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Microwave-assisted high-speed chemistry: a new technique in drug discovery

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In both lead identification and lead optimization processes there is an acute need for new organic small molecules. Traditional methods of organic synthesis are orders of magnitude too slow to satisfy the demand for these compounds. The fields of combinatorial and automated medicinal chemistry have been developed to meet the increasing requirement of new compounds for drug discovery; within these fields, speed is of the essence. The efficiency of microwave flash-heating chemistry in dramatically reducing reaction times (reduced from days and hours to minutes and seconds) has recently been proven in several different fields of organic chemistry. We believe that the time saved by using focused microwaves is potentially important in traditional organic synthesis but could be of even greater importance in high-speed combinatorial and medicinal chemistry.

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▼ Although domestic microwave ovens have been widely used since the 1970s, the first reports that these energy sources were also suitable for accelerating organic reactions did not appear until 1986[1,2]. The risks associated with the flammability of organic solvents and the lack of available systems for temperature control were major concerns. Today, however, safe microwave heating equipment is on the market that enables both accurate temperature and pressure control as well as the convenient monitoring of reactions. As a consequence, the amount of articles describing efficient rapid chemical synthesis promoted by microwave irradiation has grown quickly from ~200 in 1995 to ~1000 in 2001. Excellent reviews have been published on various aspects of microwave-assisted chemistry[3–8]. The intention of the present review is to highlight microwave-assisted rapid organic transfor mations of particular importance in pharmaceutical chemistry and to discuss some of the most recently disclosed applications to medicinal and combinatorial chemistry. An outlook on the potential of high-speed microwave chemistry in drug discovery will be given. As an introduction to the topic, a brief background on microwave irradiation as an energy source and the equipment used for the reactions is provided.

General microwave physics

The electric component of an electromagnetic field causes heating by two major mechanisms: dipolar polarization and conduction[3–8]. In polar organic-solvent systems at non-extreme temperatures, the dipolar polarization mechanism accounts for the majority of the microwave heating-effect. Thus, the heating rate is affected by the dielectric properties of a sample. The applied field interacts with the alignment of the molecular electric dipoles in a sample, and this interaction accounts for the microwave dielectric heating. The polarization is proportional both to the permittivity (a high value of which results in a high dielectric constant) and the electric susceptibility, and describes the response of a sample to an applied electric field. A frequency of 2450 MHz is typically used both for the rapid heating of food and for microwave chemistry. This frequency corresponds to a wavelength of 12.2 cm. Thus, only a specific wavelength within the microwave band, ranging from 1 cm to 1 m, is utilized for organic reactions. The major part of the microwave region is assigned to radar and telecommunications. At 2450 MHz, the polarization vector lags behind the applied field, and the effective current in the irradiated sample is out of phase with that of the applied field by a difference

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(termed δ). This difference defines the tangent loss factor, tan δ, often named the dissipation factor or the dielectric loss tangent. The word 'loss' refers to the input microwave energy that is lost to the sample by being dissipated as heat. Thus, microwave energy is not transferred primarily by convection or by conduction, as with conventional heating, but by dielectric loss[9]. The tangent loss factor is expressed as the quotient, tan δ = e″/e′, where e″ is the dielectric loss factor, indicative of the efficiency with which electromagnetic radiation is converted to heat, and e′ is the dielectric constant describing the ability of molecules to be polarized by the electric field. A high value for tan δ indicates a high susceptibility to microwave energy.

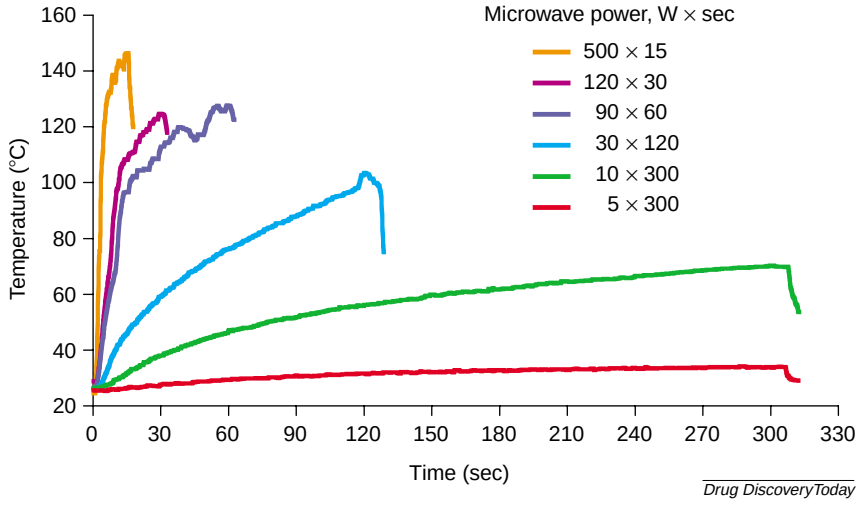

Figure 1. Temperature profiles for microwave flash-heated allylic substitutions in acetonitrile [boiling point (bp) = 81–82 °C] using different microwave powers. Microwave heating was performed with a MicroWell-10 single-mode microwave cavity (Personal Chemistry, Uppsala, Sweden). Temperature profiles were recorded using fluoroptic probes.

Polar solvents have high tan δ values and are, therefore, preferable for microwave-promoted reactions. Unfortunately, the tan δ values of most common solvents have only been determined at room temperature[7]. Among the polar solvents most frequently used, it is notable that significantly faster heating can be achieved in ethanol (e′ = 25) or dimethyl formamide (DMF; e′ = 37) than in acetonitrile (e′ = 38) or water (e′ = 78), reflecting the fact that a larger dielectric constant, that is, e′ value, does not always result in a faster temperature increase. Furthermore, the rate of temperature increase is not only a function of tan δ, but also of the ionic strength, specific heat capacity, emissivity, geometry and volume of the sample reaction mixture, and the strength of the applied field[3]. In practice, and as a general rule, almost all types of organic transformations that require heat can be performed using microwave heating. In fact, microwave-heated synthetic reactions have been performed using microwave-transparent 1,4-dioxane as a solvent[10]; in such a case, the reactants and reagents are responsible for the transformation of irradiation into bulk heat.

Microwave irradiation produces efficient internal heat-transfer (*in situ* heating), resulting in even heating throughout the sample, as compared with the wall heat-transfer that occurs when an oil bath is applied as an energy source[4]. Consequently, the tendency for seed formation (the initiation of boiling) is reduced, and superheating (i.e. temperatures much above conventional reflux temperatures) is possible even at atmospheric pressure. Superheating can be rapidly generated in closed microwave-transparent vessels. Several temperature profiles of single-mode microwave heating of septa-sealed allylic substitution reactions are exemplified in Fig. 1. The reactions were conducted in acetonitrile (boiling point = 81–82 °C) using different microwave powers (W)[11].

Most early claims of the existence of 'non-thermal microwave effects' in homogeneous systems have, after appropriate experimentation with temperature monitoring, been reinterpreted as the effects of superheating[3–8]. For example, Raner and Strauss conducted rigorous kinetic studies and significantly demonstrated that reaction rates were the same regardless of the heating method[12]. The amount of energy transmitted by the microwaves, <0.3 kcal mol^{-1}, is too small to account for any direct molecular activation, and microwave irradiation at 2450 MHz cannot excite rotational transformations because this requires higher frequencies[13]. It is possible however, that hot-spots, resulting from heterogeneity in the applied field, develop at certain zones of the reaction mixtures. In such hot-spots, higher temperatures than those monitored are reached and faster transformations might occur. However, the hot-spot effect, frequently described as the 'false microwave effect', is still of thermal origin.

Microwave equipment

To date, the majority of microwave-promoted organic synthesis has been performed in multi-mode domestic ovens. In these ovens, the power levels commonly fluctuate as a result of the patterns-of-switching of on–off cycles[3,4]. The microwaves are heterogeneously distributed within the cavity and, consequently, less-defined regions of high and

low energy intensity are produced. The multi-mode domestic ovens are well suited for many robust classical organic reactions, provided adequate safety precautions are undertaken, but the use of microwave reactors designed for organic chemistry is strongly recommended. In recent years, an increasing amount of organic transformations has been conducted in single-mode microwave cavities. In a single-mode cavity a continuous standing-wave is delivered with well defined regions of maximum and minimum field strengths, and the reaction tube is located at a fixed position. Hence, a single-mode microwave cavity combined with an adequate temperature control system allows for optimal reproducibility and energy efficiency[3,6,8]. One drawback with the single-mode cavities however, is that the reaction size is more or less fixed at a relatively small volume.

The use of single-mode cavities appears to be of particular importance when conducting reactions that proceed via labile intermediates, such as transition-metal-catalyzed reactions[14]. In general, an efficient application of microwave irradiation as an energy source requires reliable temperature monitoring and temperature-feedback control during the irradiation. These control features enable the chemist to conveniently heat a reaction mixture to a desired temperature without knowing the dielectric or conductive properties of the mixture in detail. The temperature-feedback control should be capable of a fast reduction of power in cases where either the exothermic reaction energy becomes pronounced, or when the dissipation factor increases rapidly, to avoid thermal runaways. Thus, any vessel can become over-pressurized if not fitted with an efficient temperature-feedback power control and a pressure-relief device. Furthermore, the generation of electric arcs constitute a potential hazard and might cause vessel rupture and/or explosions if flammable compounds are present[4]. Vessels can be sealed in an inert gas atmosphere to minimize the risk of explosion. The reaction vessels are made of material that is virtually transparent to microwaves at the operating frequency: borosilicate glass or polytetrafluoroethylene (teflon, which is resistant to strong bases and hydrogen fluoride), are most commonly used.

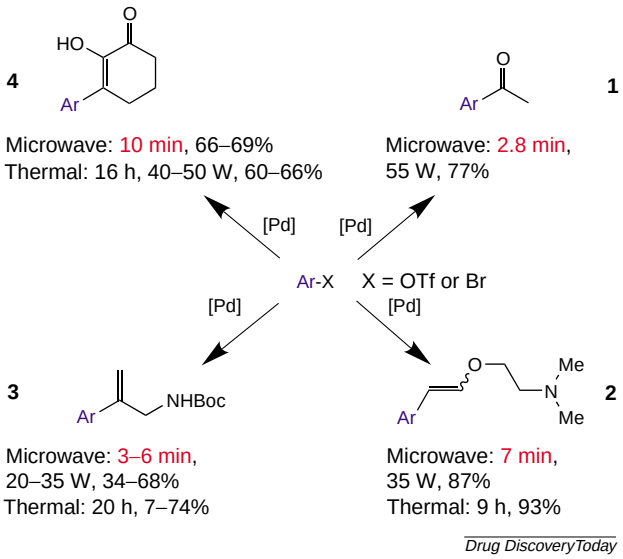

Figure 2. Examples of palladium (Pd)-catalyzed Heck arylations demonstrating retained regioselectivities under microwave-induced flash-heating conditions. The reactions with aryl halides or aryl triflates require only minutes for completion when conducted under single-mode microwave irradiation, compared with the one-day reaction-time needed to accomplish the same thermal reactions using conventional heating techniques. The reactions illustrate the scope of microwave-assisted Heck couplings with various olefins. The α-arylation product in **1** is spontaneously hydrolyzed to the corresponding acetophenone under the reaction. Yield is shown by % values. Abbreviations: Boc, *tert*-butyloxycarbonyl; OTf, OSO_2CF_3 – a triflate.

Microwave-assisted intramolecular and two-component reactions

The decoration of aromatic scaffolds that possess various versatile functionalization handles is one of the most common strategies used by the medicinal chemist for library

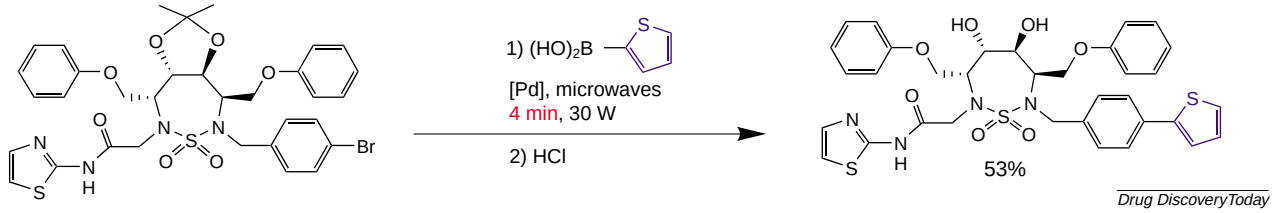

Figure 3. Fast synthesis of a non-symmetric cyclic sulfonamide HIV-1 protease inhibitor by a palladium (Pd)-catalyzed microwave-assisted Suzuki coupling and a subsequent acid-mediated deprotection. The emergence of mutant forms of the viral HIV-1 protease under selective pressure of anti-HIV drugs means that new chemical entities with unique resistance profiles are urgently required. To this end, the sulfonamides were developed as a novel class of cyclic inhibitors. To rationalize their SARs, a set of inhibitors was synthesized by microwave methodology. The SARs were found to differ significantly from the SARs of the related cyclic urea inhibitors reported by DuPont and DuPont-Merck[54], which could be useful in the development of HIV drugs that evade resistance.

generation. The palladium-catalyzed C–C bond-forming reactions are examples of the most popular methods used to achieve this. It is, therefore, not surprising that numerous reports have described accelerated Heck[14–21], Sonogashira[22], Suzuki[14,23] and Stille[14,24,25] reactions using microwave irradiation as an energy source. In early systematic studies of the Heck reaction, which involved many different alkenes, it was revealed that similar product patterns were encountered regardless of the heating method[14]. Hence, the regiochemistry dictated by electronic or palladium-chelating auxiliaries could be controlled despite the use of high temperatures (Fig. 2; Reactions 1,2). Microwave irradiation using a single-mode cavity reduced reaction times from many hours to only a few minutes. Allylamines[18] and *tert*-butyloxycarbonyl-protected allylamines[26] were arylated with impressive internal regiocontrol (Fig. 2; Reaction 3). Arylated 1,2-cyclohexanediones were also easily prepared from aryl bromides[16]; these compounds possess both hydrogen-bond donating and accepting properties and are potential zinc chelators (Fig. 2; Reaction 4).

In 1996 it was demonstrated that the highly useful Suzuki and Stille reactions could be conducted under flash-heating conditions using a single-mode cavity and would afford good yields[14]. A Suzuki reaction used in the preparation of a cyclic inhibitor of HIV-1 protease is depicted in Fig. 3[27]. Interestingly, the Suzuki and Stille reactions also worked readily on a polymeric support consisting of a benzoic acid linked to Rink amide (a common linker used in the generation of primary carboxamides) on polyethylene glycol (PEG)-grafted polystyrene (TentaGel™; Rapp Polymere, Tübingen, Germany) (Fig. 4; Reactions 1,2)[28]; the polymer was found to be stable under these harsh conditions. Further, Kappe and Stadler have reported that no degradation of Merrifield resin was detected at 200 °C in the rapid and efficient microwave-mediated attachment of carboxylic acids to the resin (Fig. 5)[29]. In addition, in a TFA-mediated flash-heated cleavage, the benzoic acid was quantitatively released from the chloromethylated polystyrene after 30 min of microwave irradiation.

Nitriles, which are valuable intermediates in synthesis, can easily be reacted to produce a broad spectrum of heterocycles, such as thiazoles, oxazolidinones, triazoles and

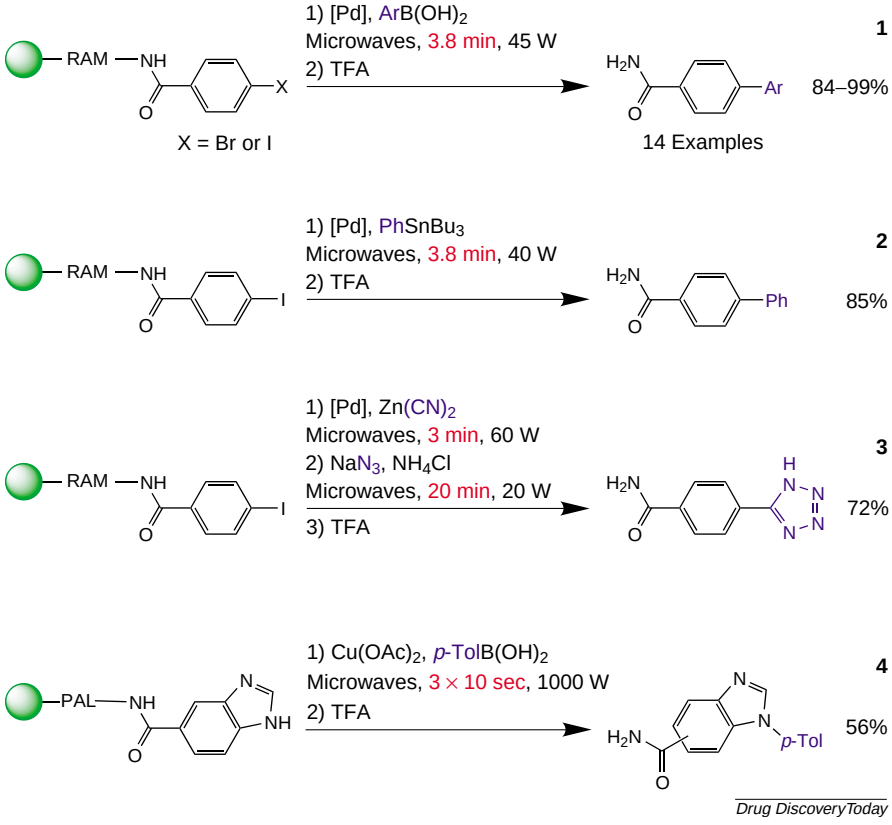

Figure 4. Examples of fast microwave-assisted organic reactions on polymeric supports. Encouraged by the increasing importance of unsymmetrical substituted biaryl derivatives as a privileged structure class in drug discovery, Suzuki (Reaction **1**) and Stille (Reaction **2**) cross-coupling reactions were adapted to high-speed solid-phase synthesis. Several cross-couplings were performed with the addition of a large excess of aryl boronic acids or phenyl tin reactant linked to Rink–TentaGel™ resin (green circles) to demonstrate the high reaction rates and the ease of application of the methodology. All reactant combinations tested produced high isolated yields in just 3.8 min. No decomposition of the polymeric support was observed. Furthermore, this microwave-promoted heating technique is also suitable for the conversion of iodides to nitriles and subsequently to tetrazoles (Reaction **3**). Tetrazoles are of particular interest to the medicinal or combinatorial chemist because they constitute probably the most commonly used bioisostere of the carboxyl group. Interestingly, a microwave power of only 20 W was applied in the cycloaddition step of Reaction **3** to avoid formation of side products. The aryl tetrazole was isolated after cleavage with trifluoroacetic acid (TFA) (Reaction **3**). *N*-arylated heterocycles comprise an important class of compounds often associated with biological activity. In Reaction **4** the first examples of microwave heated solid-phase synthesis of *N*-arylated heterocycles are described. These copper(II)-mediated reactions constitute an efficient means of library production (Reaction **4**). Abbreviations: RAM, Rink amide; PAL, an alternative to RAM based on 5-(4-aminomethyl-3,5-dimethoxy-phenoxy)-valeric acid.

tetrazoles. The tetrazole probably constitutes the most commonly used bioisostere of the carboxyl group. Therefore, to assess the scope of microwave methodology for future medicinal chemistry applications, tetrazoles were selected as attractive targets for fast synthesis. Flash-heating in a single-mode cavity was successfully employed in the palladium-catalyzed conversions of a variety of aryl and heteroaryl bromides to their corresponding nitriles[30]. In addition, a one-pot reaction that allowed for a direct synthesis of tetrazoles from aryl bromides was executed; this reaction also proceeded readily when the substrate was attached via a Rink linker to a Tentagel™ resin (Fig. 4; Reaction 3). Although the cyanation had occurred with full conversion after a few min, longer reaction times (e.g. 15–25 min) and low power was more suitable for the dipolar cycloadditions[30]. It is notable that sodium azide and ammonium chloride were used to allow for facile purification, although alkyltin and alkylsilicon azides, which usually complicate purification, worked as well with no occurrence of explosion.

Combs and coworkers reported the first examples of solid-phase aryl-heteroaryl C–N cross-coupling reactions and achieved dramatically decreased reaction times by using microwave irradiation (Fig. 4; Reaction 4)[31]. This reaction is a Cu(II)-mediated transformation and works well on polystyrene–PEG resin with a PAL-linker [an alternative to Rink amide, based on 5-(4-aminomethyl-3,5-dimethoxyphenoxy)-valeric acid]. The *N*-arylated heterocyclic products, which were prepared in high yields and purity, comprise an important class of compounds often associated with biological activity. This methodology would be suited to a high density format that could provide access to many diverse *N*-arylated heterocycles for screening. A domestic 1000 W multi-mode microwave

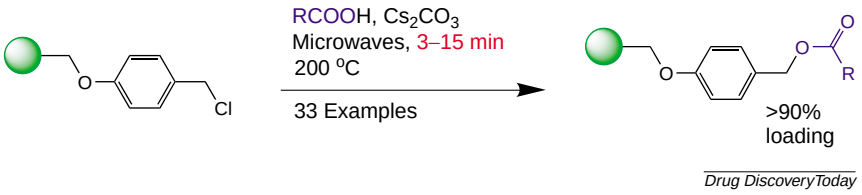

Figure 5. Reaction times and loadings in the microwave-assisted coupling of 33 carboxylic acids to Merrifield resin (green circles) via their cesium salt. Loadings >90% were achieved after only 3–15 min irradiation time as compared with 12–48 h when using conventional heating at 80 °C. Kinetic comparison studies indicated that these rate enhancements could be attributed to the rapid *in situ* heating of the solvent by microwave irradiation. Importantly, no degradation of the polymer resin could be detected.

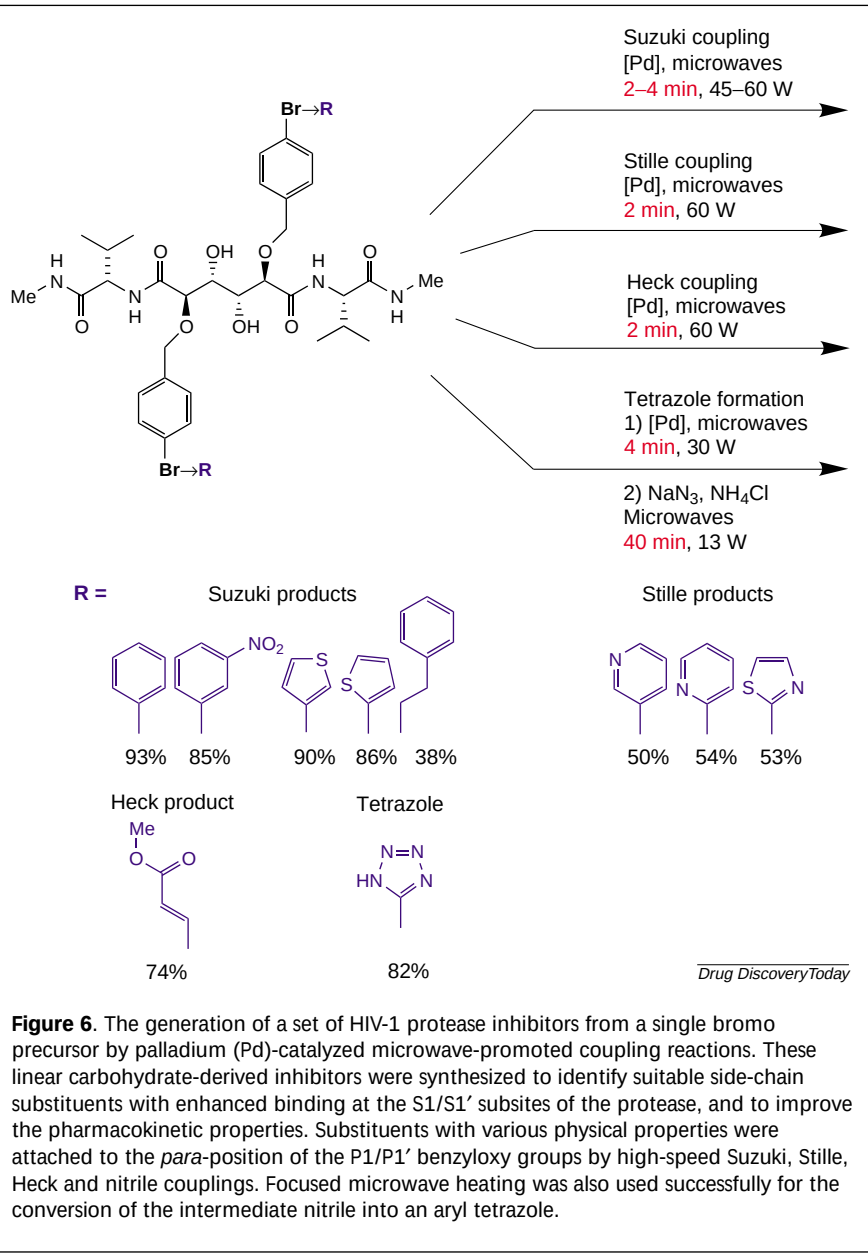

Figure 6. The generation of a set of HIV-1 protease inhibitors from a single bromo precursor by palladium (Pd)-catalyzed microwave-promoted coupling reactions. These linear carbohydrate-derived inhibitors were synthesized to identify suitable side-chain substituents with enhanced binding at the S1/S1′ subsites of the protease, and to improve the pharmacokinetic properties. Substituents with various physical properties were attached to the *para*-position of the P1/P1′ benzyloxy groups by high-speed Suzuki, Stille, Heck and nitrile couplings. Focused microwave heating was also used successfully for the conversion of the intermediate nitrile into an aryl tetrazole.

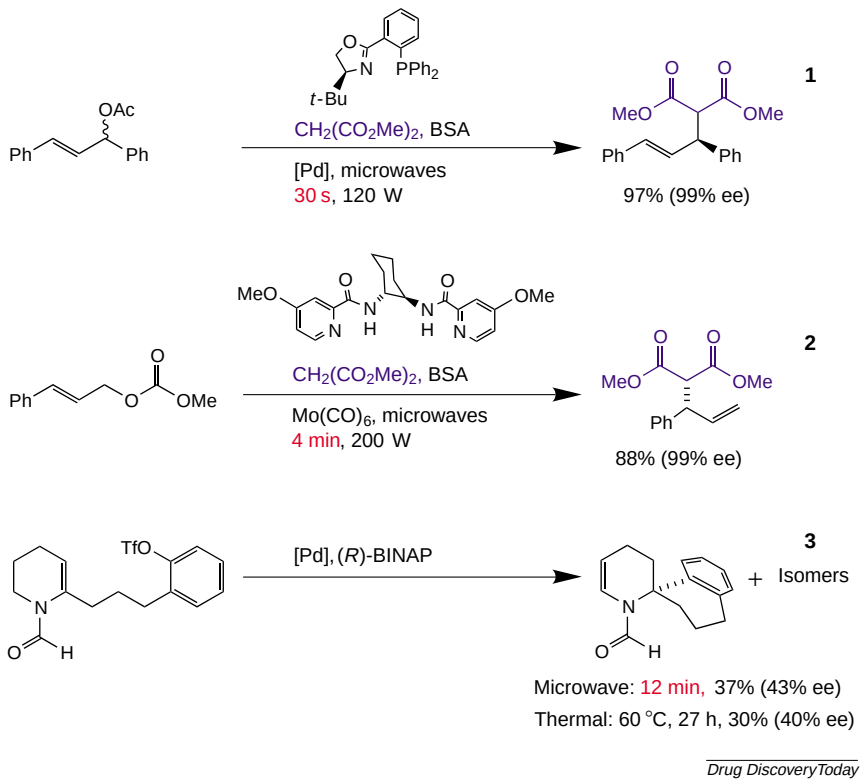

Figure 7. High-speed metal-catalyzed asymmetric reactions using single-mode microwave heating at elevated temperatures. Using thermostable chiral catalysts, this heating technology allows for selective organic transformations to be executed in a highly reproducible fashion. Reactions **1** and **2** illustrate rapid, selective and efficient asymmetric allylic alkylation reactions. The high enantioselectivities might be explained by an exceptionally large difference in activation energy for the formation of the two enantiomers. Reaction **3** is the first example of a microwave-assisted enantioselective Heck reaction. The enantiomeric excess (ee) value was similar regardless of the heating technique used. Abbreviations: BINAP, 2,2′-*bis*(diphenylphosphino)-1,1′-binapthyl; Tf, triflate.

oven at full power was used (3 × 10 sec heating interval). Using 96-well microtiter plates, an efficient method of library production was developed, although a considerable temperature gradient between the inner and outer walls of the microtiter plates was measured using a thermocouple probe. Efficient library generation was achieved however, despite the apparent non-uniform heating.

Figure 6 demonstrates that many palladium-catalyzed reactions can successfully be executed in a few min in a single-mode cavity from a common bromo precursor (a scaffold decorated with one or more bromine atoms)[32]. The C2-symmetric scaffold is derived from L-mannoic acid, and several potent inhibitors of HIV-1 protease were prepared that possess antiviral activity in HIV-infected cell assays.

Many powerful palladium-catalyzed reactions have been demonstrated as well suited to flash-heating. Therefore, the question arose: can ligand-controlled asymmetric induction (used to introduce chirality into a molecule) also be accelerated without loss of stereoselectivity under the conditions employed in microwave-assisted reactions? To answer this question, model systems were studied. For example, using selected thermostable catalytic systems it was found that the reaction times for both asymmetric palladium-catalyzed alkylation of 1,3-diaryl allylacetate[11,33] and Mo(0)-catalyzed alkylation of phenyl allyl carbonate[10,34] could be reduced to 0.5–5.0 min without loss of enantioselectivity [99% enantiomeric excess (ee); Fig. 7; Reaction 1,2]. Furthermore, an asymmetric intermolecular Heck reaction that required 27 h of conventional heating could be completed in 12 min using microwave heating with the same degree of asymmetric induction (ee = ~40%; Fig. 7, Reaction 3, joint project with Lena Ripa at AstraZeneca). The asymmetric reactions were all conducted with focused single-mode cavities and fluoroptic temperature measurements. These fast enantioselective reactions could be applied in the future in medicinal and combinatorial synthesis.

As stated by Selway and Terrett, the rate of lead optimization is often limited by the speed of orthodox organic synthesis[35]. Any methodology that enables an acceleration of analogue synthesis will have an important role in drug discovery. Selway and Terrett used microwave irradiation to achieve quick and convenient alkylations of 60 piperidines and piperazines to generate a library using parallel synthesis (Fig. 8; Reaction 1)[35]. The library was screened in a herpes simplex virus-1 (HSV-1) helicase ATPase assay and confirmed hits were identified.

Ley has successfully used polymer-supported reagents for multi-step organic synthesis and applied this methodology to a convergent synthesis of Sildenafil (Viagra™)[36], a selective inhibitor of phosphodiesterase type 5. The final dehydrative cyclization step was easily achieved by microwave irradiation in a single-mode cavity (Fig. 8; Reaction 2).

Manhas and Bose, two pioneers in the field of microwave-promoted synthesis, have prepared β-lactams in high yields using the reaction sequence shown in Fig. 8 (Reaction 3)[37]. These β-lactams are versatile intermediates

in the synthesis of β-vinyl-β-lactams and can also be rapidly transformed into a variety of heterocycles.

Focused microwave irradiation in a sealed vessel was also employed by Ley to epimerize the α-pyridyl proton of *endo*-epibatidine to the more thermodynamically stable *exo*-isomer of epibatidine[38]. Previous reports had indicated that this process could not be driven beyond 50% completion under forcing conditions (potassium *tert*-butoxide, 30 h). However, the use of microwave heating enabled conversion to a 3:1 ratio in favor of the desired *exo*-isomer (Fig. 8; Reaction 4).

In the search for novel CNS-active drugs, Olsson and coworkers[39] extended a procedure developed by Varma and Kumar[40] for thioamide synthesis that relies on Lawesson's reagent, and produced a library of 25 thioamides from the corresponding amides by a solvent-free parallel synthesis[39]. After solid-phase extraction, products with adequate purity for use in HTS were obtained (Fig. 8; Reaction 5).

The recently introduced fluorous synthesis-techniques capitalize on the immiscibility of highly fluorinated phases with organic solvents and water at room temperature[41]. Molecules equipped with fluorous tags (fluorous molecules) can, upon heating, be dissolved in organic solvents and combined with organic reactants. Upon cooling to room temperature, these fluorous molecules dissociate from the organic phase and seek the fluorous phase (fluorous solvent or a fluorous reverse-phase column[42]), thus facilitating purification. Therefore, fluorous techniques are a means of integrating synthesis and purification strategies in combinatorial chemistry. The fluorous techniques can often speed the separation process to the point where the reaction time is the limiting factor in sample throughput in combinatorial or parallel synthesis[41]. As demonstrated by the reactions shown in Fig. 9, focused flash-heating in a single-mode cavity is compatible with the use of the highly fluorous F-21 tags[43]. These reactions were sluggish under traditional thermal heating; this might be because of coalescence of fluorous-reagent organic phases upon superheating,

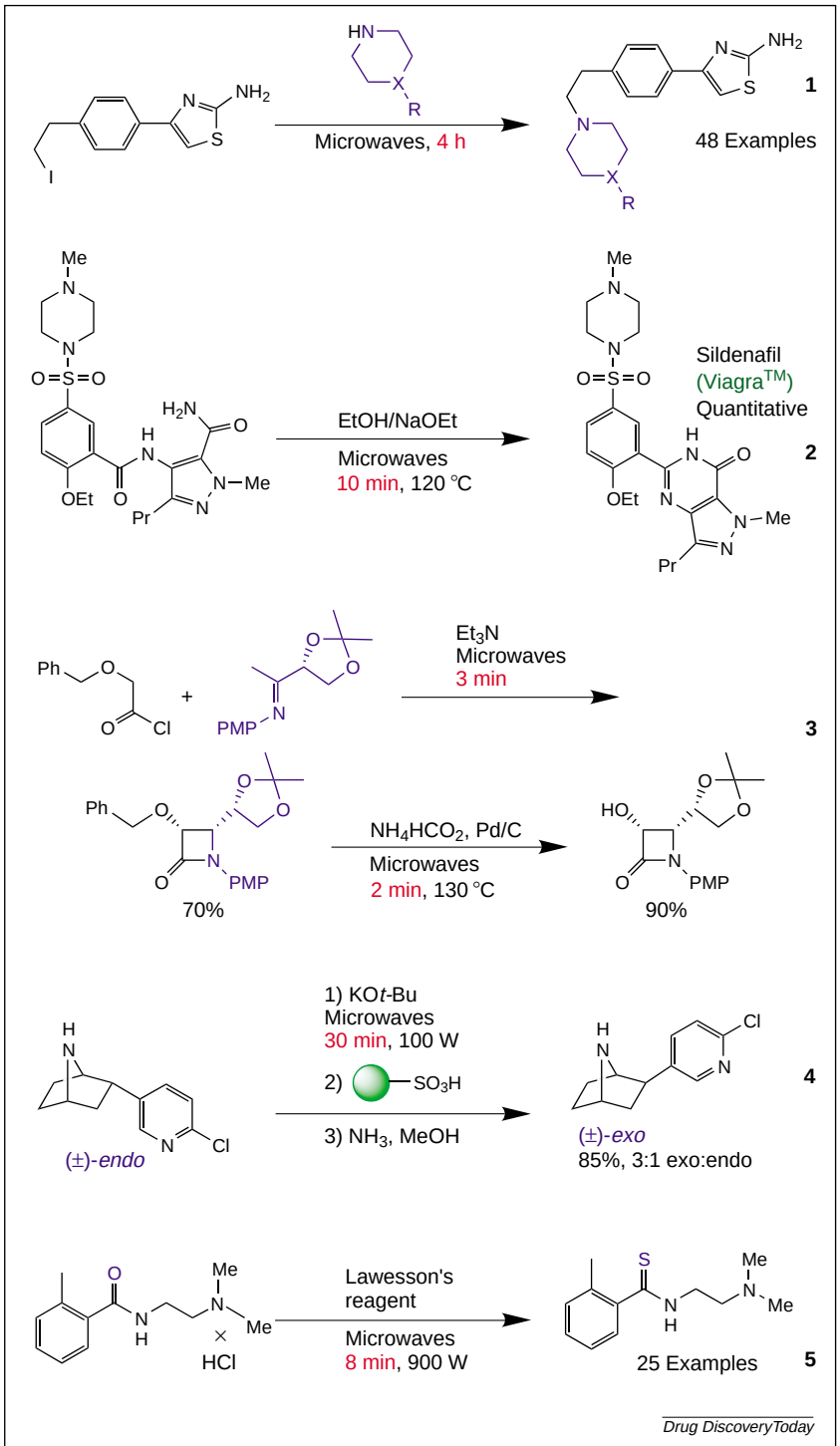

Figure 8. Five diverse examples of the application of microwave heating to the syntheses of biologically interesting molecules. Reaction **1**: a microwave-promoted nucleophilic substitution reaction, which was used to produce a library of 48 antiherpes aminothiazole derivatives. Reaction **2**: a microwave-induced cyclization and dehydration reaction used in the synthesis of Sildenafil (Viagra™). Reaction **3**: preparation of β-lactams by microwave-induced organic reaction enhancement (MORE) chemistry. Reaction **4**: epimerization of the α-pyridyl proton under microwave irradiation to give the more stable *exo*-isomer. Green circle = resin. Reaction **5**: rapid parallel and microwave-assisted transformation of a library of amides into the corresponding thioamides. Abbreviation: PMP, *p*-anidyl(*p*-methoxyphenyl).

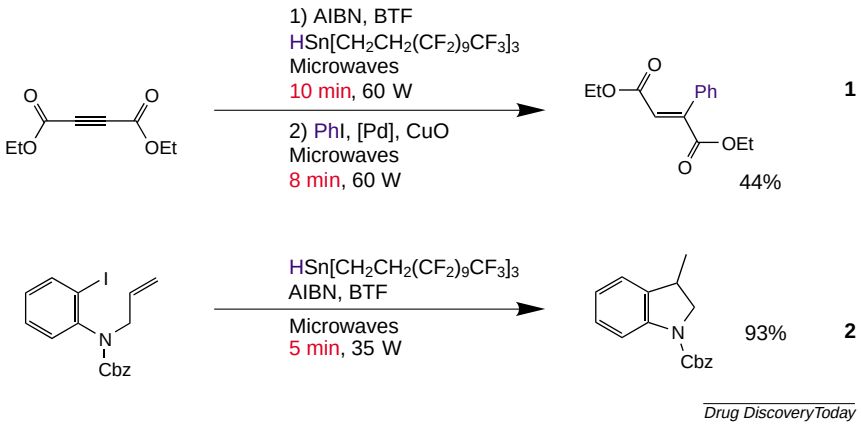

Figure 9. High-speed, highly fluorous organic reactions. Recently introduced fluorous techniques capitalize on the immiscibility of highly fluorinated phases with organic solvents and water at room temperature. Fluorous molecules (molecules equipped with perfluorinated tags) will seek the fluorous phase in a separation stage. The highly efficient purification procedures make the combination of fluorous chemistry and microwave flash-heating attractive for combinatorial chemistry. Reaction **1** is a one-pot, microwave-promoted fluorous hydrostannylation, followed by a Stille coupling of the resulting fluorous vinyl stannane with iodobenzene. Azobisisobutyronitrile (AIBN) was used as initiator. In reaction **2** a fast fluorous radical-mediated cyclization is performed in partially fluorinated benzotrifluoride (BTF). Abbreviation: Cbz, carbobenzoxy.

giving rise to a less heterogeneous reaction mixture with a highly organic/fluorous interface area. The potential of fluorous chemistry is great and, because fluorous reverse-phase silica is now commercially available, interest in the fluorous organic reactions is likely to increase significantly in the future.

Microwave-assisted multi-component reactions

The pyridine scaffold is an essential structural element of many drugs. Khmelnitsky used microwave-assisted combinatorial synthesis for the fast generation of libraries of diverse substituted pyridines employing the three-component Hantzsch synthesis[44]. A solvent-free synthesis was performed in a 96-well format for the high-throughput automated production of diverse pyridines, which could be easily separated by HPLC. Each well of the glass-filled-polypropylene 96-well filter-plate reactors contained bentonite/ammonium nitrate as a support. A household microwave oven and a reaction time of five min was used. The products were extracted from the support with ethyl acetate in parallel format. It is notable that the reactions were uniformly successful across the 96-well reactor plate, suggesting that the reactions were not adversely affected by the uneven distribution of microwave energy inside the oven (Fig. 10; Reaction 1). Interestingly, this is the first example in this review of a solvent-free protocol performed with the reactants adsorbed on a microwave-active inorganic support. However, the solvent-free methodology is not to be confused with the examples of solid-phase chemistry, wherein the reactant is covalently linked to a polymer resin.

A slightly different strategy was applied by Kappe and Varma to the parallel synthesis of 4-aryl-3,4-dihydropyridinones using a Biginelli multi-component condensation reaction[45]. Irradiation of a neat mixture of aryl aldehydes, β-ketoesters and urea derivatives, in the presence of polyphosphate ester as the reaction mediator, resulted in moderate to high yields of products after a 90 sec reaction time (Fig. 10; Reaction 2).

Varma employed solvent-free conditions for facile multi-component reactions that deliver imidazo-annulated pyridines, pyrazines and pyrimidines[46]. These Ugi reactions, using clay as the inorganic support, can be adapted for high-speed parallel synthesis and have great potential for library generation (Fig. 10; Reaction 3).

The Ugi four-component condensation often requires reaction times of up to several days using solid-phase methods. However, Nielsen found that a microwave-assisted solid-phase protocol yielded moderate to excellent amounts of high purity products after irradiation for five min in a single-mode reactor[47]; PEG-grafted polystyrene (Tentagel-S-RAM™; Rapp Polymere) and dichloromethane/methanol were used as resin and solvent, respectively, for the generation of this small library (Fig. 10; Reaction 4).

Several reports have been published on the microwave-assisted synthesis of benzimidazole and imidazoles[48–52]. Most recently, an efficient synthesis of 2,4,5- and 1,2,4,5-substituted imidazoles on solid support under solvent-free conditions was reported (Fig. 10; Reaction 5)[53], a reaction that is amenable to fast combinatorial synthesis. This synthetic procedure involved impregnating the mixture of solid alumina support and ammonium acetate, which was used as an ammonia source, with ether stock-solutions of the starting materials. The solvent was then evaporated and the solid residue heated in a microwave oven. The yields were generally high and the multi-component synthesis provided access to structurally diverse libraries of imidazole derivatives.

Outlook and conclusions

A series of representative examples of the impact of flash-heating on some reactions commonly used by medicinal

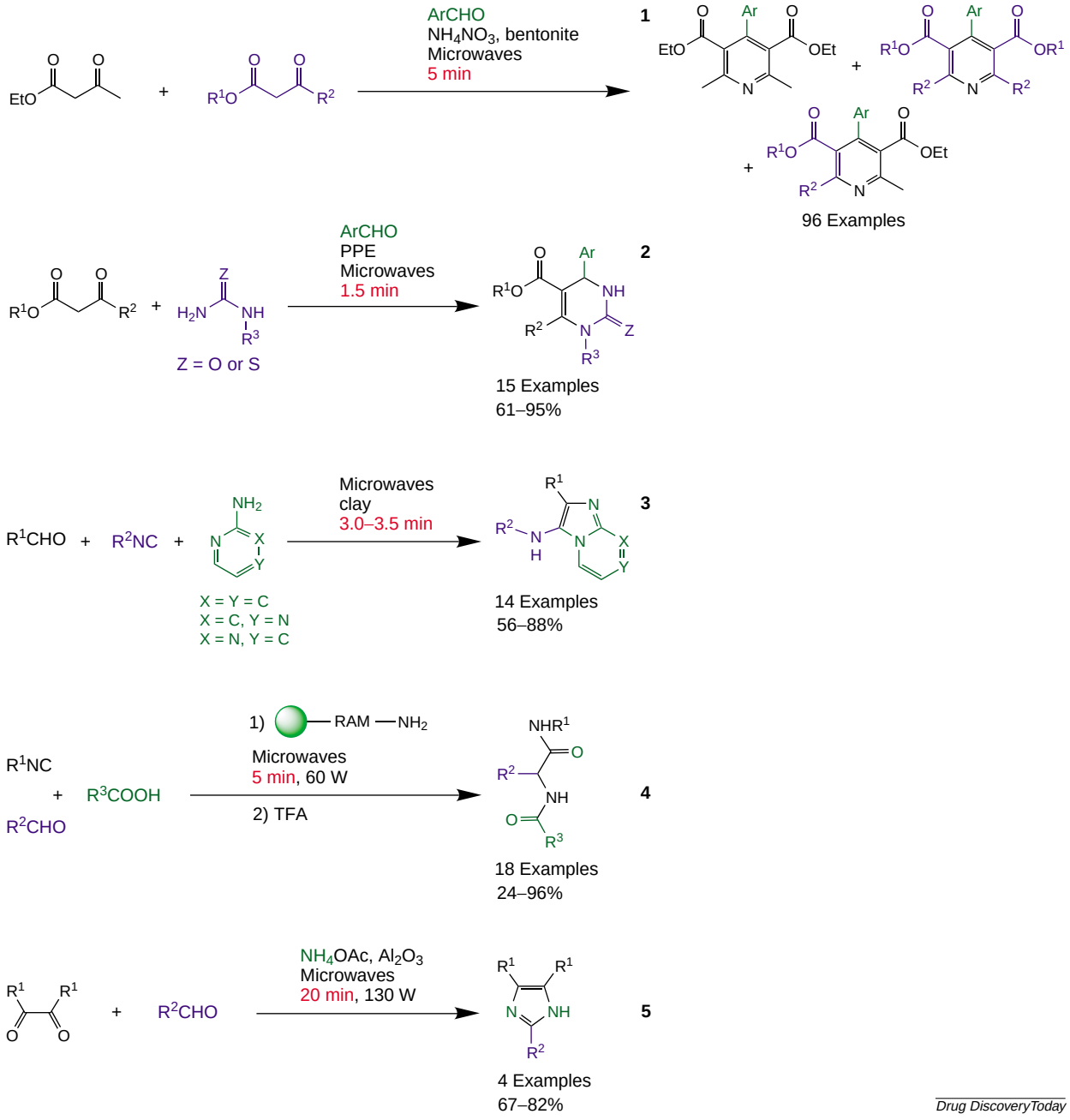

Figure 10. Powerful microwave heated multi-component reactions for substance library generation. Reaction **1**: the microwave heating technique applied to high-throughput, automated, one-step, parallel synthesis of diverse substituted pyridines using the Hantzsch protocol. Reaction **2**: pharmacologically important dihydropyrimidinones synthesized by a microwave-promoted, solvent-free modified Biginelli reaction. Reaction **3**: a facile and rapid Ugi-methodology amenable to the generation of compound libraries using microwave heating. Reaction **4**: an 18-member library constructed in high purity via microwave-induced solid-phase Ugi reactions on TentaGel™ Rink amide resin (green circles). Reaction **5**: diverse substituted imidazoles obtained in solvent-free microwave-assisted condensation reactions. Abbreviations: TFA, trifluoroacetic acid; PPE, polyphosphate ester.

and combinatorial chemists has been presented herein. In addition to the transition metal-mediated C–C and C–N bond-forming procedures, various types of condensation reactions, alkylations and radical reactions were discussed. However, there are many other reaction types that have already proven suitable for microwave acceleration, but these have not, to date, been exploited in the context of library production. Furthermore, there are many other reactions with great potential for automated medicinal and combinatorial chemistry, which traditionally have been

performed with long reaction times, that might be dramatically accelerated by microwave heating. For example, it could be expected that carbonylative reactions might respond well to microwave heating.

As has been shown by the selection of examples presented, solution as well as solid-phase, fluorous and solvent-free syntheses are compatible with microwave heating. The solvent-free reaction systems appear to be particularly suitable for the application of this heating methodology. Although the number of reports on the application of focused irradiation in single-mode cavities are steadily increasing, largely because of the well-recognized efficient heat-transfer and high reproducibility achieved, it is notable that reports on the successful use of domestic multi-mode ovens or multi-mode reactors for library production are also prevalent in the literature.

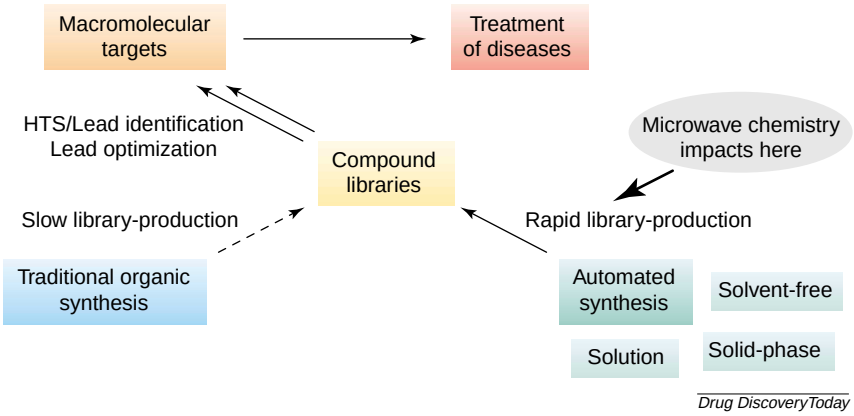

Figure 11. The drug discovery process and the foreseen impact of microwave chemistry on automated medicinal/combinatorial chemistry. Today, new therapeutic macromolecular targets are increasingly being identified as drug targets. The need for new organic small-molecules to feed the HTS facilities is, therefore, acute in the pursuit of new hits. The lead generation and lead optimization processes must be accelerated. Traditional methods of organic synthesis are simply too slow to satisfy the future demand for compounds. Microwave-assisted chemistry is a technique that has the power to accelerate the generation of organic molecules.

The reduced reaction times, compatibility with efficient separation and analysis methodologies and experimental simplification offered by microwave heating, enables significantly faster reaction optimization and substance production. Therefore, a rapid expansion in the area of microwave chemistry is expected in the near future. The amount of compounds available for high throughput biological screening will inevitably increase and consequently, the lead optimization process will probably be accelerated (Fig. 11).

Unfortunately, only a few modern microwave reactors that are designed for safe automated synthesis and are equipped with adequate and efficient temperature and temperature-feedback control systems are currently available on the market. It is probable however, that the increased demand for safe microwave cavities that are amenable for automation will, in a few years, ensure the commercial production of various types of single-mode cavity-based synthesizers that deliver reproducible results and that satisfy the requirements of both the pharmaceutical industry and academia. With these advances, the age of high-speed chemistry will be here.

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