

Microwave-Accelerated Homogeneous Catalysis in Organic Chemistry

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ABSTRACT

The efficiency of microwave flash heating in accelerating organic transformations (reaction times reduced from days and hours to minutes and seconds) has recently been proven in several different fields of organic chemistry. This specific account mainly summarizes our own experiences in developing rapid, robust, and selective microwave-assisted transition metal-catalyzed homogeneous reactions. Applications include selective Heck couplings, cross-couplings, and asymmetric substitutions. The science of green chemistry was developed to meet the increasing demand for environmentally benign chemical processes. We believe the combination of metal catalysis and microwave heating will be of importance in the search for green laboratory-scale synthesis.

I. Introduction

Homogeneous transition metal-catalyzed reactions are of utmost importance in organic synthesis. This group of reactions, which comprises a plethora of versatile carbon–carbon and carbon–heteroatom bond-forming processes and asymmetric transformations, constitutes an ever growing part of the armory of useful synthetic tools available for the organic chemist today. High yields and impressive regio- and stereoselectivities are often encountered. An important advantage is that many functional groups do not need protection, thus making the synthesis more efficient. However, the long reaction times that are frequently required for full conversions have limited the exploitation of homogeneous catalyses in high-throughput synthesis. Rapid and reliable microwave applications are therefore desired not only for high-speed production of

new chemical entities^{1,2} but also for homogeneous catalysis in general.

The application of microwaves, as an efficient heating source for organic reactions,^{1–3} was recognized in the mid-1980s. Since then, numerous successful reactions with dramatically enhanced reaction rates have been disclosed. Very high yields and clean reactions have been obtained using only small amounts of energy.^{1–4} The possibility of employing milder and less toxic reagents and solvents offers a further advantage of using this heating technology. The noninert-atmosphere condition and simple experimental procedure of many microwave reactions offer additional convenience in chemical synthesis, especially for high-throughput applications.

Up to 1995, approximately 200 articles had been published on the beneficial effect of microwave irradiation in organic synthesis. Today this number is above 1100.¹ It is convenient to divide the reported work into two broad categories: studies that involve reactions in the liquid state, and those performed in the absence of solvent (dry media synthesis). The latter technology is outside the scope of this account and will not be discussed further. Neither will reactions performed with heterogeneous catalysts be presented.

We herein review mainly our own results in the area of microwave-assisted homogeneous catalysis. After a brief theoretical background on microwaves, we will present preparative examples and discuss the impact and future potential of microwave flash heating in both catalysis and sustainable chemistry.

II. Theoretical Background

Microwave frequencies range from 0.3 to 300 GHz; domestic ovens and reactors for chemical reactions all operate at 2.45 GHz, a frequency region assigned for heating applications. At this frequency the polarization vector, which describes the response of a sample to the electric field, lags behind the applied field, and the effective current in the irradiated sample is out of phase with that of the applied field by an effective difference δ .^{1,4} This difference defines the tangent loss factor, $\tan \delta$, frequently named the dissipation factor or the dielectric loss tangent. The word “loss” is used to indicate the amount of input microwave energy that is lost to the sample by being dissipated as heat.

A reaction medium with a high $\tan \delta$ is required for efficient absorption and, consequently, for rapid heating. Since the tangent loss factor is proportional not only to the polarizability but also to the electric conductivity of the reaction medium, polar and ionically conducting solvents are preferable for microwave-assisted reactions. In Table 1, the $\tan \delta$ values and the dielectric constants ϵ' for a series of common solvents at room temperature are shown.⁵ Furthermore, the rate of temperature increase is not only a function of $\tan \delta$ but also of the specific heat

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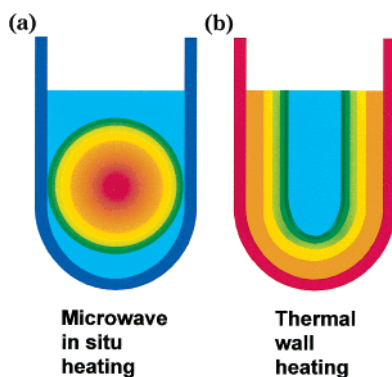


FIGURE 1. (a) Schematic illustration of microwave in-situ heating. The heat is transferred directly into the reaction mixture. (b) Classic wall heating. The heat energy must be transferred via the vessel wall.

Table 1. Loss Tangent Data for Common Pure Solvents at Room Temperature

solvent	ϵ'	$\tan \delta$ (2.45 GHz)
dichloromethane	9.1	0.042
tetrahydrofuran	7.6	0.047
acetone	21	0.054
ethyl acetate	6.0	0.059
acetonitrile	38	0.062
chloroform	4.8	0.091
water	80	0.12
dimethylformamide	37	0.16
acetic acid	6.1	0.17
methanol	33	0.66
dimethyl sulfoxide	47	0.82
ethanol	24	0.94
ethylene glycol	38	1.17

capacity, the emissivity, the geometry and the volume of the reaction mixture, and the strength of the applied field.

The reaction vessels employed are made of a material transparent (or largely transparent) to microwaves at 2.45 GHz, commonly borosilicate glass or Teflon. Heat is created efficiently in the interior of the sample (Figure 1a), whereas wall heat transfer occurs with conventional heating systems, e.g. oil bath (Figure 1b). This internal heat transfer results in minimized wall effects (no thermal boundary layer), and thus, the tendency for seed formation is reduced and superheating can occur. By using closed microwave-transparent vessels, which can sustain higher pressures, the superheating effects are substantially magnified and it is possible to maintain solutions at temperatures much above their conventional reflux temperature.^{1–4} A set of powerful temperature profiles obtained by single-mode flash heating of septa-sealed allylic substitution reactions in acetonitrile (bp 81–82 °C) are presented in Figure 2.⁶ The higher purity of products often observed after microwave irradiation can probably be largely attributed to the homogeneous and smooth in-situ heating.

Microwave heating of closed reaction vessels is a very energy efficient heating technique since only the reaction mixture is directly heated and not the reaction vessel. The heating procedure is also highly controlled since the energy input starts and stops immediately when the power is turned on or off, respectively.^{1–4}

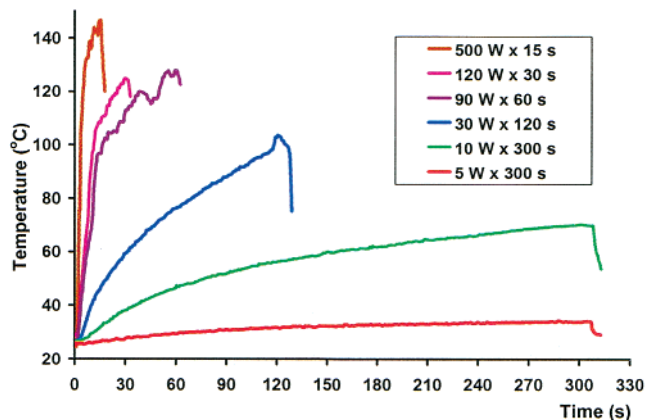


FIGURE 2. Temperature profiles for microwave flash heated palladium-catalyzed asymmetric alkylations in acetonitrile. The reactions were performed in septum-sealed Pyrex vessels by utilizing a prototype single-mode applicator (PersonalChemistry AB) equipped with a fluoroptic probe.⁶

III. Equipment

The instrumentation used for microwave chemistry is quite varied, but most of the microwave-promoted organic synthesis has so far been conducted in multimode domestic ovens, where the power levels are commonly varied by the alteration of the patterns of on–off cycles. In domestic ovens the microwaves are randomly distributed within the cavity and the regions of high and low intensity that are produced are not well defined. In a single-mode microwave cavity, on the other hand, a continuous standing wave is generated with well-defined regions of maxima and minima field strengths.^{1,4} Placement of the reaction tube at a fixed position allows the intensity at the sample to be well defined. The power level is varied by modulating the continuous-wave output.

Consequently, since a microwave device for organic synthesis should provide a high and stable electric field intensity to ensure short reactions times and to allow for an optimal reproducibility of the chemical transformations, single-mode cavities with an adequate temperature control are preferable. The use of controlled irradiation is of particular importance in the execution of strongly accelerated and selective transition-metal-catalyzed reactions in which the catalysis proceeds via the involvement of catalytic amounts of labile intermediates. The majority of the reactions discussed in this account were conducted in septum-sealed reaction vessels with single-mode microwave heating.

Offsetting the advantages of microwave-assisted organic reactions are some detractions. The processing of large quantities of material by scaling up small, low-volume single-mode reactions is not always feasible. However, the development of continuous-flow reactors may provide an attractive solution. Reliable temperature monitoring and temperature feedback power control during microwave irradiation is also of utmost importance for successful applications in synthetic chemistry. For an example of a highly controlled reaction, see Figure 3.⁷ Clearly, in the absence of an accurate temperature moni-

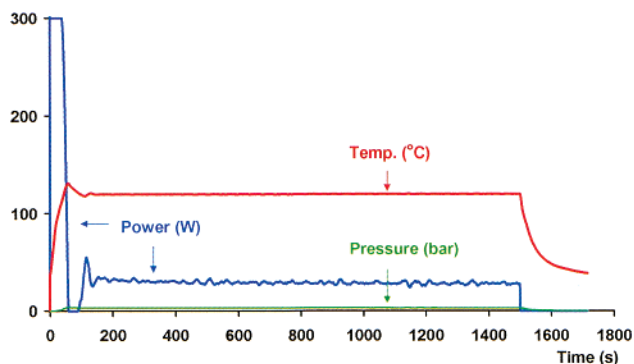


FIGURE 3. Controlled temperature, irradiation power, and pressure profiles for microwave-assisted Sonogashira reactions (SmithSynthesizer).⁷

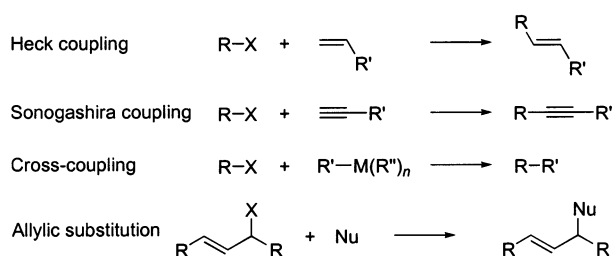


FIGURE 4. Homogeneous palladium-catalyzed reactions.

toring, a reaction may not be reproducible between two different microwave systems.³ In addition, the temperature feedback control should be capable of very rapid reduction of microwave power when exothermic reaction energy becomes significant, or when the dissipation factor increases rapidly, to avoid thermal runaways. The invention of robotized, automatic, and temperature-controlled single-mode reactors will further increase the importance of the microwave heating technology.

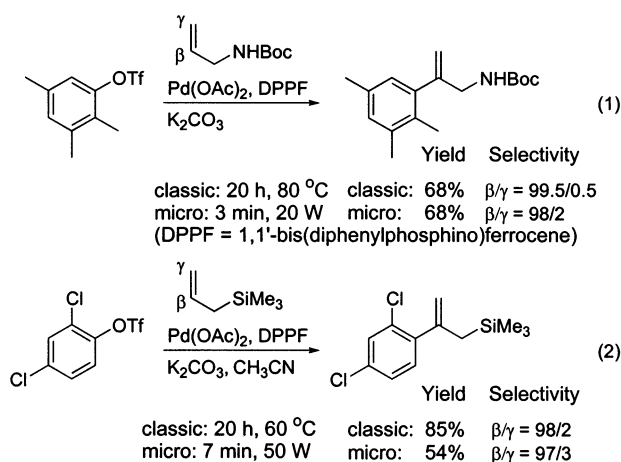
Clearly, it is unsafe to flash heat volatile and potentially flammable organic solvents in a contained space, and explosions of vessels are common in reported experiments with closed systems. Therefore, it is important to realize that when the “bomb strategy” is applied, almost any vessel can be overpressurized if not fitted with an efficient temperature feedback power control and a pressure-relief device. The usage of relevant equipment designed for microwave-assisted high-speed chemistry is most important in the safe execution of sealed vessel experiments. It is advisable to consult the manufacturer about proposed applications.

IV. Coupling Reactions

The majority of the microwave-promoted reactions reported so far that rely on homogeneous catalysis are catalyzed by palladium and of four types: Heck reactions; Sonogashira reactions; cross-coupling reactions (e.g. the Suzuki and Stille reactions); allylic substitutions (Figure 4).

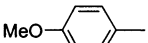

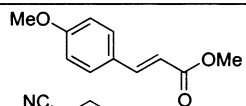
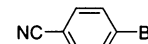

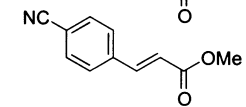
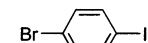

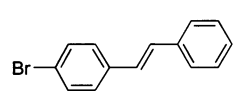
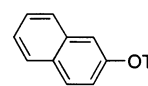
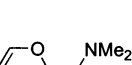
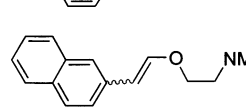
A. Heck Reactions. The Heck arylation of olefins with aryl halides and triflates is a highly versatile synthetic transformation. Monoarylated olefins are generally obtained, and good regiocontrol, affording either linear or branched products, can be achieved by careful selection of reaction parameters.⁸ Heck reactions require, with a few

exceptions where activated olefins are used, reaction times ranging from hours to days for completion. With standard catalysts, reaction temperatures of 60–120 °C are most frequently used with conventional heating sources. Attempts to reduce the reaction times by further increasing the temperature are seldom effective due to the collapse of the catalytic system. Access to new methods that permit fast coupling reactions has therefore been highly desirable. The Heck arylations shown in Table 2 were reported in 1996 and illustrate the power of the flash heating methodology.⁹ These reactions constitute the first examples of palladium-catalyzed C–C bond formation promoted by microwave heating and were conducted in a single-mode cavity in septum-sealed Pyrex vessels. The reaction times were shortened to a few minutes. The table shows that aryl bromides, iodides, and triflates work as well and, most importantly, essentially the same product patterns are observed as in reactions performed with thermal heating. For example, the arylation of *N,N*-dimethylethyl vinyl ether, suggested to proceed via an intermediate Pd–N chelation that dictates the regiochemical outcome, is not negatively affected by microwave heating (entry 4).⁹ Furthermore, the internal arylation of protected allyl amines, which under cationic conditions are believed to proceed via a regioselective chelation controlled insertion, can be completed within 3–6 min whereas 20 h are required with conventional heating (eq 1).^{10,11} The regioselectivity in the internal arylation of allylsilanes, which is believed to be governed by electronic effects (the β -effect), can also be retained in the microwave-promoted reactions (eq 2).¹² However, slightly lower yields were, in general, encountered in the microwave-mediated arylations of the allylic substrates than in the corresponding thermal reactions.



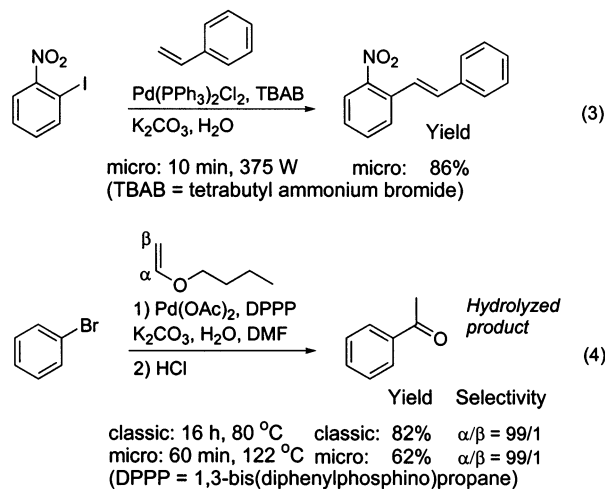
In nature, metal-catalyzed reactions occur in water. Aqueous reaction conditions offer a safe, economic, and environmentally friendly alternative in organic synthesis. In an investigation by Wang et al., microwave-mediated Heck couplings were rapidly performed in water under phase-transfer conditions (TBAB) (eq 3).¹³ A mixture of water and acetonitrile was found by Villemine to be highly efficient for microwave-assisted Heck reactions utilizing a water-soluble ligand.¹⁴

Table 2. Fast Homogeneous Intermolecular Heck Coupling Reactions under Microwave Irradiation

Entry	Aryl Halide or Aryl Triflate	Alkene	Time and Microwave Power ^a	Product	Isolated Yield (%)	Classical Heating ^b Time (min)	Yield
1			3.8 min, 60 W Pd(OAc) ₂ , DMF		70	300	68%
2			3.8 min, 60 W Pd(OAc) ₂ , DMF <i>o</i> -(Tol) ₃ P		94	120	70%
3			4.8 min, 60 W Pd(OAc) ₂ , DMF		63	1020	64%
4			7.0 min, 35 W Pd(OAc) ₂ , Ph ₃ P DMF		87	540	93%

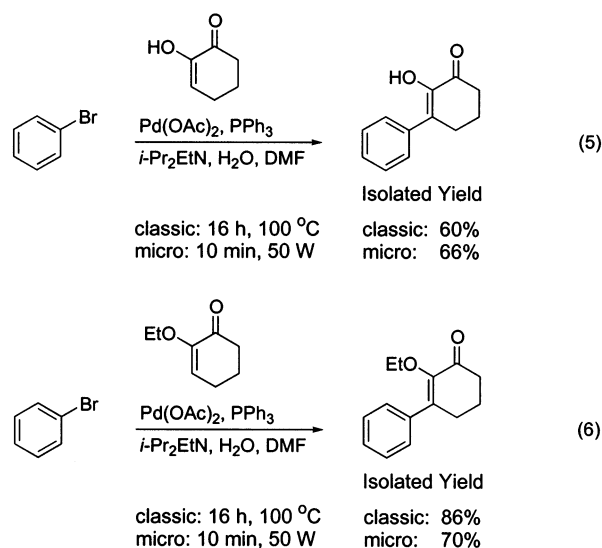
^a Single-mode reactor, PersonalChemistry AB. ^b Literature values.

Toxic thallium(I) salts are needed as additives in internal arylation reactions with aryl bromides. An alternative method to support ionization and the formation of a cationic π -complex from aryl bromides could be to increase the polarity of the DMF-based reaction mixture by the addition of water. Indeed, it was possible to perform thallium-free reactions with high selectivity not only with traditional heating but also with single-mode microwave heating (SmithSynthesizer) (eq 4).¹⁵



The first example of a Heck arylation of an enol, the reaction of 1,2-cyclohexanedione with aryl bromides, proceeds slowly with conventional heating, and at least 16 h of reaction time was needed for complete conversion of the starting materials.¹⁶ Yields ranging from 26% to 66% were obtained, and electron-poor arylating agents were reluctant to provide any coupled products at all. The moderate yields were suggested to be most likely associated with decomposition of the labile 1,2-cyclohexanedione. Upon continuous microwave irradiation with a single-mode cavity at a power of 40–50 W the transformations were completed within 10 min but the yields were only slightly better (eq 5).¹⁶ Apparently, in this particular example, the sharp temperature profiles obtained after the internal heat transfer had only a low impact on the pro-

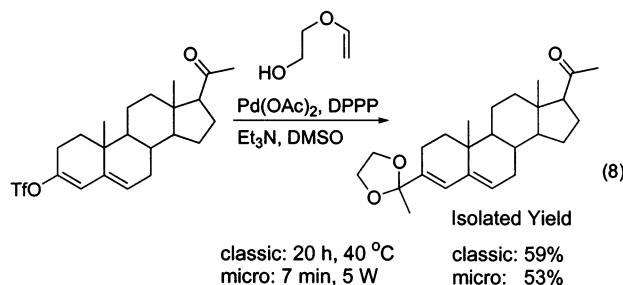
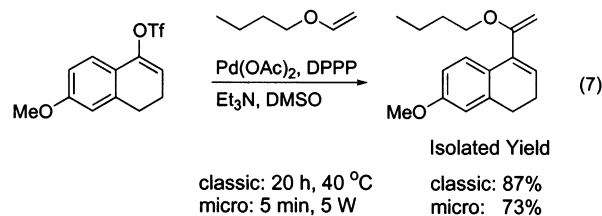
duct distribution. Furthermore, as in the thermal version of the reaction, electron-poor arylating derivatives afforded no coupling products after irradiation. Heck arylation of the corresponding vinyl ethers exhibited a similar reaction profile (eq 6).¹⁶



The reactions discussed so far were performed in polar organic solvents such as acetonitrile, DMF, or water. A dramatic decrease in reaction times, but no significant improvements regarding yields or regioselectivities, was encountered with all olefins tested. In contrast, Diaz-Ortiz has reported that much higher yields were obtained in Heck reactions performed under microwave irradiation employing a domestic oven than under classical heating, provided the same temperature of 150 °C and a reaction time of 22 min were used.¹⁷ The reactions were conducted in the absence of solvent with triethylamine as the base and with activated olefins such as styrene and methyl vinyl ketone. Unfortunately, it is not clear whether starting material remained in the thermal reactions, and the results are therefore somewhat difficult to rationalize. It is relevant to mention here that palladium on porous glass is an efficient heterogeneous catalyst for microwave-pro-

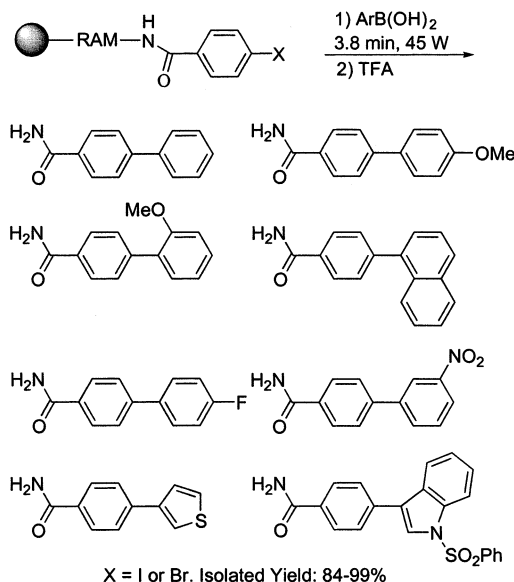
moted Heck and Sonogashira reactions performed in a pressure-tight batch reactor (MBR).¹⁸ This catalyst was developed by Strauss, who is one of the true pioneers of microwave chemistry.³ Furthermore, Wali et al. reported a microwave-induced Heck reaction of 1-decene, where various supported palladium catalysts were employed.¹⁹

Palladium-catalyzed vinylations of electron-rich olefins deliver dienes that are useful for various Diels–Alder reactions. Thus, vinyl triflates react with alkyl vinyl ethers to give 2-alkoxybutadienes with an extremely high regioselectivity provided that a chelating ligand is employed.²⁰ Relatively low temperatures (40–60 °C) combined with long reaction times (typically 20 h) have been used to avoid decomposition. Despite the high reactivity of the product, this transformation has successfully been promoted by microwave irradiation to provide high yields of products with high regioselectivity after 5 min (eq 7).²⁰ In this reaction, a power of only 5 W was employed and the reaction temperature reached 76 °C (fluoroptic thermometer). By substitution of the alkyl vinyl ether for the commercially available 2-hydroxyalkyl vinyl ether, a new facile preparation of masked α,β -unsaturated methyl ketones was accomplished. This reaction was extended to the preparation of monoprotected methyl ketones as depicted in eq 8.²⁰ These examples demonstrate the beneficial effect of microwaves as the energy source even in the absence of superheating.



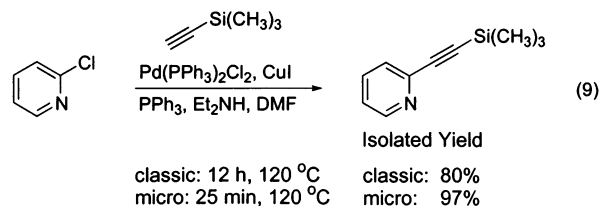
B. Sonogashira Coupling Reactions. The palladium-catalyzed Sonogashira coupling is closely related to the Heck reaction. The coupling, which is an acetylenic substitution reaction, is conducted with terminal alkynes and organic halides or pseudohalides. Erdélyi and Gogoll have very recently highlighted the potential of controlled microwave heating to promote homogeneous Sonogashira couplings.⁷ An illustration is shown in eq 9 in which 2-chloropyridine was completely consumed in 25 min.⁷ This is in contrast with the reported very slow reaction of this substrate under classical heating. Copper(I) iodide has also been reported to be an efficient catalyst under mic-

Table 3. Rapid Microwave-Assisted Suzuki Couplings on Solid Phase^a



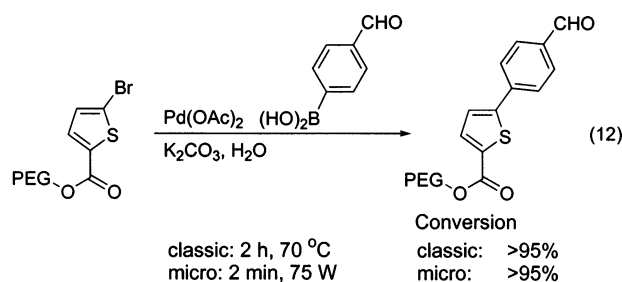
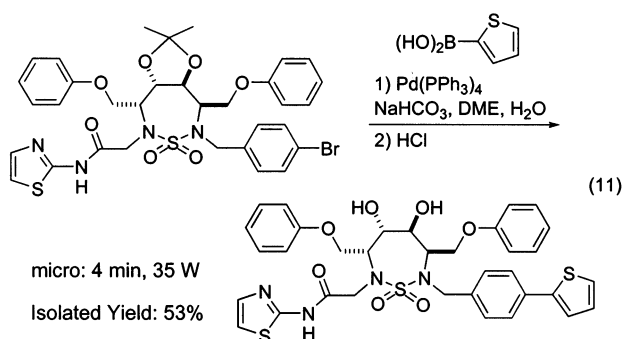
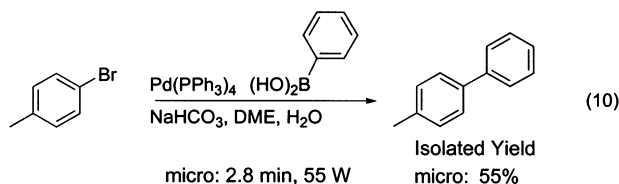
^a Single-mode, PersonalChemistry AB (RAM = Rink amide).

rowave irradiation for the coupling of aryl iodides or aryl chlorides with terminal alkynes.^{21,22}

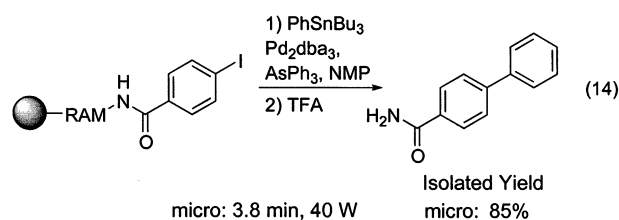
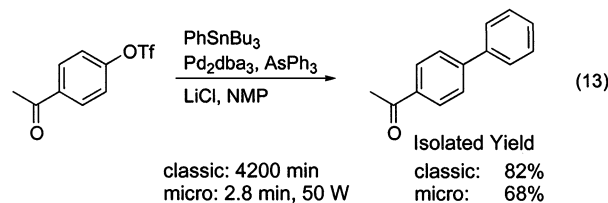


C. Cross-Coupling Reactions. The Suzuki reaction is probably the most versatile among the cross-coupling reactions and the reaction has attracted the interest of scientists involved in high-throughput chemistry. We disclosed the first microwave-promoted Suzuki couplings in 1996.^{9,23} Phenyl boronic acid was coupled with 4-methylphenyl bromide in dimethoxyethane/water to give a fair yield of coupled product after a reaction time of less than 4 min (eq 10).⁹ Equation 11 shows an example of a microwave-promoted Suzuki coupling that delivers a HIV protease inhibitor.²⁴ More interestingly, the Suzuki reaction also worked smoothly on solid support affording high yields of products. 4-Bromo- and 4-iodobenzoic acid linked to Rink amide TentaGel were used, and a conversion of more than 99% was accomplished within 4 min (Table 3).²³ The high yields suggest that microwave-assisted reactions on polymer supports are potentially powerful transformations. Suzuki couplings were also recently performed in water using PEG as a soluble support (eq 12).²⁵ The reactions utilized the intrinsic solubilizing and phase-transfer catalytic properties of the polymer support, and no organic cosolvent was used. Compared to thermal heating, the microwave irradiation shortened the reaction time from 2 h to 2–4 min and, as in the previous example, the polymer was stable under the reaction conditions. In contrast, the conventional thermal conditions induced a considerable ester cleavage

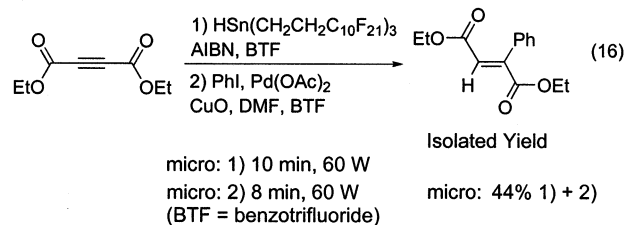
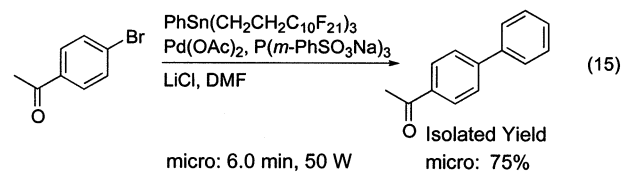
(up to 45%).²⁵ The Varma group has reported closely related Suzuki couplings with PEG as a nontoxic reaction medium.²⁶ Tetraphenylborate has also proven to be an efficient Suzuki phenylation reactant in water under microwave irradiation.²⁷



The Stille reaction is similar to the Suzuki cross-coupling, but alkyltin reagents, instead of boronic acids, are employed as coupling partners to the organopalladium intermediates. The reaction was soon found to be suitable for flash heating conditions, and successful, very fast Stille reactions in solution (eq 13)⁹ as well as on solid phase (eq 14) were reported.²³ Maleczka recently published a one-pot microwave-assisted hydrostannylation–Stille coupling sequence.²⁸



Although the Stille reaction has emerged as an important reaction in high-throughput chemistry, there are disadvantages such as the toxicity and the separation of tin compounds. To circumvent these problems and to integrate the synthetic strategy with a separation strategy, Curran introduced a modification of the Stille reaction in which highly fluorinated tin reactants are used. The key advantage with this fluorous concept is that inorganic-, organic-, and fluorous-containing products can be efficiently separated using simple three-phase extractions with water, organic, and fluorocarbon solvent. Unfortunately, these fluorous Stille reactions require long reaction times, typically 1 day at 80 °C. By application of the microwave heating technique, the reaction times in these reactions could be shortened to 2 min or less.²⁹ A single-mode cavity and a power of 50–70 W were used. Table 4 presents preparative examples of the coupling of aryl bromides, iodides, and triflates as well as a benzyl bromide with organostannanes containing –CH₂CH₂C₆F₁₃ tags (shortened F-13).²⁹ The use of the more fluorous –CH₂CH₂C₁₀F₂₁ (F-21) tag resulted in very sluggish reactions and poor yields when traditional heating sources were used, whereas reactions conducted with microwave promotion delivered high yields of products after reaction times of 6 min and at 50 W (eq 15).³⁰ In eq 16 an example of a one-pot, microwave-assisted F-21 fluorous hydrostannylation of diethyl acetylenedicarboxylate in benzotrifluoride (BTF), followed by a Stille-coupling, is illustrated.³⁰ Both reactions work smoothly. Notably, the F-21 tin reagents are highly insoluble in organic solvents and in hybrid solvents, such as BTF, the solubility is also poor. For the exploitation of the high partition coefficient in the liquid–liquid extraction or of the silica gel filtration in the separation stage, an ability to promote highly fluorous reactions is crucial. The power of the microwave heating technique is clear here.



Nitriles are valuable intermediates that can be transformed to yield a broad spectrum of functionalities, e.g. thiazoles, oxazolidones, triazoles, and tetrazoles. The tetrazoles are of particular interest to the medicinal chemist since they probably constitute the most com-

Table 4. Fast Homogeneous Stille Couplings with Fluorous Tin Reactants under Microwave Irradiation

Entry	Tin Reactant	Organic Halide or Organic Triflate	Time and Microwave Power ^a	Product	Isolated Yield
1			1.5 min, 70 W PdCl ₂ (PPh ₃) ₂		76%
2			1.5 min, 70 W PdCl ₂ (PPh ₃) ₂		96%
3			2.0 min, 50 W PdCl ₂ (PPh ₃) ₂		90%
4			2.0 min, 60 W PdCl ₂ (PPh ₃) ₂		83%
5			1.5 min, 70W PdCl ₂ (PPh ₃) ₂		87%
6			2.0 min, 60 W PdCl ₂ (PPh ₃) ₂		79%
7			2.0 min, 60 W PdCl ₂ (PPh ₃) ₂		54%

^a Single-mode, PersonalChemistry AB.**Table 5. Fast Homogeneous Preparation of Aryl and Vinyl Nitriles under Microwave Irradiation**

Entry	Organic Bromide	Time and Microwave Power ^a	Product	Isolated Yield	Classical Heating ^b	
					Time (min)	Yield
1		2.0 min, 60 W Zn(CN) ₂ , Pd(PPh ₃) ₄		81%	420	95%
2		2.0 min, 60 W Zn(CN) ₂ , Pd(PPh ₃) ₄		78%	540	91%
3		2.0 min, 60 W Zn(CN) ₂ , Pd(PPh ₃) ₄		90%	360	84%
4		2.0 min, 60 W Zn(CN) ₂ , Pd(PPh ₃) ₄		88%	240	71%
5		2.5 min, 60 W Zn(CN) ₂ , Pd(PPh ₃) ₄		80%	960	89%
6		2.0 min, 60 W Zn(CN) ₂ , Pd(PPh ₃) ₄		93%	120	94%

^a Single-mode reactor Microwell 10, PersonalChemistry AB. ^b Literature values.

monly used bioisostere of the carboxyl group. Reaction times of many hours are typically required for the palladium-catalyzed cyanation of aryl bromides with thermal heating, and the subsequent conversion of the nitriles to the tetrazoles requires even longer reaction times, up to 10 days, for completion. Both aryl and vinyl nitriles have been prepared in high yields from the corresponding bromides using palladium-catalyzed reactions and mi-

crowaveirradiation in a single-mode cavity.³¹ The reactions were completed in a few minutes (Table 5; Figure 5). These nitriles are smoothly converted to tetrazoles in high yields by microwave promotion. One example of a one-pot reaction is displayed in eq 17.³¹ A more careful heating was employed in the cycloaddition step. The flash heating methodology is also suitable for conversion of iodides to tetrazoles on solid support as demonstrated in eq 18,

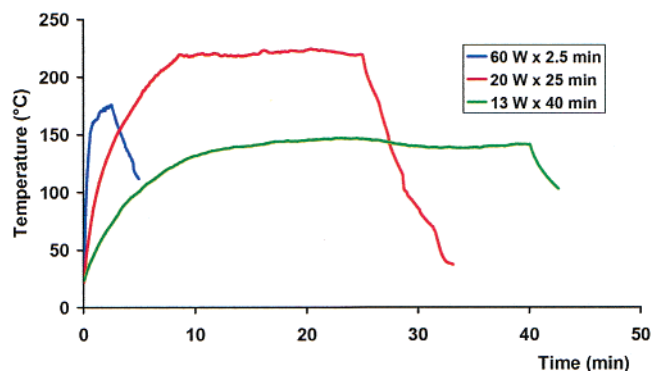
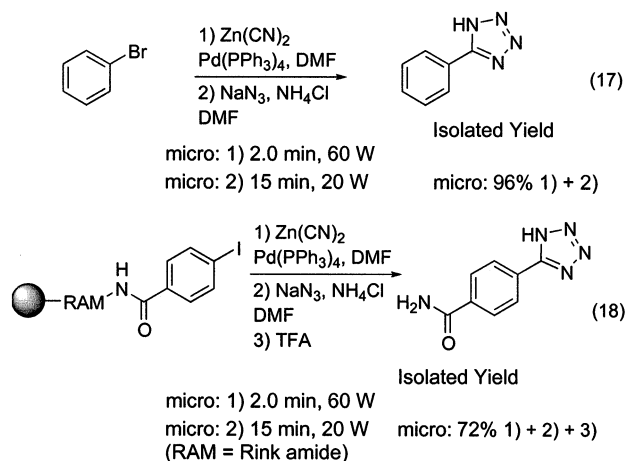


FIGURE 5. Temperature profiles for microwave-heated preparation of nitriles and tetrazoles at different power. The reactions were performed in septum-sealed Pyrex vessels by utilizing a prototype single-mode applicator (PersonalChemistry AB) equipped with a fluoroptic probe.³¹

where a Rink linker on Tentagel was used.³¹ Only a negligible decomposition of the solid support occurred.



A series of potent C_2 -symmetric HIV-1 protease inhibitors with K_i values in the nanomolar range were prepared from a single aryl bromide precursor (a carbohydrate-based scaffold) by application of the Heck, Suzuki, Stille, and cyanation reactions previously discussed.³² The first

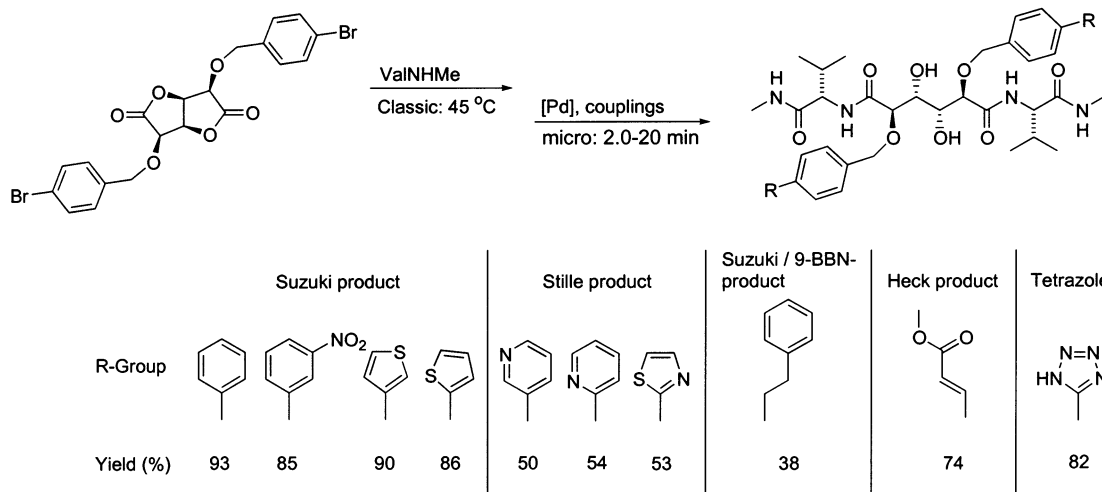
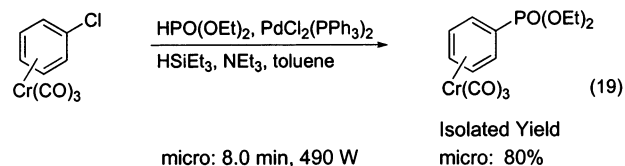


FIGURE 6. Palladium-catalyzed and microwave-assisted diverse functionalization of a linear HIV-1 inhibitor.

reported microwave-promoted Suzuki coupling with an alkyl borane is included in the series (Figure 6). Reactions occur at both of the P1 sites. These reactions are the first examples of the application of homogeneous palladium-catalyzed processes conducted with flash heating to the area of medicinal chemistry of which we are aware.

Aryl phosphonates, common precursors to aryl phosphonic acids, have been prepared in a Teflon autoclave in a commercial microwave oven in fair yields from aryl iodides and bromides. Villemin found that while chlorobenzene was inert under the conditions used, (chlorobenzene)tricarbonylchromium reacted smoothly with no reported decomposition of the complex (eq 19).³³ It is notable that the transformation was performed in non-polar toluene and that the product was obtained after a reaction time of only 8 min.



V. Asymmetric Catalysis

Combinatorial methods are finding increased use in the development of efficient chiral catalysts for asymmetric synthesis. To allow rapid screening of new ligands, short reaction times are desirable. This can be achieved with microwave heating. High enantioselectivity is observed for processes having large differences in the ΔG^\ddagger values for the reactions that give the two enantiomers. Provided that the selectivity determining step remains the same, the selectivity decreases with increasing temperature, as shown by the relation $E = e^{-\Delta\Delta G^\ddagger/RT}$ (E is the enantiomeric ratio as defined originally for kinetic resolutions that involve enzymatic systems). Further, if the selectivity does not change during the catalytic reaction, E is correlated to ee ($E = (ee - 1)/(ee + 1)$). Plots of ee as a function of $\Delta\Delta G^\ddagger$ at 0, 100, and 200 °C (Figure 7) show that, for highly selective processes ($ee > 99\%$ at 0 °C), heating can be employed without the selectivity deteriorating, provided

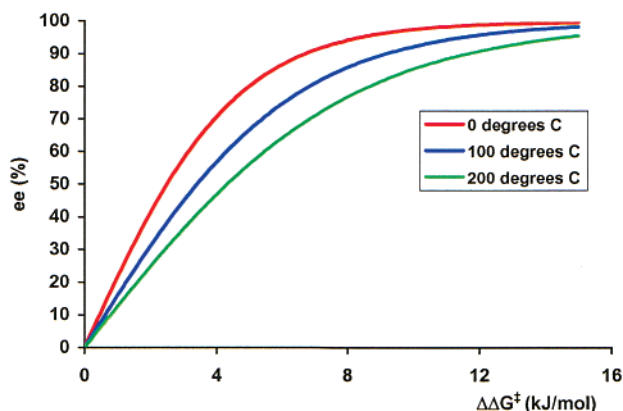
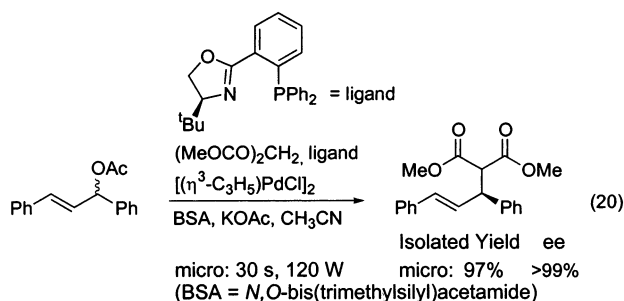


FIGURE 7. Enantiomeric excess as a function of the difference in activation energy ($\Delta\Delta G^\ddagger$) for an enantioselective process at different reaction temperatures.

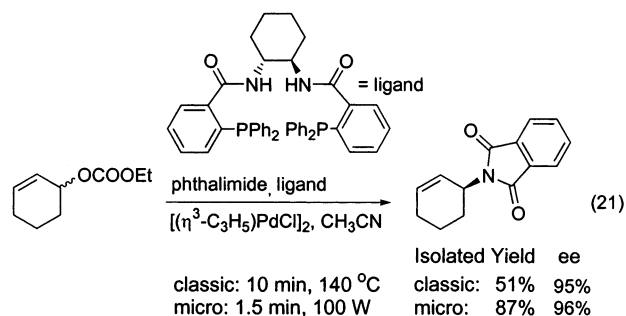
that the catalyst is not degraded and the mechanism of the reaction not changed.³⁴ Microwave heating occasionally prevents degradation due to rapid heating of the entire reaction mixture and may thus constitute a more favorable way to heat than conventional heating.

A. Allylic Substitutions. Like the cross-coupling reactions, the palladium-catalyzed allylic substitution reactions, and in particular the asymmetric versions, have attracted a considerable interest due to their synthetic potential.³⁵ Highly enantioselective palladium-catalyzed allylic substitutions can be accelerated by microwave irradiation.^{6,34} Thus, highly enantioselective and fast allylic substitutions were performed in the presence of a thermostable palladium–phosphinooxazoline catalytic system as shown in eq 20.^{6,34,36–38} This class of P,N-ligands produced higher enantiomeric excesses than e.g. the P,P-ligand BINAP.³⁹ Quantitative yields, enantiomeric excesses of 99% and up to 7000 turnovers/h could be achieved after very short irradiation times in a prototype single-mode applicator.^{6,34} The reactions were conducted in acetonitrile (bp 81–82 °C) in sealed Pyrex vessels with superheating to 145 °C (Figure 3).

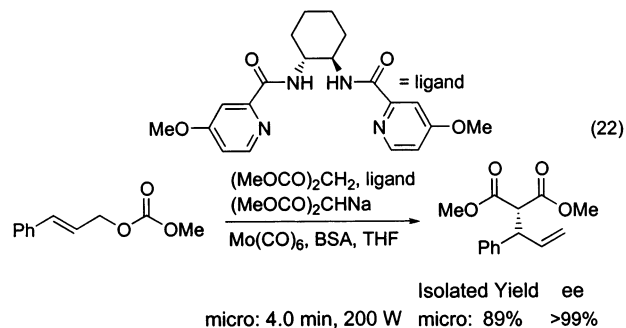


The palladium-catalyzed substitution of *rac*-ethyl 3-cyclohexenyl carbonate with dimethyl malonate as the nucleophile occurred smoothly and delivered very high enantiomeric excesses and yields after a few minutes of irradiation.³⁴ *p*-Methoxyphenol and phthalimide were also found to be good nucleophiles in this reaction (eq 21).³⁴ The reactions with *p*-methoxyphenol, when irradiated for 1.0 min up to 100 °C, delivered yields (91%) and ee values (94–95%) identical to those performed in closed vessels

and heated in an oil bath at 100 °C for 5 min.³⁴ However, when a related experiment was performed using phthalimide as the nucleophile and a higher temperature of 140 °C, much higher yields were obtained using microwave rather than classical heating (eq 21).³⁴ The enantiomeric excesses were the same (95–96%) in each case.



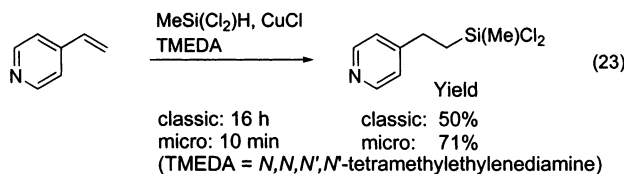
In contrast to the palladium-catalyzed allylations, the molybdenum-catalyzed allylations suffer from significantly lower reactivity. To circumvent this disadvantage, but at the expense of experimental convenience, Trost has employed labile ligands such as propionitrile in the precatalyst $\text{Mo}(\text{CO})_3(\text{EtCN})_3$.⁴⁰ A synthetically useful and easily handled microwave protocol for very fast and selective molybdenum(0)-catalyzed allylic malonate alkylations under noninert conditions was developed.⁴¹ The initial, more sensitive two-step reaction procedure was fine-tuned into a robust one-step procedure, employing a low concentration of the inexpensive and stable precatalyst $\text{Mo}(\text{CO})_6$. The alkylations were conducted with microwave flash heating under air and resulted in complete conversions, high yields (87%), and an impressive enantiomeric excess (98%) in only 5 min.⁴¹ Despite the high temperatures, reaching 220 °C in THF (bp = 65–67 °C), the high enantiomeric purity remained constant, suggesting that the ligand coordinates strongly to the metal. After optimization of reactions involving the chiral 1,2-bis(pyridine-2-carboxamido)cyclohexane ligands, a 4-methoxypyridine derivative was identified that exhibited superior qualities.⁴² This was reflected by the high yield (88%, >95% GC/MS) of the branched product, high ee (>99%), and high regioisomer ratio of 41:1 after only 4 min of heating (eq 22).⁴²



VI. Additional Metal-Catalyzed Reactions

As early as 1991, Abramovitch applied microwave energy to significantly improve the CuCl-mediated hydrosilylation

of 2-vinylpyridine and 4-vinylpyridine in the presence of TMEDA and observed a 100-fold decrease in reaction time and a considerable improvement in yield (eq 23).⁴³ Shortly thereafter, Hajek investigated the related CuCl₂-propylamine-catalyzed addition of tetrachloromethane and ethyltrichloroacetate to styrene and reported a more modest increase in the reaction rate.⁴⁴



A number of interesting new microwave reports have appeared recently in addition to those discussed in this short Account. Homogeneous transition-metal-catalyzed aziridination of olefins,⁴⁵ copper(II)-mediated C–N couplings,⁴⁶ and metathesis of functional alkynes⁴⁷ have, for example, been performed.

VII. Green Context and Future Directions

Our main aim has been to develop robust microwave-assisted methodologies for conducting high-speed homogeneous metal-catalyzed reactions. In addition, we have found it possible to perform the reactions very cleanly and selectively. Readily adjustable and controlled bulk heating allows the transformations to be performed very safely and with a low energy input. The presented examples indicate that the microwave/catalysis strategy provides broad scope in the future development of clean and sustainable organic chemistry. Specific advantages include the following: the successful combination of metal catalysis under air and with water as solvent; the use of milder and less toxic reagents at high temperature; the possibilities to integrate efficient synthesis with nonchromatographic purifications (solid or fluorous separations). Furthermore, there are still many other catalytic reactions that have not been explored in a flash heating context. For example, it can be expected that many aqueous biocatalytic reactions might respond well to microwave heating.

It is already clear that modern automatic microwave synthesizers have much to offer the medicinal and high-throughput chemists engaged in library generation.^{2,48} It is also likely that the widespread acceptance of this technique, as an important tool for the development of laboratory-scale environmentally conscious chemistry,³ will result in microwave synthesizer becoming an integral part of every modern organic laboratory.

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