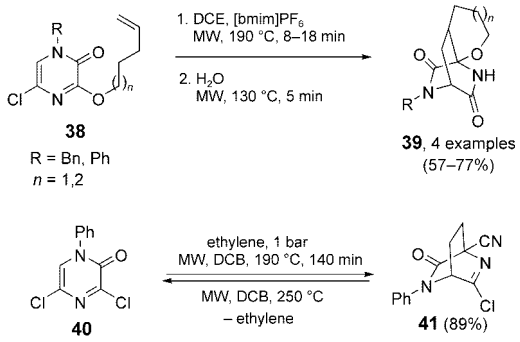
microwave heating. Scheme 32 shows two recent examples of Diels–Alder cycloadditions performed by microwave dielectric heating. In both cases the diene and dienophile were



Scheme 32. Examples of Diels–Alder cycloadditions.

reacted neat without the addition of solvent. For the transformation **35**→**36** described by Trost and Crawley, irradiation for 20 minutes at 165 °C (or for 60 min at 150 °C) gave the cycloadduct **36** in near quantitative yield.[177] In the process reported by de la Hoz and co-workers, open-vessel irradiation of 3-(2-arylethenyl)chromones with maleimides at 160–200 °C for 30 minutes furnished the tetracyclic adducts of type **37** along with minor amounts of other diastereoisomers.[178]

Inter- and intramolecular hetero-Diels–Alder cycloaddition reactions of a series of functionalized 2(1*H*)-pyrazinones have been studied in detail by the research group of Van der Eycken (Scheme 33).[54,179,180] In the intramolecular series, cycloaddition of alkenyl-tethered 2(1*H*)-pyrazinones **38** requires 1–2 days under conventional thermal conditions



Scheme 33. Hetero-Diels–Alder cycloaddition reactions of 1*H*-pyrazin-2-ones.

(chlorobenzene, reflux, 132 °C). The use of 1,2-dichloroethane doped with the ionic liquid [bmim]PF_6 and sealed-vessel microwave technology at 190 °C enabled the same transformations to be completed within 8–18 minutes.[54] The primary imidoyl chloride cycloadducts were not isolated, but rapidly hydrolyzed by addition of small amounts of water and microwave irradiation (130 °C, 5 min). The overall yields of **39** were in the same range as reported for the conventional thermal protocols.[54]

In the intermolecular series, the Diels–Alder cycloaddition reaction of the pyrazinone heterodiene **40** with ethylene led to the bicyclic cycloadduct **41** (Scheme 33).[54] Under conventional conditions, these cycloaddition reactions have to be carried out in an autoclave at an ethylene pressure of 25 bar before the setup is heated to 110 °C for 12 hours. In contrast, the Diels–Alder addition of pyrazinone precursor **40** with ethylene in a sealed vessel that had been flushed with ethylene before sealing was completed after irradiation for 140 minutes at 190 °C. It was however not possible to further increase the reaction rate by raising the temperature. At temperatures above 200 °C an equilibrium between the cycloaddition **40**→**41** and the competing retro-Diels–Alder fragmentation process was observed (Scheme 33).[54] Only by using a microwave reactor that allowed pre-pressurization of the reaction vessel with 10 bar of ethylene could the Diels–Alder addition **40**→**41** be carried out much more efficiently at 220 °C within 10 minutes.[179]

2.8.3. Oxidations

The osmium-catalyzed dihydroxylation reaction, the addition of osmium tetroxide to olefins to produce a vicinal diol, is one of the most selective and reliable organic transformations. Recent work by Sharpless, Fokin, and co-workers has uncovered that electron-deficient olefins can be converted into the corresponding diols much more efficiently when the reaction medium is kept acidic.[181] One of the most useful additives in this context is citric acid (2.0 equiv), which

in combination with 4-methylmorpholine *N*-oxide (NMO) as the reoxidant for Os^{VI} and $K_2OsO_2(OH)_4$ (0.2 mol%) as a stable, nonvolatile substitute for OsO_4, allows the conversion of many olefinic substrates into their corresponding diols at ambient temperatures. In specific cases, such as for the extremely electron-deficient olefin **42** (Scheme 34), the reaction had to be carried out under microwave irradiation at 120°C to produce the pure diol **43** in 81% yield.[181]

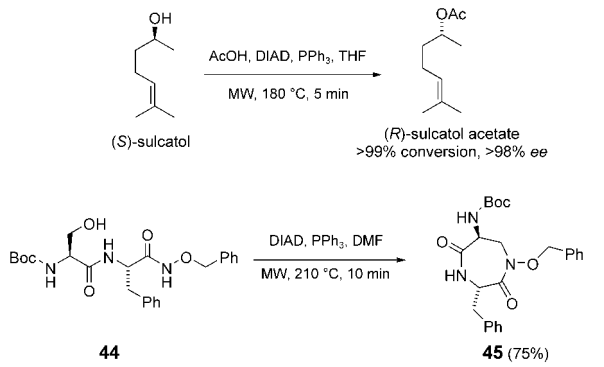
Scheme 34. Osmium-catalyzed dihydroxylation of electron-deficient alkenes.

Another industrially important oxidation reaction is the conversion of cyclohexene into adipic acid. The well-known Noyori method uses hydrogen peroxide, a catalytic amount of tungstate, and a phase-transfer catalyst to afford the clean oxidation of cyclohexene to adipic acid. Ondruschka and co-workers have demonstrated that a modified protocol employing microwave heating without solvent gave comparable yields of the desired product, but in a much shorter time.[182] Rhodium and ruthenium-catalyzed hydrogen transfer type oxidations of primary and secondary alcohols have also been reported recently.[183]

2.8.4. *Mitsunobu Reactions*

The Mitsunobu reaction is a powerful stereochemical transformation. This reaction is very efficient for inverting the configuration of chiral secondary alcohols since a clean S_N2 process is generally observed ("Mitsunobu inversion"). The fact that the Mitsunobu reaction is typically carried out at or below room temperature would suggest that high-temperature Mitsunobu reactions performed under microwave conditions would have little chance of success. It was established in 2001 that Mitsunobu reactions can indeed be carried out at high-temperatures to effect an enantioconvergent approach to the aggregation pheromones (*R*)- and (*S*)-sulcatol (Scheme 35).[184] While the conventional Mitsunobu protocol carried out at room temperature proved to be extremely sluggish, complete conversion of (*S*)-sulcatol to the *R* acetate (S_N2 inversion) using essentially the standard Mitsunobu conditions (1.9 equiv DIAD, 2.3 equiv Ph_3P) was achieved within 5 minutes at 180°C under sealed-vessel microwave conditions. Despite the high reaction temperatures, no by-products could be identified in these Mitsunobu experiments, and the *R* acetate was formed in >98% *ee*.

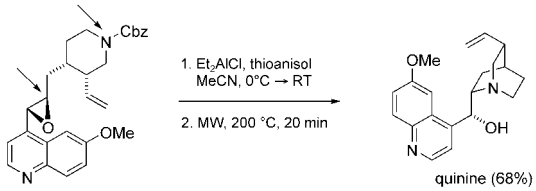
An application of these rather unusual high-temperature Mitsunobu conditions for the preparation of conformationally constrained peptidomimetics based on the 1,4-diazepan-2,5-dione core was recently disclosed by the group of Taddei and co-workers.[185] Cyclization of the dipeptide hydroxyhydroxamate **44** under the DIAD/Ph_3P microwave conditions



Scheme 35. Mitsunobu reactions. DIAD = diisopropylazodicarboxylate.

(210°C, 10 min) provided the desired 1,4-diazepan-2,5-dione **45** in 75% yield. Standard room-temperature conditions (DMF, 12 h) were significantly less efficient and gave only 46% of the desired compound.

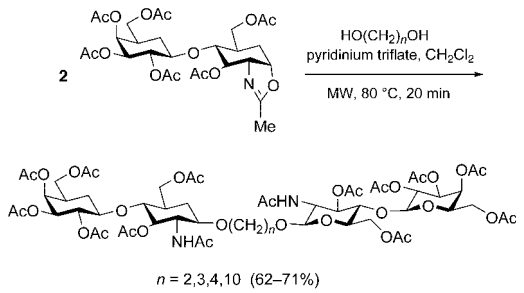
Another microwave-mediated intramolecular S_N2 reaction results in the formation of one of the key steps in a recent catalytic asymmetric synthesis of the cinchona alkaloid quinine by Jacobsen and co-workers.[186] The strategy to construct the crucial quinuclidine core of the natural product relies on an intramolecular S_N2 reaction/epoxide ring opening (Scheme 36). After removal of the benzyl carbamate (Cbz) protecting group with Et_2AlCl/thioanisole, microwave heating of the acetonitrile solution to 200°C for 20 minutes provided a 68% yield of the natural product as the final transformation in a 16-step total synthesis.



Scheme 36. Intramolecular S_N2 reaction in the total synthesis of quinine.

2.8.5. *Glycosylation Reactions*

Glycosylation reactions involving oxazoline donors are generally rather slow and require prolonged reaction times because of the low reactivity of the donors. Oscarson and co-workers have reported the preparation of dimers of *N*-acetyllactosamine linked by alkyl spacers by microwave-assisted glycosylations with oxazoline donors in the presence of pyridinium triflate as a promoter (Scheme 37).[187] Rapid and efficient coupling was achieved in dichloromethane with four different diols using 2.2 equivalents each of the oxazoline donor and pyridinium triflate promotor. Microwave irradiation at 80°C for 20 minutes led to moderate to high yields of the dimers, with yields increased by 12–15% over the conventional process. Fraser-Reid and co-workers recently described related saccharide couplings by employing *n*-pentenylglycosyl donors and *N*-iodosuccinimide (NIS) as

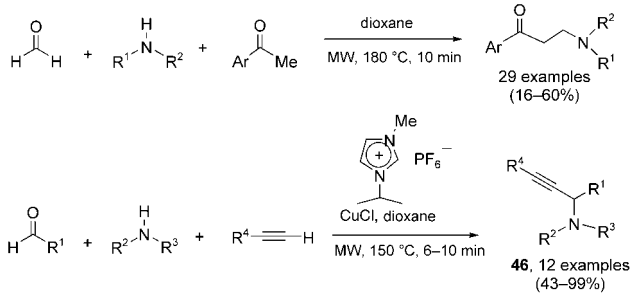


Scheme 37. Microwave-assisted glycosylation reactions.

the promotor in acetonitrile.[31] Various rapid microwave-assisted protection and deprotection methods are also known in the area of carbohydrate chemistry.[188]

2.8.6. Multicomponent Reactions

The Mannich reaction has been known since the early 1900s and has since then been one of the most important transformations to produce β-amino ketones. Although the reaction is powerful, it suffers from some disadvantages, such as the need for drastic reaction conditions, long reaction times, and sometimes low yields of products. Luthman and co-workers have reported microwave-assisted Mannich reactions that employed paraformaldehyde as a source of formaldehyde, a secondary amine in the form of its hydrochloride salt, and a substituted acetophenone (Scheme 38).[189] Optimized



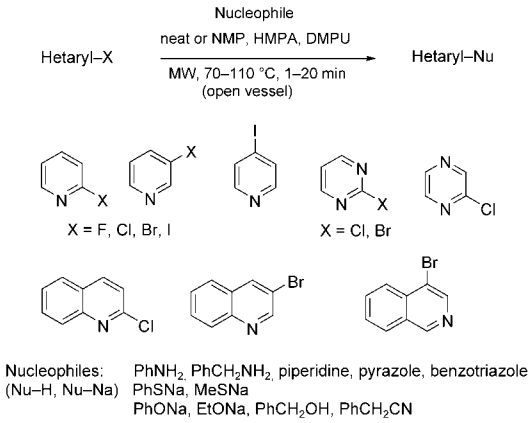
Scheme 38. Examples of Mannich condensations and related reactions.

reaction conditions utilized equimolar amounts of reactants, dioxane as solvent, and microwave irradiation at 180 °C for 8–10 minutes to produce the desired β-amino ketones in moderate to good yields. Importantly, in several examples the reaction was performed both on a 2-mmol scale using a single-mode microwave reactor and also on a 40-mmol scale using a dedicated multimode instrument. As seen with other transformations described earlier (Scheme 1), all the microwave-assisted Mannich reactions studied proved to be "directly scalable": nearly identical yields were obtained on a 2-mmol and 40-mmol scale without the need for reoptimization of the reaction conditions.[189]

The research group of Leadbeater reported a different type of Mannich reaction, which involved condensation of an aldehyde (1.5 equiv) with a secondary amine and a terminal acetylene in the presence of CuCl (10 mol%) to activate the terminal acetylene (Scheme 38).[58] Optimum yields of propargylamines **46** were obtained by microwave irradiation of the three building blocks with the catalyst in dioxane doped with an ionic liquid at 150 °C for 6–10 minutes. A high-speed microwave approach also exists for the Petasis multicomponent reaction (boronic-Mannich reaction)[190] and for the Kindler thioamide synthesis (the condensation of an aldehyde, amine, and sulfur).[191]

2.8.7. Nucleophilic Aromatic Substitution

An alternative to the palladium-catalyzed Buchwald–Hartwig reactions and the related copper-catalyzed methods for C(aryl)–N, C(aryl)–O, and C(aryl)–S bond formations (Section 2.3) are nucleophilic aromatic substitution reactions. A benzene derivative substituted by a leaving group may be treated, for example, with an amine, but here the benzene derivative must generally also contain an electron-withdrawing group. Such nucleophilic aromatic substitution reactions are notoriously difficult to perform and often require high temperatures and long reaction times. A number of publications report efficient nucleophilic aromatic substitutions driven by microwave heating involving either halogen-substituted aromatic[192,193] or heteroaromatic systems.[72,73,194–196] Scheme 39 summarizes some heteroaromatic

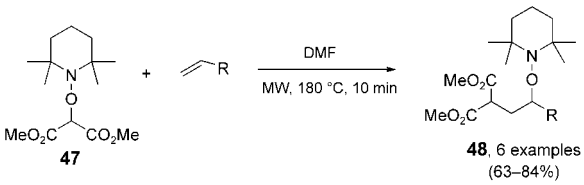


Scheme 39. Nucleophilic aromatic substitution reactions involving halo-substituted N-heterocycles. DMPU = *N*,*N*′-dimethyl-*N*,*N*′-propylene urea, HMPA = hexamethyl phosphoramide.

systems and nucleophiles along with the reaction conditions that have been developed by Cherng for microwave-assisted nucleophilic substitution reactions.[194–196] In general, the microwave-driven processes provide significantly higher yields of the desired products in much shorter reaction times.

2.8.8. Radical Reactions

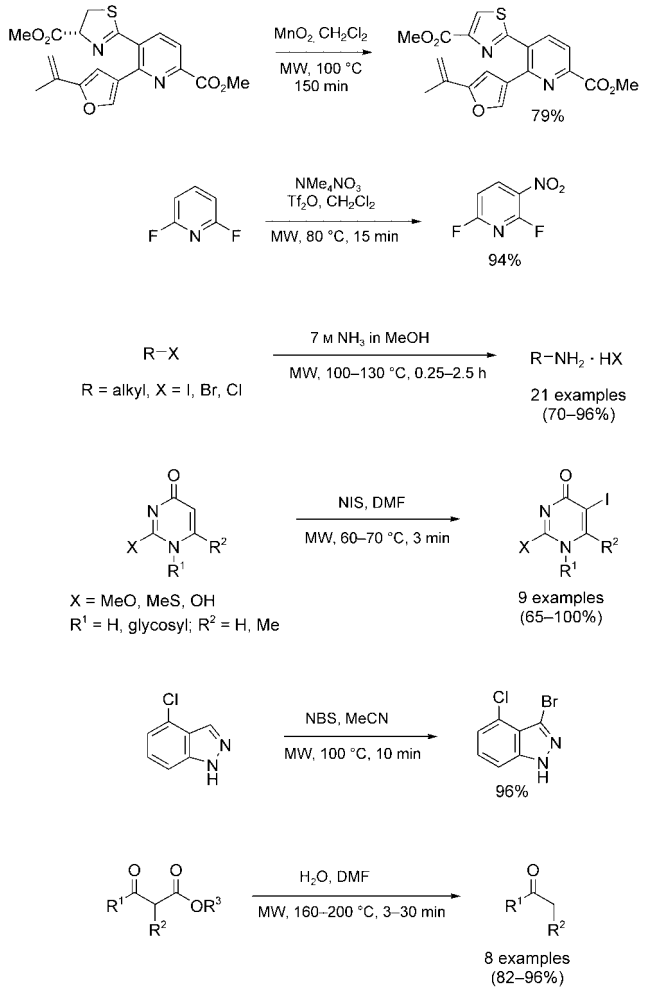
There are only a limited number of examples in the literature that involve radical reactions under controlled microwave heating conditions.[197] Wetter and Studer have described radical carboaminoxylations of various nonactivated olefins and difficult radical cyclizations (Scheme 40).[198]



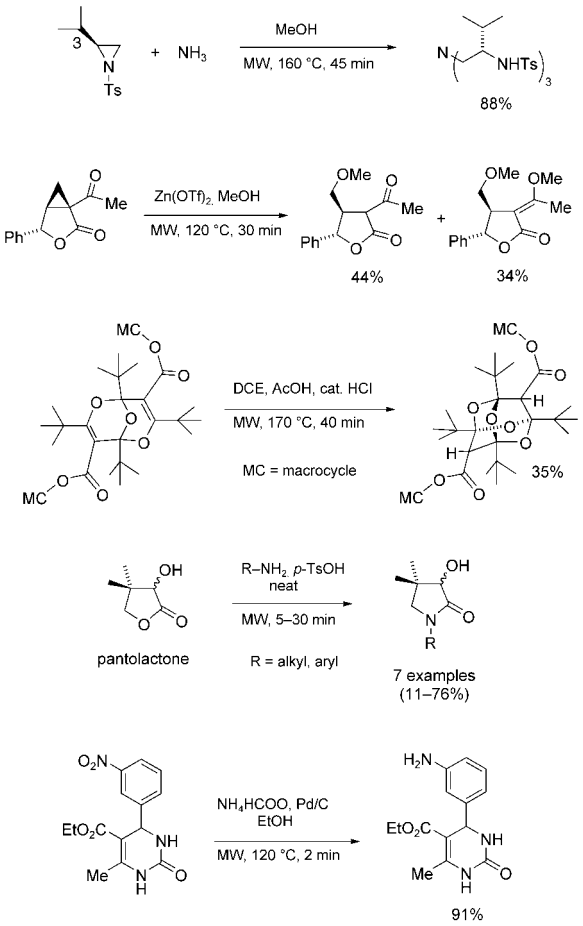
Scheme 40. Radical carboxaminations with malonyl radicals.

The thermally reversible homolysis of alkoxyamine **47** generates the stable radical 2,2,6,6-tetramethylpiperidinyl-1-ol (TEMPO) and a stabilized transient malonyl radical, which subsequently reacts with an alkene to afford the carboaminoxylation product **48**. These radical addition processes take up to three days under conventional conditions (DMF, sealed tube, 135 °C), while the same transformation was complete after microwave heating at 180 °C for 10 minutes in a sealed vessel; higher yields were also obtained in all but one example.

Several other selected examples of microwave-assisted organic transformations are summarized in Schemes 41 and 42.



Scheme 41. Oxidation of thiazolidines,[199] electrophilic nitration,[200] amination,[201] iodination,[87] bromination,[73] and dealkoxycarbonylation reactions.[202] NBS = *N*-bromosuccinimide.



Scheme 42. Aziridine[203] and cyclopropane ring-opening,[204] double Michael addition,[205] lactam formation,[206] and reduction of a nitro group by catalytic transfer hydrogenation.[207] Ts = toluenesulfonyl.

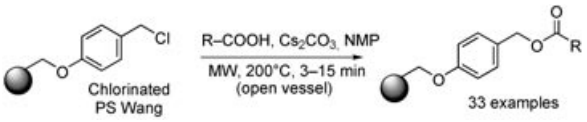
2.9. Combinatorial and High-Throughput Methodologies

2.9.1. Solid-Phase Organic Synthesis

Solid-phase organic synthesis (SPOS) exhibits several advantages compared with classical protocols in solution. Reactions can be accelerated and driven to completion by using a large excess of reagents, as these can easily be removed by filtration and subsequent washing of the solid support. In addition, SPOS can easily be automated by using appropriate robotics and applied to "split-and-mix" strategies, useful for the synthesis of large combinatorial libraries.[208] However, SPOS also exhibits several shortcomings, as a result of the inherent nature of the heterogeneous reaction conditions; nonlinear kinetic behavior, slow reactions, solvation problems, and degradation of the polymer support, because of the long reaction times, are some of the problems typically experienced in SPOS. A technique such as microwave-assisted synthesis which is able to address some of these issues is therefore of considerable interest, particularly for research laboratories involved in high-throughput synthesis. As far as the polymer supports for microwave-assisted SPOS are concerned, the use of cross-linked macroporous or microporous polystyrene resins has been most prevalent. In contrast to the common belief that the use of polystyrene

resins limits the reaction conditions to temperatures below 130 °C, it has recently been amply demonstrated, both in microwave-assisted SPOS and in the use of polymer-supported reagents and catalysts (see Section 2.9.4), that these resins can withstand microwave irradiation for short periods of time even at temperatures above 200 °C.

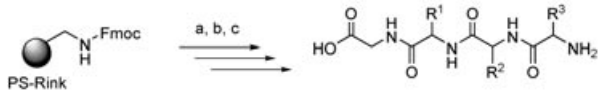
Early examples of SPOS under controlled microwave conditions[12] typically involved the use of microwaves in one single step to either attach or cleave material onto or off the resin. A study published in 2001 demonstrated that high-temperature microwave heating (200 °C) can be effectively employed to attach aromatic carboxylic acids to chloromethylated polystyrene resins (Merrifield and Wang) by the cesium carbonate method (Scheme 43).[209] Significant rate



Scheme 43. Attachment of aromatic carboxylic acids to chlorinated polystyrene Wang resin.

accelerations and higher loadings were observed when the microwave-assisted protocol was compared to the conventional thermal method. Reaction times were reduced from 12–48 hours with conventional heating at 80 °C to 3–15 minutes with microwave heating at 200 °C in NMP in open glass vessels. A comparison of the kinetics of the thermal coupling of benzoic acid to the chlorinated Wang resin at 80 °C with the microwave-assisted coupling at the same temperature demonstrated the absence of any microwave effects.

Peptide synthesis has long been one of the cornerstones of solid-phase organic synthesis, and attempts to speed up the rather time-consuming process by microwave heating were made as early as 1992.[210] Erdélyi and Gogoll recently applied controlled microwave irradiation to the synthesis of a small tripeptide containing three of the most hindered natural amino acids (Thr, Val, Ile; Scheme 44).[211]



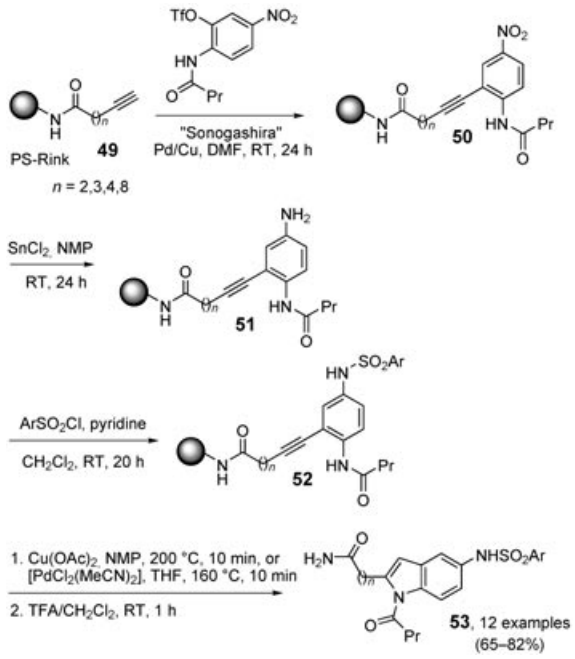
Scheme 44. Synthesis of a tripeptide. a) deprotection with piperidine at RT; b) coupling reagent, Fmoc-protected amino acid, iPr$_2$NEt, DMF, MW, 110 °C, 20 min; c) TFA, RT, 2 h. Fmoc = 9-fluorenylmethoxycarbonyl, TFA = trifluoroacetic acid.

A variety of common coupling reagents have been investigated for the synthesis of this rather difficult peptide sequence on standard Rink polystyrene resin. The coupling of the activated amino acids under microwave conditions was completed in a few minutes (1.5–20 min) without the need for double or triple coupling steps as in conventional protocols. Most of the coupling reagents used showed increased coupling efficiency up to 110 °C, with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) being the most effective, and allowed complete coupling within 1.5 minutes at 110 °C. Decomposition of the reagents was indicated by a color change of the reaction mixtures above this temperature. However, no degradation of the solid support was observed. Furthermore, both LC-MS and ^{1}H NMR spectroscopic analysis confirmed the absence of racemization during the high-temperature treatment, despite the presence of the diisopropylethylamine base.

The formation of a number of related peptide bonds have been reported under optimized microwave conditions.[212] In fact, specialized equipment dedicated specifically to microwave-assisted solid-phase peptide synthesis is commercially available.[36]

As in solution-phase chemistry (see Sections 2.2 and 2.3), many transition-metal-catalyzed transformations have been conducted successfully on a solid phase by using microwave-assisted techniques. Examples include solid-phase Suzuki-,[213] Stille-,[213] and Sonogashira couplings,[214] Negishi reactions,[92] Mo-catalyzed allylic alkylations,[117] aminocarbonylations,[110] cyanation reactions,[215] trifluoromethanesulfonations,[82] Buchwald–Hartwig aminations,[216] and Cu-catalyzed Ullmann-type C-N arylations.[217]

An interesting example of a transition-metal-mediated microwave-assisted SPOS involving either Cu^{II}- or Pd^{II}-mediated cyclizations of 2-alkynylanilides to indoles has been studied by Dai et al. (Scheme 45).[218] The required alkynylanilide precursor **52** was constructed on Rink resin following standard SPOS procedures. The desired cyclization step **52**→**53** was extremely sluggish under conventional thermal conditions and only partial ring closure was observed (80 °C, 4–5 h). In contrast, dielectric heating with microwaves for 10 minutes at 160 °C in THF in the presence of 20 mol % of [PdCl$_2$(MeCN)$_2$] afforded indole **53** (Ar = p-CF$_3$C$_6$H$_4$, n =

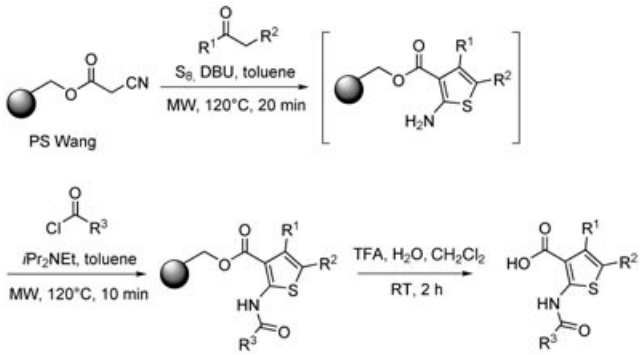


Scheme 45. Pd- or Cu-mediated ring closure of resin-bound 2-alkynyl anilides to indoles.

8) in 75% yield and 94% purity after cleavage. Alternatively, the equivalent Cu^{II}-mediated process (1 equiv of $Cu(OAc)_2$, NMP, 200 °C, 10 min) also provided the desired indoles in similar yields and purities. The authors specifically note that no decomposition of the resin was observed even at 200 °C.

A related indole synthesis on Rink resin based on the Pd-catalyzed cyclization of propargylamines to iodoanilines was published by Berteina-Raboin and co-workers.[219] In this case, open-vessel microwave technology was used for all the three steps of the synthesis (< 15 min, < 140 °C) as well as for the final cleavage reaction, which was carried out at room temperature. Higher yields of final products were achieved in much shorter reaction times by using the microwave protocol as compared to conventional heating.

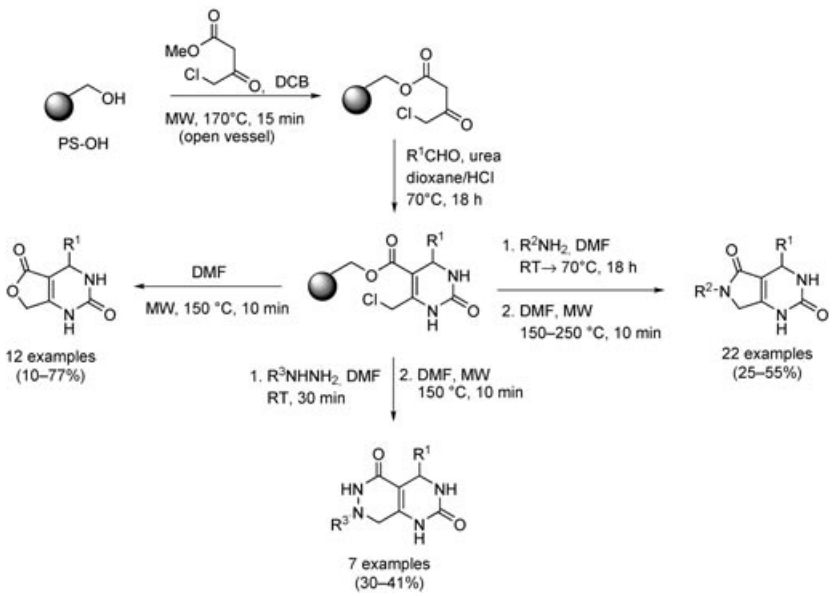
An interesting multicomponent reaction is the Gewald synthesis of 2-amino-3-acylthiophenes. Earlier reports of the classical Gewald synthesis had described the rather long reaction times required by conventional heating and the laborious purification of the resulting thiophenes. In view of these issues, researchers from Morphochem investigated a "one-pot" microwave-assisted Gewald synthesis on a commercially available cyanoacetylated Wang resin as the solid support (Scheme 46).[220] The overall two-step reaction procedure,



Scheme 46. Gewald synthesis of 2-acylaminothiophenes through a three-component reaction.

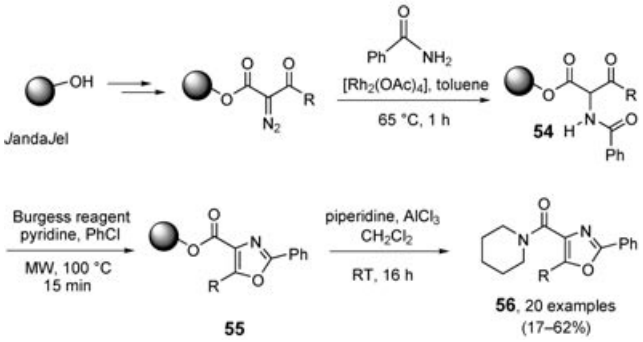
including the acylation of the initially formed 2-aminothiophenes, could be performed in less than one hour. This process is an efficient route to 2-acylaminothiophenes which requires no filtration between the two reaction steps. Various aldehydes, ketones, and acylating agents have been employed to generate the desired thiophene products in high yields (81–99%) and in generally good purities.

Kappe and co-workers have reported a multistep solid-phase synthesis of bicyclic pyrimidine derivatives by a Biginelli muticomponent reaction combined with multidirectional cyclative cleavage reactions (Scheme 47).[221] This approach required the synthesis of the 4-chloroacetoacetate resin as the key starting material, which was prepared by microwave-assisted acetoacetylation of hydroxymethyl polystyrene resin. In analogy to earlier work,[222] this transesterification was best carried out under open-vessel conditions in 1,2-dichlorobenzene (170 °C) to allow the formed methanol to be removed from the equilibrium (see also Scheme 20). This resin precursor was subsequently treated with urea and various aldehydes in an acid-catalyzed Biginelli multicomponent reaction (dioxane, 70 °C) to afford the corresponding resin-bound dihydropyrimidinones. The desired furo[3,4-*d*]pyrimidine-2,5-diones were obtained by cyclative release in DMF at 150 °C. Pyrrolo[3,4-*d*]pyrimidine-2,5-diones were also synthesized using the same pyrimidine resin precursor, which was first treated with a representative set of primary amines to substitute the chlorine atom. Subsequent cyclative cleavage was carried out at temperatures between 150 and 250 °C and led to the corresponding pyrrolopyrimidine-2,5-dione products in high purity. The synthesis of pyrimido[4,5-*d*]pyridazine-2,5-diones was carried out in a similar manner, by employing hydrazines for the nucleophilic substitution prior to cyclative cleavage. A number of related microwave-assisted cyclative-release protocols have been reported.[223,224]



Scheme 47. Preparation of various bicyclic dihydropyrimidinones by cyclative cleavage.

Apart from traditional cross-linked polystyrene resins a number of different supports and formats have been used in microwave-assisted SPOS. These include tentagel resins,[117,213,214,225] cellulose membranes (SPOT synthesis),[226,227] cellulose beads,[228] and glass surfaces.[229] Janda and co-workers have described the use of *J*anda*J*el as the support in the solid-phase synthesis of oxazoles (Scheme 48).[230] In this case, resin-bound α-acylamino-β-ketoesters **54** were treated with Burgess reagent to form oxazoles **55**, which were then cleaved from the resin by using a diversity-building amidation reaction. The conditions for the key cyclization step **54**→**55** were carefully optimized with microwave dielectric heating and by monitoring the reaction by on-bead IR spectroscopy. The best conditions utilized 3.0 equivalents of the Burgess reagent and 20 equivalents of pyridine in chlorobenzene (100 °C, 15 min). Interestingly,



Scheme 48. Preparation of oxazoles by cyclization of α-acylamino-β-ketoesters.

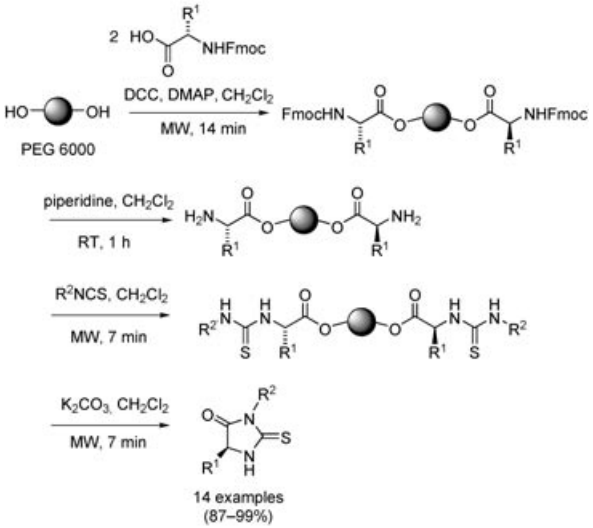
conventional thermal heating at 80 °C for 4 hours was used for the production of the final library since it provided conversions as high as the 15 minutes microwave run.

One reason why microwave-assisted SPOS has not been as powerful a technique as it perhaps could be is the lack of suitable technology that would allow the combination of sealed-vessel microwave heating and bottom filtration (or related) methods for automated removal of excess reagents or solvents and for performing the required washing steps.[231] Currently such vessel equipment is not generally available, and therefore the advantages of SPOS in conjunction with microwave technology can not be fully exploited. Additional examples of SPOS with controlled microwave heating are found in ref. [232].

2.9.2. *Liquid-Phase Synthesis on Soluble Polymer Supports*

Besides solid-phase organic synthesis (SPOS) involving insoluble cross-linked polymer supports, chemistry on soluble polymer matrices, sometimes called liquid-phase organic synthesis, has emerged as a viable alternative.[233] Problems associated with the heterogeneous nature of the ensuing chemistry and on-bead spectroscopic characterization in SPOS have led to the development of soluble polymers as alternative matrices for the production of combinatorial libraries. Synthetic approaches that utilize soluble polymers couple the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis) with those of solid-phase methods (use of excess reagents and easy isolation and purification of products). Separation of the functionalized matrix is achieved by either solvent or heat precipitation, membrane filtration, or size-exclusion chromatography.[233]

A variety of successful microwave-assisted transformations involving soluble polymers such as polyethylene glycol (PEG) have been reported since 1999,[234] and most recently by Sun and co-workers using controlled open-vessel microwave conditions.[235,236] In the example shown in Scheme 49 polyethylene glycol of molecular weight 6000 (PEG 6000) was used as a support for the synthesis of a small library of thiohydantoins.[235] In the first step Fmoc-protected amino acids (3.0 equiv) were loaded onto the support by standard peptide coupling with classical DCC/DMAP activation. The coupling was carried out in dichloromethane and required



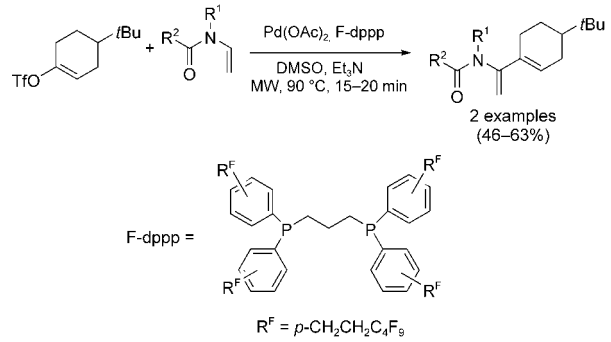
Scheme 49. Preparation of thiohydantoins on a PEG support. All microwave-assisted steps were carried out under open-vessel conditions.

14 minutes of microwave irradiation under open-vessel reflux conditions. Following deprotection with 10% piperidine in dichloromethane at room temperature, various isothiocyanates (3.0 equiv) were introduced by heating under reflux conditions (7 min), again in the same solvent. The cyclization/traceless cleavage step was completed under mildly basic conditions (K_2CO_3) within 7 minutes and provided the desired thiohydantoins in high overall yield and purity. Although the authors did not report any reaction temperatures apart from "reflux conditions" they noted that control experiments under conventional reflux conditions required significantly longer reaction times, which would indicate the presence of a specific microwave effect (namely, a superheating effect at atmospheric pressure).

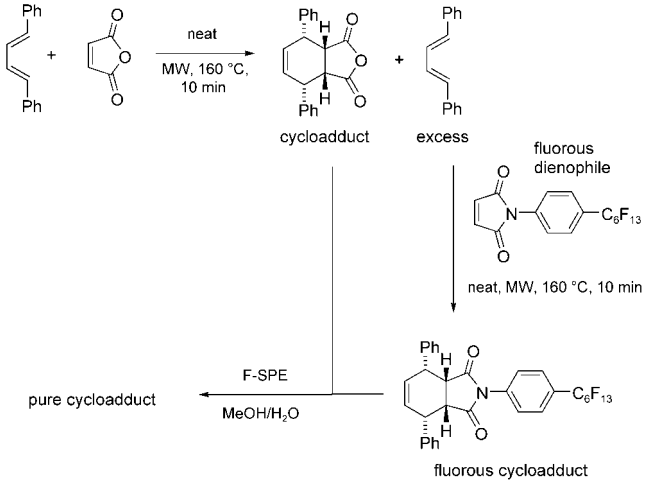
2.9.3. *Reactions in Fluorous Phases*

Tagged fluorous substrates, reagents, catalysts, and scavengers are becoming increasingly popular in organic synthesis, particularly since the advent of high-speed purification techniques such as fluorous solid-phase extraction (F-SPE).[237] The first reports on fluorous synthesis under microwave conditions date back to 1997 and involved Stille coupling reactions with fluorous tin reagents.[238] This was later followed by examples of radical reactions initiated by fluorous tin hydrides.[197] More recently there have been reports on very efficient Pd-catalyzed cross-coupling reactions of perfluoroalkylsulfonates with thiols,[239] and on the use of fluorous-tagged bidentate ligands in microwave-assisted Heck reactions of vinyl triflates with enamides (Scheme 50).[240] F-SPE was used to remove excess reagents or ligands, respectively, in the two cases.

An interesting application of the use of fluorous scavenging in conjunction with microwave synthesis and F-SPE purification was recently illustrated by Werner and Curran[241] in their investigation of the Diels–Alder cycloaddition of maleic anhydride with diphenylbutadiene (Scheme 51). After



Scheme 50. Heck vinylation of enamides in the presence of fluorous-tagged ligands.



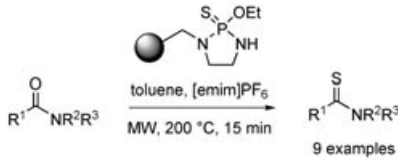
Scheme 51. Fluorous dienophiles as diene scavengers in Diels–Alder cycloadditions.

performing a microwave-assisted cycloaddition (160 °C, 10 min) with a 50% excess of the diene, the excess diene reagent was rapidly scavenged by a structurally related fluorous dienophile under the same reaction conditions. Elution of the product mixture through a F-SPE column with MeOH/H_2O provided the desired cycloadduct in 79% yield and 90% purity. Subsequent elution with diethyl ether furnished the fluorous Diels–Alder cycloadduct.

2.9.4. *Polymer-Supported Reagents, Catalysts, and Scavengers*

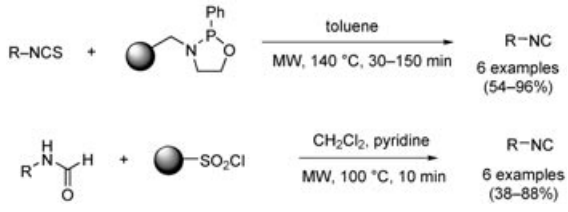
Apart from traditional solid-phase organic synthesis (SPOS), the use of polymer-supported reagents (PSR) has gained increasing attention from practitioners in the field of combinatorial chemistry.[242] The use of PSRs combines the benefits of SPOS with many advantages of traditional solution-phase synthesis. The most important advantages of these reagents are the simplification of reaction work-up and product isolation, with the former being reduced to simple filtrations. In addition, PSRs can be used in excess without affecting the purification step. Reactions can be driven to completion more easily by using this technique than in conventional solution-phase chemistry.

The combination of MAOS and PSR technology is a rapidly growing field.[243] An early example of microwave-assisted PSR chemistry published by Ley et al. involves the rapid conversion of amides into thioamides by employing a polystyrene-supported Lawesson-type thionating reagent.[51] A range of secondary and tertiary amides was converted within 15 min with 3–20 equivalents of the PSR into the corresponding thioamides in high yield and purity by using microwave irradiation at 200 °C (Scheme 52). These thionation reactions showed a marked acceleration in the reaction rate compared to classical reflux conditions, with reaction times being reduced from 30 hours to 10–15 minutes. Interestingly, heating at these elevated temperatures caused no damage to the polymeric support. As toluene itself is a less than optimum solvent for absorption and dissipation of microwave energy (see Table 1), a small amount of ionic liquid (1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate) was added to the reaction mixture to ensure an even and efficient distribution of heat.



Scheme 52. Thionation of amides using a polymer-supported thionation reagent.

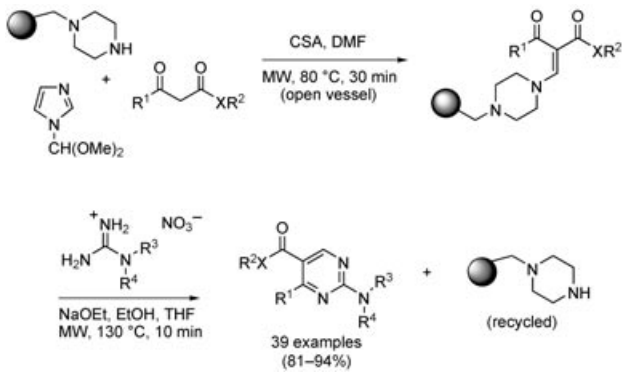
Isonitriles represent an important class of monomers, and their unique reactivity in MCRs (see for, example, Scheme 26) have made them ideal targets for synthesis. Since the preparation and subsequent purification of the sometimes unstable isonitriles prepared by solution-phase methods is not trivial, a process allowing the rapid generation of isonitriles "on demand" is highly desirable. Two independent routes to isonitriles involving microwave-assisted PSR chemistry were reported in 2002 (Scheme 53).[244–246] In the approach described by Ley and Taylor, a suspension of an isothiocyanate and a polymer-supported 1,3,2-oxazaphosphopholidine reagent (1.5–3.0 equiv) in toluene was heated under sealed-vessel microwave irradiation conditions at 140 °C. This method enabled the preparation of primary, secondary, tertiary and aromatic isocyanides in high yields and purities.[244] In an alternative method presented by Bradley and co-workers,[245] formamides (which themselves can be efficiently prepared by MAOS)[246] were treated with a sulfonyl



Scheme 53. Preparation of isonitriles by using polymer-bound reagents.

chloride resin (3.0 equiv) and pyridine (50 equiv) in dichloromethane. The optimum conditions involved heating the mixture at 100 °C for 10 minutes and provided the desired isonitriles in moderate to high yields.[245,246]

Very recently, Porcheddu et al. described an attractive "resin capture and release" strategy for the preparation of libraries of 2,4,5-trisubstituted pyrimidines (Scheme 54).[247]

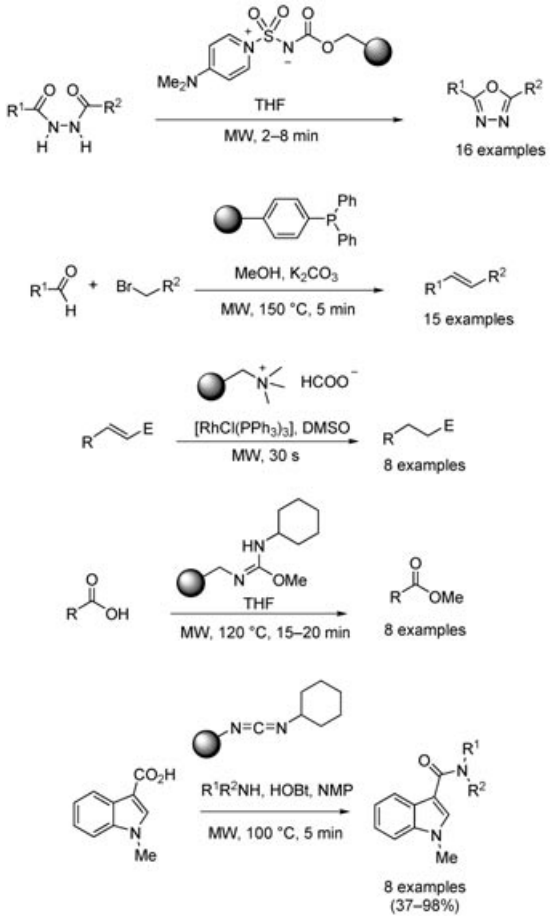


Scheme 54. Resin capture and release strategy for the solid-phase synthesis of pyrimidine libraries.

The key to the success of the "traceless" synthesis of the pyrimidines is the capturing of β-ketoesters or β-ketoamides on a solid-supported piperazine. Heating a mixture of the piperazine resin, *N*-formylimidazole dimethyl acetal, and the 1,3-dicarbonyl compound in DMF in the presence of 10 mol % camphersulfonic acid (CSA) at 80 °C for 30 minutes provided resin-bound enaminones in high yields. As in earlier examples described in this Review (see Schemes 20 and 47), it was found to be advantageous to work under open-vessel conditions to allow the removal of the formed methanol from the equilibrium. The desired pyrimidines were then released from the resin by heating the resin-bound enaminones in the presence of 1.0 equivalent of guanidinium nitrates (prepared by a MAOS method) at 130 °C for 10 minutes. A 39-member library of pyrimidines was prepared in excellent overall yields and purities. Related microwave-assisted capture and release strategies have been reported by Turner and co-workers.[248] Some other applications of microwave-assisted PSR chemistry are summarized in Scheme 55.

A truly remarkable combination of polymer-bound reagents, catalysts, and scavengers was used by Ley and co-workers in their total synthesis of the natural product (+)-plicamine (Scheme 56).[254] Microwave dielectric heating was used as the primary means of accelerating a number of slow reactions to maximize the quantities of intermediates that could be progressed through the synthetic sequence. The rapid optimization and screening of reaction conditions permitted by the adoption of automated microwave synthesis was crucial to the successful completion of this synthesis. Further details are found in the original references.[254]

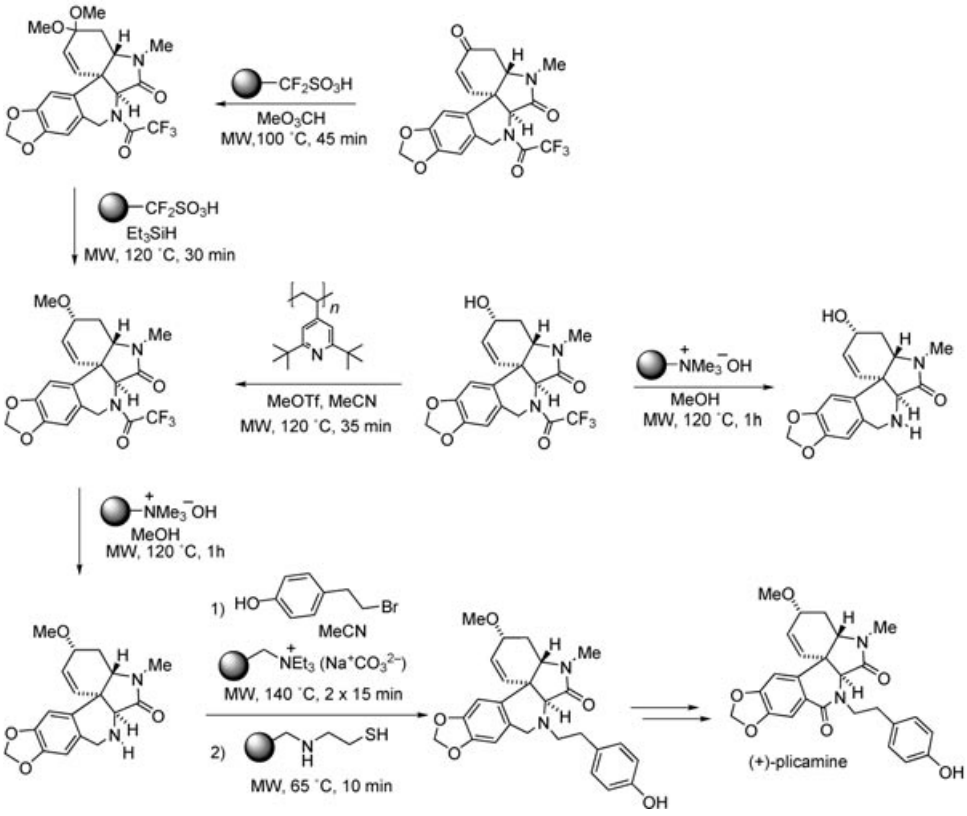
The methodical examination of microwave-assisted scavenging techniques has only been explored recently. An appealing sequence of microwave-assisted synthesis and scavenging was reported by Ellman and co-workers



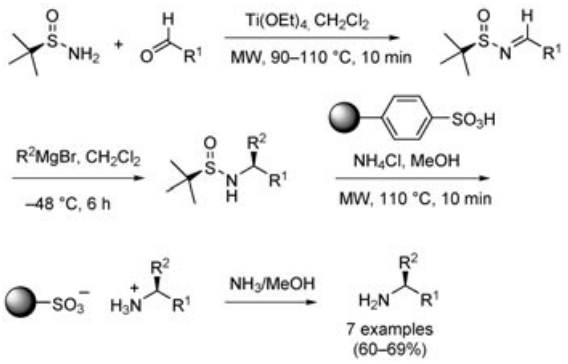
Scheme 55. Examples of resin-bound reactions: synthesis of 1,3,4-oxadiazoles using Burgess reagent,[249] Wittig reactions with triarylphosphanes,[250] catalytic transfer reaction involving formate,[251] *O*-alkylation with *O*-alkyl isoureas,[252] and formation of amide bonds with carbodiimide.[253] HOBt = 1-hydroxybenzotriazole.

(Scheme 57).[255] The authors used microwave heating in the first step of their asymmetric synthesis of α-substituted amines to facilitate the formation of an imine intermediate from chiral 2-methylpropan-2-sulfinamide and an aldehyde precursor. Optimized conditions involved heating the sulfinamide with the aldehyde (1.2 equiv) in the presence of the Lewis acid and water scavenger $Ti(OEt)_4$ (2.2 equiv) in dichloromethane at 90–110 °C for 10 minutes. Excess titanium reagent was removed by treatment of the crude mixture with water-saturated diatomaceous earth and subsequent filtration through silica gel. The nucleophilic addition of organomagnesium reagents to sulfinylimines proceeded with high diastereoselectivity at −48 °C. Finally, cleavage of the sulfinyl group with concomitant capture using a macroporous sulfonic acid resin in the presence of catalytic amounts of ammonium chloride (110 °C, 10 min) provided the desired amine tightly bound to the acidic ion-exchange resin. After washing the resin with methanol and dichloromethane, elution with ammonia furnished the chiral amines in high overall yield and purity.

A related, microwave-assisted scavenging process involving the rapid sequestration of amines by a high-loading Wang



Scheme 56. Total synthesis of (+)-plicamine.[243]



Scheme 57. Preparation of chiral amines from sulfinylimines.

aldehyde resin was reported by Messeguer and co-workers,[256] and a systematic kinetic study on microwave-assisted scavenging techniques involving various types of supports was published in 2003.[257]

A recent review has highlighted the growing importance of utilizing immobilized catalysts (namely, nanopalladium species) in conjunction with microwave dielectric heating.[258]

2.10. Scale-Up Problems

It has to be noted that, with very few exceptions, most examples of microwave-assisted synthesis discussed in this Review were performed on a less than 1 g scale (typically 1–5 mL reaction volume). This is in part a consequence of the recent availability of single-mode microwave reactors that allow the safe processing of small reaction volumes under sealed-vessel conditions by microwave irradiation (see Section 1.3).[36,38] While these instruments have been very successful for small-scale organic synthesis, it is clear that for microwave-assisted synthesis to be become a fully accepted technology in the future there is a need to develop larger scale MAOS techniques that can ultimately provide products routinely on a multikilogram scale (or even higher).

Two different approaches to closed-vessel microwave synthesis on a larger scale (> 100 mL processing volume) have emerged that have taken into consideration the physical limitations of microwave dielectric heating.[259] While some research groups have employed larger batch-type multimode[35,42,46,137,189,200,260] or monomode reactors,[261] others have used continuous-flow techniques (multi- and monomode)[59,262] to overcome the inherent problems associated with scaling-up MAOS.

Modern single-mode microwave technology allows the performance of MAOS in very small reaction volumes (0.2 mL).[263] Several authors have reported independently the feasibility of directly scaling reaction conditions from small-scale single-mode (typically 0.5–5 mL) to larger scale multimode batch microwave reactors (10–500 mL) without reoptimization of the reaction conditions.[42,131,137,189,200] In particular, volumes of up to 1000 mL have been reported to be processed successfully in open-vessel environments under microwave conditions.[46] The preferable option for processing volumes of > 1 L seems to be a continuous-flow technique, although here the number of published examples using dedicated microwave reactors is limited.[59,262] At the present time there are no documented published examples of the use of microwave technology for organic synthesis on a production-scale level (> 1000 kg), which is a clear limitation of this otherwise so successful technology.[26]

3. Summary and Outlook

The examples provided in Section 2 of this Review should make it clear that many types of chemical transformations can be carried out successfully under microwave conditions. This

does not necessarily imply that dramatic rate enhancements compared to a classical, thermal process will be observed in all cases,[264] but the simple convenience of using microwave technology will make this nonclassical heating method a standard tool in the laboratory within a few years. In the past, microwaves were often used only when all other options for performing a particular reaction have failed, or when exceedingly long reaction times or high temperatures were required to complete a reaction. This practice is now slowly changing and, as a result of the growing availability of microwave reactors in many laboratories, routine synthetic transformations are also now being carried out by microwave heating.

The benefits of controlled microwave heating, in particular in conjunction with using sealed-vessel systems, are manifold:

- Most importantly, microwave processing frequently leads to dramatically reduced reaction times, higher yields, and cleaner reaction profiles. In many cases the observed rate enhancements may be simply a consequence of the high reaction temperatures that can rapidly be obtained by using this nonclassical heating method, or may result from the involvement of so-called specific or nonthermal microwave effects (Section 1.2).
- The choice of solvent for a given reaction is not governed by the boiling point (as in a conventional reflux setup) but rather by the dielectric properties of the reaction medium which can be easily tuned by, for example, addition of highly polar materials such as ionic liquids.
- The monitoring mechanisms for temperature and pressure in modern microwave reactors allow for an excellent control of reaction parameters (Figure 2), which generally leads to more reproducible reaction conditions.
- The overall process is more energy efficient than classical oil-bath heating, since direct "in-core" heating of the medium occurs (Figure 1).
- Microwave heating can rapidly be adapted to a parallel or automatic sequential processing format. In particular, the latter technique allows for the rapid testing of new ideas and high-speed optimization of reaction conditions (see Figure 3). The fact that a "yes or no answer" for a particular chemical transformation can often be obtained within 5 to 10 minutes (as opposed to several hours in a conventional protocol) has contributed significantly to the acceptance of microwave chemistry both in industry and academia. The recently reported incorporation of real-time, in situ monitoring of microwave-assisted reactions by Raman spectroscopy will allow a further increase in efficiency and speed in microwave chemistry.[265]

Apart from traditional organic and combinatorial synthesis protocols covered in this Review (see Section 2), more recent applications of microwave chemistry include biochemical processes such as a high-speed polymerase chain reaction (PCR),[266] rapid enzyme-mediated protein mapping,[267] and general enzyme-mediated organic transformations (biocatalysis).[268] Furthermore, microwaves have been used in conjunction with electrochemical[269] and photochemical processes,[270] and are also employed in polymer chemistry[271] and material science applications,[272] such as the fabrication and modification of carbon nanotubes or nanowires.[273]

So why isn't everybody using microwaves? 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.[36–38] As with any new technology, the current situation is bound to change over the next several years, and less expensive equipment should become available. Microwave reactors will then truly have become the "Bunsen burners of the 21st century"[274] and will be standard equipment in every chemical laboratory.

Addendum

Many additional applications of controlled microwave-assisted organic synthesis have appeared in the literature since the submission of the original manuscript. A selection is described below.

A series of air- and moisture-stable [Pd(allyl)Cl(NHC)] complexes with N-heterocyclic carbene ligands has been shown by Nolan and co-workers to catalyze Suzuki–Miyaura cross-coupling reactions of aryl chlorides with boronic acids.[275] This catalytic system is compatible with microwave conditions and rapid couplings were observed within 1.5 minutes at 120 °C. The conventionally heated reactions (60 °C) required several hours to reach completion. The same article also reports on microwave-assisted dehalogenations of aryl chlorides by using the same catalytic system.

Alterman and co-workers have employed a tandem carbonylation/lactonization sequence for the synthesis of phthalides.[276] Optimum conditions involved the use of $[Mo(CO)_6]$ as a solid source of CO, and $Pd(OAc)_2$/dppf as a catalyst (5 mol%) at 180 °C. The microwave-assisted carbonylation/cyclization method was also applied for the synthesis of other scaffolds, such as dihydroisocoumarins, dihydroisoindones, and phthalimides.

Harmata et al. have disclosed an efficient protocol for the Pd-catalyzed N-arylation of enantiopure sulfoximines with aryl chlorides.[277] Optimal results were achieved by using $Pd(OAc)_2$ as the Pd source in combination with *rac*-binap or $PtBu_3$ as ligands under microwave irradiation conditions. The corresponding benzothiazines were obtained with aryl chlorides bearing *ortho*-carbonyl substituents.

Hydrozirconation is a mild method for the selective preparation of functionalized organometallic compounds, and its compatibility with a range of common protecting groups represents a considerable advantage of these species over traditional organometallic reagents. Wipf et al. recently reported that the hydrozirconation of alkynes with $[Cp_2Zr(H)Cl]$ can be greatly accelerated by microwave irradiation.[278] A synthetically useful one-pot method for the preparation of allylic amides was elaborated where an alkyne was first hydrozirconated by microwave irradiation, followed by rapid addition of imines in the presence of dimethylzinc.

Several research groups have reported other high-speed microwave-assisted transition-metal-catalyzed transforma-

tions, such as Suzuki,[279] Heck,[280] Sonogashira,[281] Negishi,[282] and Liebeskind–Srogl reactions, [283] Buchwald–Hartwig aminations,[284] and related reactions.[285]

Bahn and Adolfsson have demonstrated that functionalized 2,5-dihydropyrroles can be obtained by microwave-mediated ruthenium-catalyzed ring-closing metathesis (RCM).[286] The required olefin precursors were conveniently obtained from aza-Baylis–Hillman adducts. Microwave irradiation for 1–2 minutes at 100 °C of a dilute solution of the diene with 5 mol% Grubbs II catalyst in dichloromethane produces the desired dihydropyrroles in high yield. Microwave-assisted enyne-RCM chemistry has been reported by Brown and co-workers.[287]

A simple, high-yielding synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketones and aldehydes in the presence of ammonium acetate was recently reported by Wolkenberg et al.[288] Alkyl-, aryl-, and heteroaryl-substituted imidazoles were formed in very high yields ranging from 76–99% by utilizing microwave irradiation. Further microwave-assisted alkylation of 2,4,5-trimethylimidazole with benzyl chloride in the presence of base led to the alkaloid lepidiline B in 43 % overall yield.

Wellner and co-workers have made extensive use of microwave chemistry in the preparation of cyclic thioureas and guanidines.[289] It was possible to assemble all intermediates and target molecules by MAOS without any need for activation or protecting groups, thus reducing reaction and workup times to a minimum. A variety of other heterocycle syntheses based on microwave protocols have also been published.[290]

A recent publication by the research group of Baran reports the total synthesis of ageliferin, an antiviral agent with interesting molecular architecture.[291] Just one minute (!) of microwave irradiation of sceptrin, another natural product, at 195 °C in water under sealed-vessel conditions provides ageliferin in 40 % yield, along with 52 % of recovered starting material. Remarkably, if the reaction is performed without microwaves at the same temperature only starting material and decomposition products are observed.

Moody and co-workers have employed a "biomimetic" hetero-Diels–Alder/aromatization sequence for the construction of the pyridine ring in amythiamicin D.[292] The key cycloaddition reaction between the azadiene and enamine component was carried out by microwave irradiation at 120 °C for 12 hours and gave the required 2,3,6-tris(thiazolyl)pyridine intermediate in moderate yield. Coupling of the remaining building blocks then completed the first total synthesis of the thiopeptide antibiotic amythiamicin D.

The synthesis of fully N-differentiated heparin oligosaccharides has been demonstrated by Lohman and Seeberger. One of the many synthetic steps involves the simultaneous installment of an *N*,*N*-diacetate and *O*-acetyl functionality in a trisaccharide building block.[293] Microwave irradiation of a solution in isopropenyl acetate in the presence of *p*-TsOH at 90 °C for 5 hours led to the desired product in 86 % yield. This transformation could not be achieved under a variety of thermal conditions, with only poor yields achieved even after several days.

Vasudevan and Verzal have found that terminal alkynes can be hydrated under neutral conditions in the absence of metal compounds (such as $AuBr_3$) in distilled water.[294] Extension of this methodology led to a one-pot conversion of alkynes into imines (hydroamination).

A recent report by Takvorian and Combs discloses the rapid synthesis of 2-amino-substituted purines by rapid, microwave-assisted nucleophilic aromatic substitution (SN_2Ar).[295] Importantly, the authors also describe the use of small-scale reaction vessels (0.2 mL) for optimization of reaction conditions under optimal reaction concentrations.

Fukase and co-workers have reported the solid-phase synthesis of indol-2-ones (four diversity centers) by a radical cyclization pathway.[296] The key cyclization step was carried out by using Bu_3SnH and azodiisobutyronitrile (AIBN) in DMF under microwave irradiation conditions and provided a small library of 40 compounds. Interestingly, the related radical cyclization in the solution phase was considerably less effective.

A recent publication by Blackwell and co-workers reports the multistep synthesis of a spatially addressed pyrimidine library on planar membrane supports (SPOT synthesis).[297] Microwave irradiation was used to speed up all three steps of the synthesis on the planar support. Importantly, microwave irradiation did not affect the integrity of the cellulose support and the reaction could be easily scaled up by employing other (nonplanar) types of cellulose supports.

A study by Zhang and co-workers describes a new strategy for improving the efficiency of Suzuki coupling reactions by combining rapid microwave synthesis with fluorous separation techniques (F-SPE).[298] The aryl perfluorooctylsulfonate precursors for Suzuki-type couplings were readily prepared from phenols and commercially available perfluorooctylsulfonyl fluoride. Subsequent Suzuki reaction with aryl boronic acids in the presence of a suitable Pd catalyst provided the desired biaryls in high yield. Workup simply involved filtration of the reaction mixture through a F-SPE cartridge. The same authors have also recently reported on the deoxygenation reactions of aryl perfluorooctylsulfonates.[299]

Lei and Porco have demonstrated the usefulness of a thermally stable polymer-supported anthracene derivative for scavenging dienophiles under microwave conditions.[300] This strategy was used successfully to rapidly sequester reactive dienophiles from reaction mixtures containing Diels–Alder cycloadducts prepared by microwave-assisted Diels–Alder reaction of flavonoid dienes. Diels–Alder reactions under microwave conditions have also been used to modify single-wall carbon nanotubes (SWNT).[301]

Two recent review articles highlight the importance of microwave chemistry for carbohydrate chemistry.[302]

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only be a small fraction of the density on the surface. Therefore, solvents or reagents in the center of the reaction vessel are heated by convection and not by direct microwave dielectric heating. This physical limitation is one of the main reasons for the development of continuous-flow reactors, where the reaction mixture is passed through a relatively small microwave-heated flow cell, thus avoiding problems of penetration depth. On the other hand, continuous-flow reactors with pumping systems may not be appropriate for processing solids, highly viscous liquids, or heterogeneous reaction mixtures.

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