Microwave-Assisted Synthesis in Water as Solvent

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Contents

1. Introduction

Within the past decade, green chemistry has attained the status of a major scientific discipline.[1,2] The investigation and application of green chemistry principles has led to the development of cleaner and more benign chemical processes, with many new technologies being developed each year. In today's world, synthetic chemists in both academia and industry are constantly challenged to consider more environmentally benign methods for generation of the desired target molecules. Among the 12 principles of green chemistry,[3] the desire for utilizing "safer solvents" and to "design for energy efficiency" can be considered two key principles of relevance to synthetic chemists.

Solvent usage is often an integral part of a chemical or manufacturing process. The unavoidable choice of a specific solvent for a desired chemical reaction can have profound economical, environmental, and societal implications. The pressing need to develop alternative solvents to some extent originates from these implications and constitutes an essential strategy under the emerging field of green chemistry.[1−3] Toward this end, considerable efforts have been devoted to develop and use nontraditional solvents for chemical synthesis.[4] Such unconventional media include, among others, solvent-free conditions,[5] supercritical carbon dioxide,[6] ionic liquids,[7] perfluorinated solvents,[8] and last but not least water.[9,10] There is widespread current debate over the relative "greenness" of these individual reaction media, but water can undoubtedly be considered the cleanest solvent available, and the use and release of clean water clearly will have the least impact to the environment.[11]

On the other hand, for many chemical processes a major adverse effect to the environment is the consumption of energy for heating and cooling. To overcome these problems it is highly desirable to develop efficient methods that use alternative energy sources such as ultrasound or microwave irradiation to facilitate chemical reactions. In particular, the use of microwave energy to directly heat chemical reactions has become an increasingly popular technique in the scientific community.[12−14] Although there is still considerable debate and speculation on the nature and/or existence of so-called "nonthermal" microwave effects that could provide a rationalization for the often observed significant rate and yield enhancements,[14] there is little doubt that microwave heating will become a standard technique in most laboratories within a few years. Is microwave chemistry green chemistry? A recent study comparing the energy efficiency of conventional oil-bath synthesis (heating by conduction and convection currents) and microwave-assisted synthesis (direct "molecular" heating of the reaction mixture) has indicated that for most chemical transformations a significant energy savings (up to 85-fold) can be expected using microwaves as an energy source on a laboratory scale.[15] If those data also hold true for larger scale microwave applications on a pilot or production scale remains to be seen.[16] The possibility of performing reactions in a very short time period by direct

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interaction of microwave energy with the reaction mixture as opposed to the indirect transfer of energy by utilizing an oil bath or similar device certainly can be considered "green", not only because of the reduced energy consumption, but also because of the associated time savings, thereby increasing efficiency.

During the past two decades many publications have described the successful combination of microwave irradiation as a nonclassical energy source with alternative reaction media. Particularly noteworthy is the concept of performing microwave synthesis under solvent-free (dry media) conditions, where the reagents are reacted neat or preadsorbed onto either a more or less microwave transparent (silica, alumina, or clay) or strongly absorbing (graphite) inorganic support that additionally can be doped with a catalyst or reagent.[17] Particularly in the early days of microwave synthesis the solvent-free approach was very popular since it allowed the safe use of domestic household microwave ovens and standard open-vessel technology. More recently microwave-assisted reactions using ionic liquids as solvents have been described.[18] Ionic liquids interact very efficiently with microwaves through an ionic conduction mechanism and are rapidly heated at rates easily exceeding 10 °C/s without any significant pressure build up. Therefore, safety problems arising from overpressurization of heated sealed reaction vessels can be minimized. Similarly, microwave chemistry has been conducted in conjunction with the use of fluorous solvents or fluorous reagents/catalysts.[19] The advantage of microwave heating lies in the rapid coalescence of the organic and fluorous phase to form a homogeneous solution.

As far as water as solvent is concerned, numerous recent publications report the combination of water as an environmentally benign solvent for chemical transformations with the use of microwave irradiation as an efficient heating method. Early work in this area was conducted by Strauss in the mid-1990s and involved the generation of superheated water using a dedicated reactor for microwave heating of solvents under sealed-vessel conditions.[20−22] In recent years the combination of these two prominent green chemistry principles,[3] "microwaves" and "water", has become very popular and received substantial interest due to the work of Leadbeater[23] and others who demonstrated that a great variety of synthetic organic transformations—in particular, transition-metal-catalyzed processes—can be carried out very efficiently and rapidly under these environmentally benign conditions. Despite this fact no general and comprehensive literature survey on this topic exists.

This review will cover microwave-assisted organic synthesis (MAOS) using water as solvent (or cosolvent) ranging from ambient temperatures to chemistry performed in near-critical water at 300 °C and 80 bar pressure. Examples from the literature will deal mainly with synthetic organic chemistry ranging back to the late 1980s when the first examples of microwave-assisted organic synthesis were published. Although most journals today are reluctant to publish microwave chemistry carried out in domestic microwave ovens,[24] this review will include some examples from the literature where domestic microwave ovens have been used. The reader should bear in mind that the exact reaction conditions (for instance, the reaction temperature) have not always been determined accurately, therefore potentially limiting the reproducibility of the work in question.

2. Organic Synthesis in Water

Approximately 70% of the earth's surface is comprised of water, making it the most abundantly existing liquid solvent. In fact, for many hundreds of years water was the only solvent available to chemists to carry out their reactions. It was not until organic solvents came into use that a whole new area of chemistry was born, and many types of reactions were conducted and compounds made that previously had not been thought possible. Nevertheless, in the most recent decades, chemists have begun to reinvestigate the possibility of using water as solvent for organic reactions. The concept

of efficient and selective synthesis in water has been confirmed as the rates, yields, and selectivities observed for many reactions in water have begun to match those in organic solvents.[9,10] Some of the reactions that were only considered possible in organic solvents are now being conducted using water as solvent, and this is very much at the forefront of solvent replacement research following green chemistry principles. The low solubility of substrates in pure water at room temperature can often be overcome by use of organic cosolvents, ionic derivatization, surfactants, or hydrophilic auxiliaries.[9,10]

Why water as solvent? Not only is water nontoxic and readily available at low cost, it is also nonflammable and environmentally benign, providing opportunities for clean processing and pollution prevention. Synthetic organic reactions in aqueous media at ambient or slightly elevated temperatures have therefore become of great interest as water as a solvent for organic reactions often displays unique reactivity and selectivity,[9,10] exploiting, for example, so-called hydrophobic effects.[10,25] Significant advantages have been made in this area, directing the selectivity of synthetic organic reactions in water through the interaction of nonpolar, or hydrophobic, regions of the reactants. These forces are normally too weak to compete with any steric and electronic effects in organic solvents. In water, on the other hand, hydrophobic surfaces associate strongly as a result of the tendency of water to exclude nonpolar species and thus minimize the Gibbs energy of solvation, a phenomenon known as the hydrophobic effect.[10,25] Several reviews on organic synthesis in room-temperature water have appeared during the past decade, containing hundreds of pertinent references on this topic.[9,10]

Apart from performing reactions in aqueous solutions in a moderate temperature range (0−100 °C), chemical processing in water is also possible and of considerable interest under "superheated conditions" (>100 °C) in sealed vessels because of the favorable changes that occur in the chemical and physical properties of water at high temperatures and pressures.[26] Water around its critical point (374 °C, 221 bar) possesses properties very different from those of ambient liquid water and is attracting increased attention as a medium for organic chemistry.[27] Supercritical water (SCW, >374 °C) has been studied extensively for materials synthesis, waste destruction, plastics recycling, coal liquefaction, and biomass processing.[27,28] Its application for preparative organic synthesis is somewhat limited due to its degenerative properties.

In contrast, the so-called near-critical (also termed subcritical) region of water at temperatures between 150 and 300 °C is of greater importance to organic synthesis.[27] High-temperature near-critical water (NCW) under autogenic pressure provides a more favorable reaction medium for organic synthesis than does water under supercritical conditions (>374 °C). At 250 °C, water exhibits a density and polarity similar to those of acetonitrile at room temperature. The dielectric constant of water (ϵ') drops rapidly with temperature, and at 250 °C it has fallen from 78.5 (at 25 °C) to 27.5 (Table 1).[26] This means that as the water temperature is increased, the solubility of organic compounds increases much more than expected for the natural effect of temperature. In addition to the environmental advantages of using water as so-called pseudo-organic solvent in place of conventional organic solvents, isolation of products is normally facilitated. Once cooled, the organic products are no longer soluble in ambient temperature water, and this allows for easy postsynthesis product separation.

Table 1. Properties of Water under Different Conditions[a]

fluid	ordinary water (T < 150 °C, p < 4 bar)	near-critical water (NCW) (T = 150−350 °C, p = 4−200 bar)	supercritical water (SCW) (T > 374 °C, p > 221 bar)
temp (°C)	25	250	400
pressure (bar)	1	50	250
density (g cm^{-3})	1	0.8	0.17
dielectric constant, ϵ'	78.5	27.1	5.9
pK_W	14	11.2	19.4

[a] Data from ref 26.

Most importantly, the ionic product (dissociation constant) of water is increased by 3 orders of magnitude on going from room temperature to 250 °C. The pK_W therefore decreases from 14 to 11.2 but interestingly increases again for SCW (Table 1).[26] This means that water becomes both a stronger acid and a stronger base as the temperature increases to the NCW range. Thus, in addition to the natural increase in kinetic rates with temperature, both acid and base catalyses by water are enhanced at higher temperatures. NCW can therefore act as an acid, base, or acid−base bicatalyst without the need for costly and cumbersome neutralization and catalyst regeneration.[26,27] It is the high-temperature water reaction environment (100−300 °C) that lends itself ideally to processing utilizing microwave heating under sealed-vessel conditions.

3. Microwave-Assisted Organic Synthesis

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,[29] more than 3500 articles have been published in the area of microwave-assisted organic synthesis (MAOS).[12−14] Since the late 1990s the number of publications related to MAOS has increased dramatically 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. In many instances, controlled microwave heating under sealed-vessel conditions has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional synthetic methods.[12−14] The many advantages of this enabling technology have not only been exploited for organic synthesis (MAOS)[12−14] and in the context of medicinal chemistry/drug discovery,[30] but also penetrated fields such as polymer synthesis,[31] material sciences,[32] nanotechnology,[33] and biochemical processes.[34]

Microwave chemistry generally relies on the ability of the reaction mixture to efficiently absorb microwave energy, taking advantage of "microwave dielectric heating" phenomena such as dipolar polarization or ionic conduction mechanisms.[35] In most cases this means that the solvent used for a particular transformation must be microwave absorbing. The ability of a specific solvent to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent (tan δ), expressed as the quotient, tan $\delta = \epsilon''/\epsilon'$, where ϵ'' is the dielectric loss, indicative of the efficiency with which electromagnetic radiation is converted into heat, and ϵ' is the dielectric

Table 2. Loss Tangents (tan δ) of Different Solvents (2.45 GHz, 20 °C)[a]

solvent	tan δ	solvent	tan δ
ethylene glycol	1.350	water	0.123
ethanol	0.941	chloroform	0.091
DMSO	0.825	acetonitrile	0.062
methanol	0.659	acetone	0.054
1,2-dichlorobenzene	0.280	tetrahydrofuran	0.047
acetic acid	0.174	dichloromethane	0.042
DMF	0.161	toluene	0.040
1,2-dichloroethane	0.127	hexane	0.020

[a] Data from ref 12c.

constant, describing the ability of molecules to be polarized by the electric field.[35] A reaction medium with a high tan δ at the standard operating frequency of a microwave synthesis reactor (2.45 GHz) is required for good absorption and, consequently, efficient heating (Table 2).

In general, solvents used for microwave synthesis can be classified as high (tan $\delta > 0.5$), medium (tan δ 0.1−0.5), and low microwave absorbing (tan $\delta < 0.1$).[12] Other common solvents without a permanent dipole moment such as carbon tetrachloride, benzene, and dioxane are more or less microwave transparent. Therefore, microwave synthesis in low-absorbing or microwave transparent solvents is often not feasible unless either the substrates or some of the reagents/catalysts are strongly polar and therefore microwave absorbing, raising the overall dielectric properties of the reaction medium to a level that allows sufficient heating by microwaves. Water can be considered only a medium microwave absorbing solvent with a loss tan δ of 0.123 (Table 2).

Traditionally, organic synthesis at elevated temperatures is being carried out by conductive heating with an external heat source (i.e., 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 (e.g., 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 as compared to conventional thermal heating results. The very efficient internal heat transfer results in minimized wall effects which may lead to, for example, diminished catalyst deactivation. Reviewing the present literature it appears that today most scientists agree that in the majority of cases the reason for the observed rate enhancements is the result of a thermal/kinetic effect, which means a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field.[13,14]

Although many of the early pioneering experiments in microwave-assisted organic synthesis have been carried out in domestic microwave ovens, the current trend undoubtedly is to use dedicated instruments for chemical synthesis.[36] 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. Combined with the inhomogeneous field produced by the low-cost magnetrons and the lack of safety controls, use of such equipment cannot be recommended.[24] In contrast, all of today's commercially available dedicated microwave reactors for synthesis 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.[37]

4. Microwave Chemistry in Water—General Aspects

As with most organic solvents, the loss tangent (tan δ) for water is strongly influenced by temperature. Since the dielectric constant ϵ' for water drastically decreases with temperature (Table 1), the dielectric loss ϵ'' and therefore the loss tangent are also reduced.[35] For that reason it is not a trivial affair to heat pure water to high temperatures under microwave conditions. While water can be heated rather effectively from room temperature to 100 °C, it is more difficult to superheat water in sealed vessels from 100 to 200 °C and very difficult to reach 300 °C by microwave dielectric heating.[38] In fact, SCW is transparent to microwave radiation.

The loss tangent of a solvent such as water—in other words the ability of the medium to convert electromagnetic energy into heat—can be significantly increased, for example, by addition of small amounts of inorganic salts.[35,39] The electric component of an electromagnetic field causes heating by two main mechanisms: dipolar polarization and ionic conduction.[35] When irradiated at microwave frequencies, the dipoles or ions of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field, and in the process, energy is lost in the form of heat through molecular friction and dielectric loss.[35] 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. From a chemical point of view, introduction of ions into a solution leads to a marked increase in dielectric heating rates due to the ionic conduction mechanism.[35,39]

As shown in Figure 1, constant microwave irradiation of a 5 mL sample of water with 150 W power leads indeed to a marked difference in heating profiles between pure water and a 0.03 M sodium chloride solution. While the water sample only reaches ca. 130 °C after 90 s of irradiation and the temperature cannot be further increased, the dilute salt

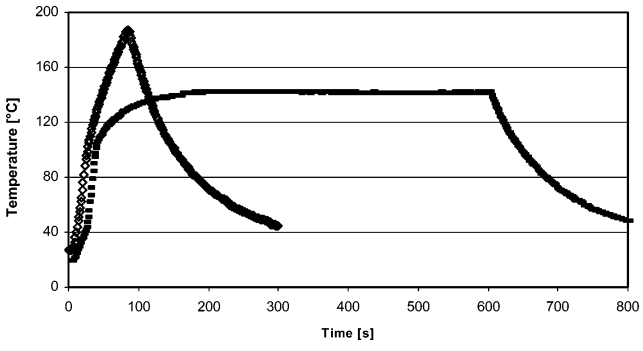


Figure 1. Microwave heating profiles for pure water (—) and 0.03 M sodium chloride solution (◇) at constant 150 W power: single-mode microwave irradiation, 5 mL sample volume, fiber-optic temperature measurement, sealed 10 mL quartz reaction vessel, magnetic stirring. Also shown is the rapid cooling by compressed air. For more details, refer to ref 38. Reproduced with permission from ref 38. Copyright 2005 Wiley-VCH.

solution can easily be heated to 190 °C. The concentration of 0.03 M of sodium chloride proves to be optimal: while at lower salt concentrations heating is less efficient, there is little change in the heating profile on going from 0.03 M to, for example, a 0.04 or 0.05 M concentration.[40] Similar heating curves can be obtained with other additives such as tetrabutylammonium bromide.[40] For most applications in high-temperature water chemistry it can be assumed that the comparatively low salt concentrations (0.03 M, 0.18 w/w %) would not significantly influence the reactivity of the water medium but would mainly improve microwave absorbance by ionic conduction.[41]

It should be stressed that the above-mentioned problems associated with the use of water as solvent in microwave-assisted reactions are only experienced under high dilution conditions and/or in the high-temperature region (>200 °C) where the loss tangent (tan δ) of water is reduced to such an extent that efficient absorbance of microwave energy is not possible. In most cases either the substrates or some of the reagents/catalysts dissolved in the aqueous reaction mixture are strongly polar and therefore microwave absorbing, raising the overall dielectric properties of the reaction medium to a level that allows sufficient heating by microwaves. Furthermore, in most microwave reactors the reaction vessels are made out of not entirely microwave transparent glass, and therefore, heating of the reaction mixture often occurs in part by conventional conduction and convection phenomena.[40]

Microwave-assisted chemistry using water as solvent can be carried out in all of the commercially available microwave reactors either under open-vessel (reflux) or sealed-vessel conditions. In general, two different philosophies with respect to microwave reactor design are currently emerging: multimode and monomode (also referred to as single-mode) reactors.[37] In the so-called multimode instruments the microwaves that enter the cavity are being reflected by the walls and the load over the typically large cavity. In the much smaller monomode cavities, only one mode is present and the electromagnetic irradiation is directed through an accurately designed rectangular or circular wave guide onto the reaction vessel mounted in a fixed distance from the radiation source, creating a standing wave. 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 by compressed air after completion of the irradiation period. The dedicated single-mode instruments available today can process volumes ranging from 0.2 to ca. 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. For both single- and multimode cavities continuous flow reactors are nowadays available that allow the preparation of kilograms of materials using microwave technology.[16]

Because of the existing pressure limit of ca. 20 bar for most of today's commercially available microwave reactors for synthesis, microwave-assisted water chemistry has generally been restricted to reaction temperatures below 200 °C. In fact, there are very few publications today where dedicated microwave reactors with higher pressure limits (80−100 bar) have been employed for the generation of near-critical water at 300 °C. In the present review, these examples are treated separately at the end of the literature survey.

5. Transition-Metal-Catalyzed Reactions

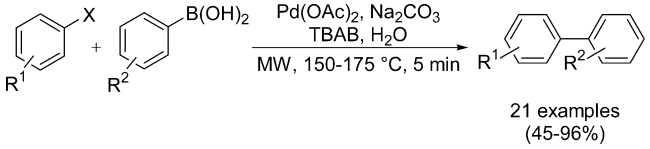
Homogeneous and heterogeneous transition-metal-catalyzed carbon−carbon and carbon−heteroatom bond-forming reactions represent one of the most important reaction types performed in MAOS. These reactions, which are known to need hours or days for completion, often in an inert atmosphere, can be conducted very efficiently in a rapid manner under microwave heating. In recent years, use of water as a solvent for microwave-assisted metal-catalyzed transformations in the high-temperature water region (<200 °C) gained considerable interest because of the many advantages over organic solvents (see above).

5.1. Suzuki Reactions

The Suzuki reaction (palladium-catalyzed cross-coupling of aryl halides with boronic acids) is one of the most often used C−C cross-coupling reactions and displays a convenient method for the synthesis of biaryls.[23,42]

Leadbeater and Marko reported in 2002 on the ligand-free palladium-catalyzed Suzuki couplings of aryl halides with boronic acids using water as solvent.[43] Palladium acetate loadings as low as 0.4 mol % proved to be sufficient, and with addition of 1 equiv of the phase-transfer catalyst tetrabutylammonium bromide (TBAB), aryl bromides and iodides could be coupled successfully in high yields and short reaction times (see Scheme 1 and Table 3). The role of

Scheme 1



TBAB is to facilitate the solubility of the organic substrates and activate the boronic acid by formation of an $[ArB(OH)_3]^-[R_4N]^+$ species. For reactions with aryl chlorides the temperature had to be raised to 175 °C, although lower yields were obtained.

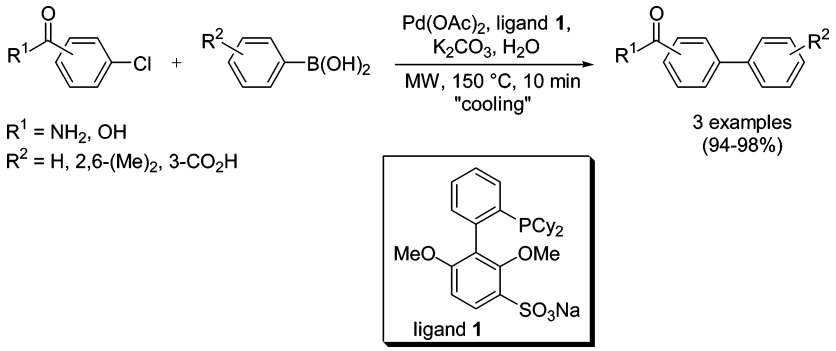
Applying the same protocol a 10-fold scale-up was possible under microwave-assisted open-vessel reflux conditions for 10 min at 110 °C, achieving nearly identical yields to the closed-vessel runs.[44] In addition, comparison studies to conventionally heated Suzuki couplings were investigated by performing the reactions in a preheated oil bath at 150 °C, which resulted in similar yields to the microwave experiments.[44]

The same authors also reported on the so-called "transition-metal free Suzuki-type coupling" where, without addition of any palladium source, high yields for aryl bromides and iodides were achieved under similar reactions conditions as

Table 3. Suzuki Coupling of 4-Bromotoluene with Phenylboronic Acid

entry	$Pd(OAc)_2$ (mol %)	TBAB	temp (°C)	time (min)	yield (%)
1	5		200	5	32
2	0.4		150	5	40
3	0.4	1 equiv	150	5	96

Scheme 2



described above (1 equiv of TBAB, 3.8 equiv of Na_2CO_3, 150 °C, 5 min).[45,46] Aryl chlorides did not show any reactivity, and the reaction is limited to electron-poor and -neutral boronic acids. A re-examination of these results indicated that ultralow levels of palladium (50 ppb) found in the sodium carbonate base were responsible for successful Suzuki couplings.[47] A revised protocol for the reaction of aryl halides with aryl and vinylic boronic acids was presented using 1−2.5 ppm of Pd catalyst, 1 equiv of TBAB, and 3.8 equiv of Na_2CO_3 at 150 °C for 5 min. This ultralow palladium Suzuki coupling method was also used for scaling the reaction up from 1 to 10 mmol in a stop-flow manner.[48] For the reaction of 4-bromoacetophenone and phenyl boronic acid (X = Br, R^1 = 4-COMe, R^2 = H; see Scheme 1) a 1:1 mixture of water/ethanol instead of TBAB, only 1 equiv of Na_2CO_3, and 250 ppb of palladium had to be used to give a 95% product yield over 10 cycles (10 mmol each). For a further scale-up, the authors changed to an open-vessel microwave protocol again using low levels of Pd catalyst.[49] The TBAB/water combination was changed to a 1:1 water/ethanol medium due to troublesome purification issues and economy reasons when going from small scale to larger scale. Different substituted aryl bromides could be coupled with phenylboronic acid in good to excellent yields under reflux microwave conditions (20 min at 80−83 °C) with a Pd loading of 1−5 ppm. The reaction can be scaled-up from 5 mmol employing a single-mode instrument in a 100 mL round-bottom flask up to 1 mol using a 3 L reaction vessel in a multimode reactor.

Because of solubility issues in a flow-through or stop-flow setup, Leadbeater and Chanthavong developed a protocol where the mineral base, which is typically used in the Suzuki coupling, is replaced by a liquid amine base.[50] Best results were obtained applying 1 equiv of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as base and 0.4 mol % of $Pd(OAc)_2$ in a 1:1 mixture of water/ethanol at 150 °C for 10 min on a 1 mmol scale. Employing this protocol, a set of 14 aryl halides (X = Cl, Br, I; see Scheme 1) were coupled with phenylboronic acid in 8−99% yield. The stop-flow scale-up to 20 mmol under the same reaction conditions provided the biaryls (R^1 = OMe, COMe, X = Br; see Scheme 1) in similar yields as in the small-scale experiment. A related protocol was employed by Leadbeater and Smith for the real-time monitoring of Suzuki couplings using in situ Raman spectroscopy in a modified single-mode microwave instrument.[51] For this technique, the reaction mixture needs to be homogeneous, which was achieved by applying a 1:2 water/EtOH mixture as the solvent system and DBU as base. They found that according to the Raman spectra all the Suzuki couplings which were performed reached complete conversion already after 135 s.

Aryl chlorides, which did not show as good coupling reactivity compared to the aryl bromide counterparts,[43,44] were coupled with phenylboronic acid in excellent to moderate yields using a similar protocol as described above (see Scheme 1).[52] Here, 1 mol % of heterogeneous palladium on carbon (Pd/C) served as catalysts at 120 °C for 10 min. Simultaneous cooling[13] in combination with microwave heating proved to give superior yields for substrates with electron-neutral or -donating groups due to diminished decomposition of the aryl chlorides.[52]

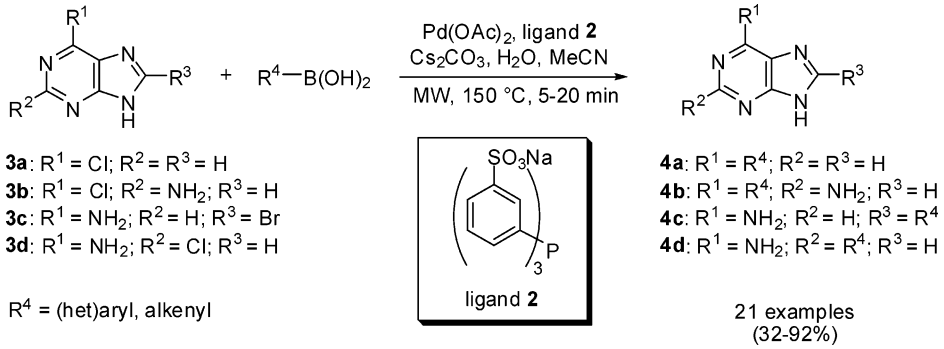
Recently, Buchwald and Anderson presented a new ligand for the coupling of aryl chlorides and otherwise difficult substrate combinations (steric hindrance, heterocyclic aryl halides) under aqueous conditions.[53] With the sulfonated ligand **1**, excellent yields of biaryls could be obtained from aryl chlorides as well as from thiophenebromide substrates (Scheme 2). Going from room temperature to 150 °C under microwave heating, the catalyst loading could be reduced from 2 to 0.1 mol % without any deterioration in yield. Remarkably, the reaction time could be reduced from 2 to 8 h to only 10 min.

Hocek and co-workers applied similar reaction conditions as described in Scheme 2 for the Suzuki coupling of free halopurine bases with 4-boronophenylalanine.[54] They reported that the water-soluble phosphine ligand **2** in combination with 5 mol % of $Pd(OAc)_2$ in a 2:1 water/acetonitrile mixture worked best under microwave irradiation at 150° (see Scheme 3). In a subsequent study the authors described the scope and limitations of this protocol toward the coupling of the 9-unsubstituted 2-, 6-, and 8-halopurine bases **3a**−**d** with diverse aryl- and alkenylboronic acids to obtain the corresponding arylpurines **4a**−**d** in a single step (Scheme 3).[55] The highest yields are achieved with electron-rich arylboronic acids, whereas hetarylboronic acids showed lower reactivity. Importantly, the purification issue is simplified under these aqueous conditions since in most cases the product crystallized directly upon cooling and could be further purified by recrystallization.

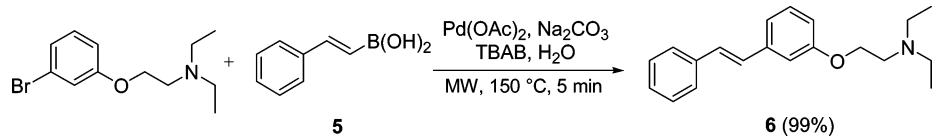
The Suzuki reaction conditions depicted in Scheme 1 proved also to be optimal for the synthesis of the styrene-based nicotinic acetylcholine receptor (nAChR) antagonist **6** starting from vinylboronic acid **5** (Scheme 4).[56] However, for the one-pot, two-step amination/Suzuki sequence which was chosen for a library production of diversely amine-substituted nAChR antagonists (see also Scheme 31), Pd/C was used as catalyst and a MeOH/water mixture as solvent.

Coupling of the electron-rich 4-bromo-2-methoxyphenol **7** with various substituted boronic acids was performed by Freundlich, again utilizing 1 mol % of the heterogeneous Pd/C catalyst in combination with 2 equiv of 1 M aqueous

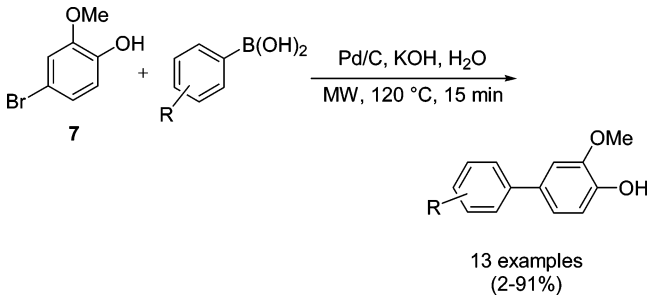
Scheme 3



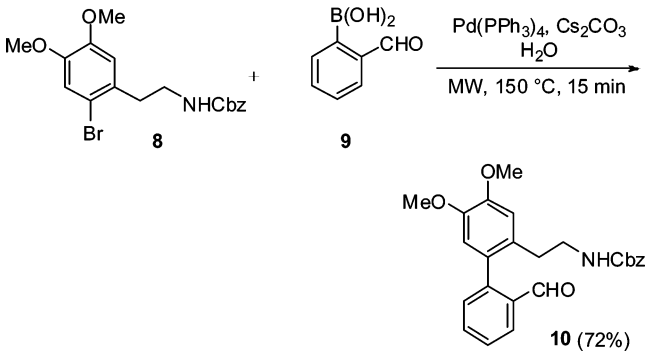
Scheme 4



Scheme 5



Scheme 6

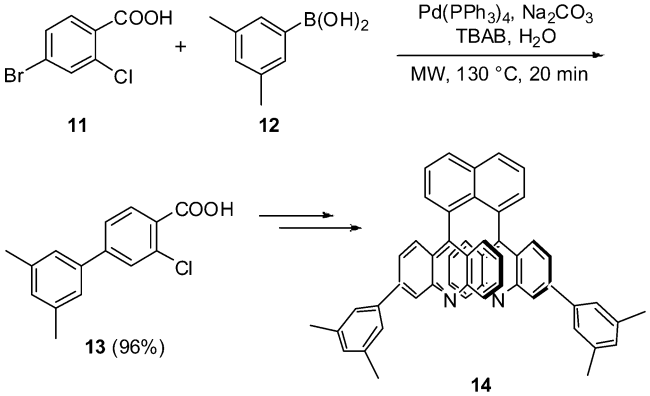


KOH at 120 °C for 15 min (Scheme 5).[57] To avoid degradation of boronic acids with hydrolyzable functional groups (R = CN, CO_2Me, NHAc) only 1 equiv of KOH has to be used for reaching good yields. Importantly, complete chemoselectivity was achieved for the bromide versus the chloride when 2-bromo-4-chlorophenol was utilized as the arylphenol substrate. 4-Chloro-2-methoxyphenol as starting material did not show any reactivity.

Synthesis of a small library of highly electron-rich phenethylamines via the Suzuki coupling in order to develop novel biaryl receptor ligands for binding studies was investigated by Van der Eycken.[58] Reactions of phenethylamine **8** with various boronic acids were conducted with tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) as catalyst and $NaHCO_3$ as base in DMF/H_2O 1:1 as solvent mixture. Since very good yields (79−94%) could be achieved with this method, the authors wanted to apply this protocol on boronic acids bearing electron-withdrawing groups at the sterically unfavored ortho position in order to produce apogalanthamine analogues. A change in base to Cs_2CO_3 was necessary, and the coupling of bromide **8** with (2-formylphenyl)boronic acid **9** gave 84% of biaryl product **10**. Only a slightly decreased yield (72%) was obtained utilizing pure water as solvent (Scheme 6). Conventional heating experiments could not be performed successfully, resulting in significantly reduced product yields.

Wolf and co-workers applied slightly modified standard Suzuki coupling conditions (see Scheme 1) for the first step in the synthesis of 1,8-diacridyl-naphthalene **14** (Scheme 7), a highly congested enantioselective fluorosensor that operates in two different detection modes (fluorescence lifetime and intensity).[59] One mole percent of $Pd(PPh_3)_4$ was utilized as

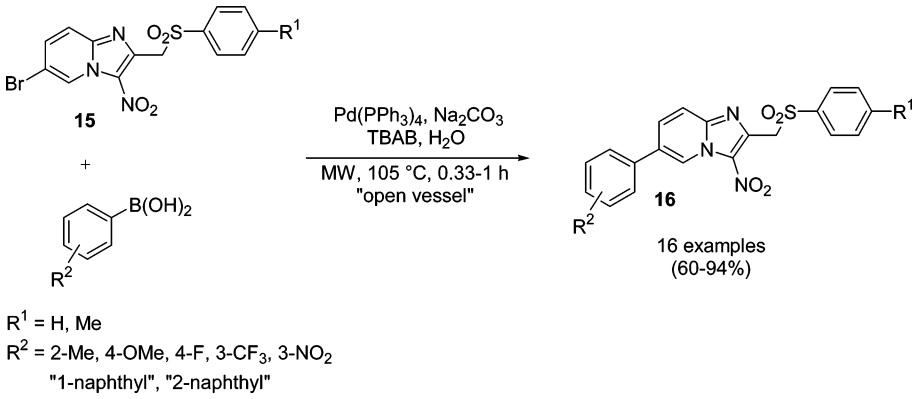
Scheme 7



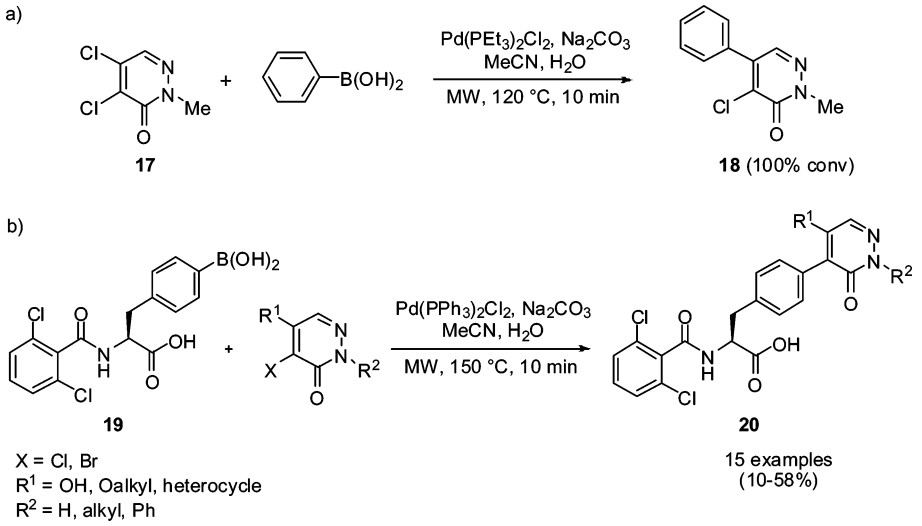
catalyst for the bromo-selective coupling of 4-bromo-2-chlorobenzoic acid **11** and 3,5-dimethylboronic acid **12** at 130 °C for 20 min to give biaryl **13** (Scheme 7), and in four additional steps product **14** was obtained in 57% overall yield, the last step being a Stille cross-coupling of 9-acridylstannane with 1,8-dibromonaphthalene under conventional conditions.

The same catalyst system was employed by the group of Vanelle for the coupling of 2-arylsulfonylmethyl-6-bromo-3-nitro-imidazo[1,2-*a*]pyridines **15** with a range of arylboronic acids (Scheme 8).[60] However, in this open-vessel protocol 10 mol % of $Pd(PPh_3)_4$ catalyst and 5 equiv of Na_2CO_3 were necessary to obtain the coupled products **16** in good to excellent yields. The microwave approach, with the aid of TBAB, prevented aggregation which was otherwise

Scheme 8



Scheme 9



observed under classical heating using identical conditions but without the use of TBAB as phase-transfer reagent, and thus a simplification of the workup was achieved. Furthermore, reaction times could be reduced up to 60 times, producing the 6-arylimidazo[1,2-*a*]pyridines **16** in higher or similar yields as compared to conventional oil-bath heating.

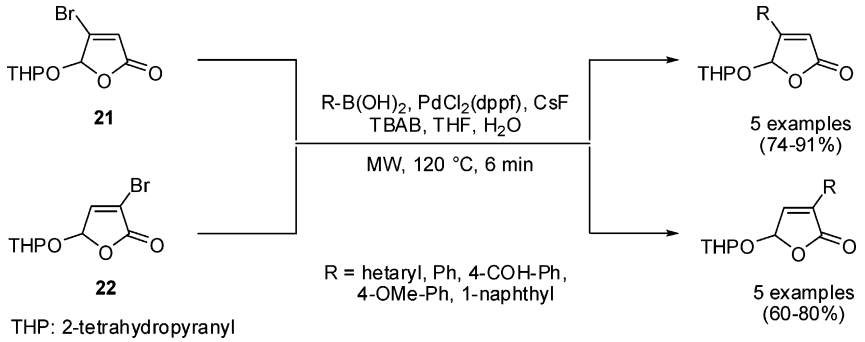
For the direct synthesis of selectively 5-aryl-substituted chloropyridazinones starting from the 4,5-dichloro pyridazinone **17** via Suzuki reaction, which under standard conditions solely furnished 4,5-diarylpyridazinones bearing the same aryl moiety,[61] He and Gong performed a catalyst screening with a variety of commercially available palladium catalysts.[62] Typical screening conditions were 2 equiv of **17** in combination with 5 mol % of Pd catalyst and 2 equiv of Na_2CO_3 in a 1:1 mixture of acetonitrile/water at 120 °C for 10 min (Scheme 9a). The palladium catalyst $Pd(PEt_3)_2Cl_2$ showed excellent selectivity for product **18** due to the less hindered PEt_3 ligand groups (7.7/1.4 = 5-aryl/4-aryl), whereas ligand-free palladium catalysts (Pd/C, $Pd(OAc)_2$) proved to be poorer in reactivity. However, the best selectivity (300-fold greater for 5-aryl over 4-aryl) was reached at room temperature in 5 h using a 1:1 mixture of DMF/water.

The same authors applied a similar protocol for the Suzuki coupling of 2,6-dichlorobenzoyl-protected 4-borono-L-phenylalanine **19** with diversely substituted 4-halopyridazinones to obtain a series of pyridazinone-functionalized phenylalanine analogues **20** which proved to be potent α_4 integrin receptor antagonists (Scheme 9b).[63] The optimized reaction conditions (5 mol % $Pd(PPh_3)_2Cl_2$, 2.5 equiv Na_2CO_3, acetonitrile/water 1:1, 150 °C, 10 min) were adopted from an earlier publication where unprotected 4-aryl phenylalanines were prepared via the Suzuki reaction.[64] Besides the amide-linked phenylalanine derivatives **20**, compounds with a urea and carbamate linkage to the phenylalanine nitrogen were prepared as well.

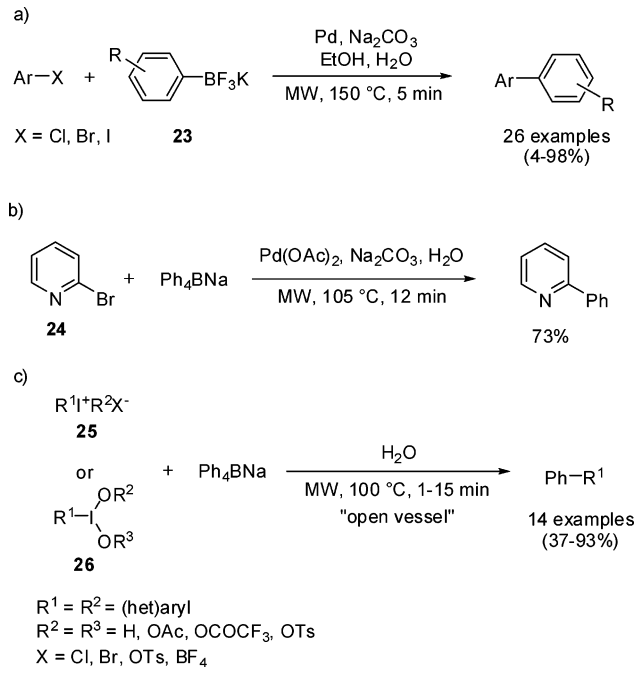
In the course of the regioselective synthesis of 3-bromo- and 4-bromo-butenolides, respectively, the group of Riccio performed Suzuki couplings to further enhance the diversity of these scaffolds which led to two regioisomeric series of natural product-like derivatives.[65] The best conditions for the reaction of *O*-protected bromo-butenolides **21** and **22**, respectively, with different boronic acids were found to employ 0.03 mol % of $PdCl_2$(dppf), 4 equiv of CsF as base, and 1 equiv of TBAB at 120 °C for 6 min in a water/THF 1:1 mixture (Scheme 10). Importantly, CsF had to be used as base since the butenolide moiety is not stable under basic conditions when common bases like carbonates or phosphates are applied.

Typically, Suzuki reactions are performed with boronic acids or esters, but more recently several groups have utilized alternative and more stable boron reagents for the cross-coupling. One of these newly applied boron reagents are potassium organotrifluoroborates **23** (Scheme 11a), which have the advantage of simplified purification compared to boronic acids.[66] Applying their ultralow palladium protocol (2.5 ppm),[47] the group of Leadbeater successfully prepared a small library of biaryls in moderate to excellent yields (Scheme 11a).[66] The solvent mixture EtOH/water 1:1 pro-

Scheme 10



Scheme 11



vided somewhat better yields than the TBAB/water combination. As expected, aryl chlorides could not be coupled effectively; alkyltrifluoroborates did not produce any results either.

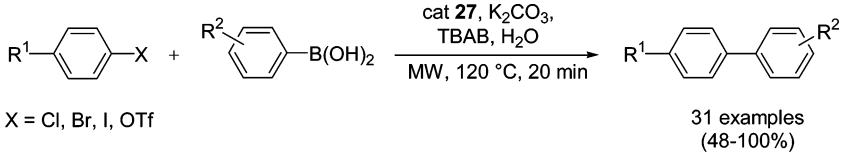
Another substitute for boronic acids in Suzuki couplings is sodium tetraphenylborate (Ph_4BNa) (Scheme 11b,c). Otherwise problematic nitrogen-containing arylhalides, like 2-bromopyridine **24**,[66] were converted to the corresponding biaryls in very good yields (73%) using $Pd(OAc)_2$ as catalyst, Na_2CO_3 as base, and water as solvent at 105 °C for 10−12 min (Scheme 11b).[67] It has to be noted that here a higher catalyst loading (1 mol %) compared to the ultralow Pd protocol was used and that the reaction was conducted under an argon atmosphere. Comparison experiments in a preheated oil bath (105 °C, 12 min) gave 30% lower yields.

A further example for the use of sodium tetraphenylborate as boronic acid replacement is the catalyst- and base-free Suzuki-type coupling with hypervalent iodonium salts **25** or iodanes **26**, respectively, used instead of aryl halides (Scheme 11c).[68] Both symmetrical and unsymmetrical biaryls could be synthesized under mild open-vessel reflux conditions. Iodanes reacted more rapidly than iodonium salts (1−2 vs 3−4 min), the yields of the latter being affected by the anions, e.g., bromides reacted in higher yields than tetrafluoroborates.

Apart from examples involving Suzuki couplings with standard soluble palladium catalysts, there are a growing number of publications reporting the use of immobilized, recyclable palladium catalysts under aqueous conditions. Kirschning and co-workers developed a heterogeneous Pd(II) precatalyst (**27**) that is insoluble in water and organic solvents.[69] Excellent yields were achieved for the coupling of aryl halides and triflates with diversely substituted boronic acids utilizing 1 mol % of catalyst **27**, 2 equiv of K_2CO_3 as base, and 1 equiv of TBAB at 120 °C for 20 min (Scheme 12). Loaded into an IRORI Kan, the precatalyst could be recycled and reused up to 14 times without any significant loss of activity.

In a recent publication the same authors reported on the immobilization of an oxime-based palladacycle on polyvinylpyridine resin.[70] The resulting air, moisture, and thermally stable Pd precatalyst **28** (see Chart 1) showed moderate to excellent activities for the coupling of aryl chlorides (R^1 = NO_2, COMe; Scheme 12) with various boronic acids at 130 °C in only 3 min (0.25 mmol Pd/g polymer). Thermal heating at 150 °C for 10 min gave slightly lower yields. Due to the low degree of leaching, reuse and efficient regeneration was possible, and thus, catalyst **28** was applied under continuous-flow Suzuki conditions, albeit without the assistance of microwaves.

Scheme 12



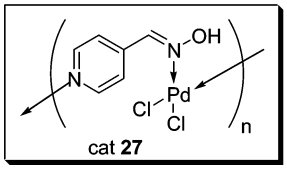
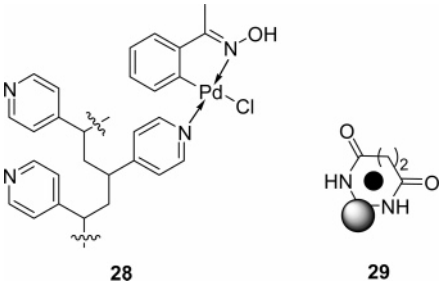


Chart 1



28 29

Preparation of cross-linked resin-captured palladium **29** (Chart 1) and its application to the Suzuki reaction was reported by the Bradley group.[71] The principle of this "nanopalladium particles" is that $Pd(OAc)_2$ can enter swollen aminomethylated TentaGel resin which is then reduced to Pd(0). To fix the captured palladium cross-linking of the resin with succinyl chloride is necessary. Using microwave heating, reaction times could be reduced from 4 to 16 h to 10 min at slightly higher temperatures (120 vs 80 °C). Virtually no leaching of Pd into the solution was detected, making this catalyst amenable for syntheses where Pd contaminants could cause serious problems, e.g., in the microwave-assisted Suzuki reaction of sulfophthalein dyes.[71]

Not only can the catalyst be immobilized on a polymeric support, Schotten and co-workers performed the Suzuki coupling also with aryl halides bound on soluble poly(ethyleneglycol-600) (PEG) **30** (Scheme 13) which serves both as polymeric support and phase-transfer catalyst.[72] Compared to conventional heating, reactions performed in a domestic microwave oven could be accelerated from 2 h to 1−4 min. Additionally, ester cleavage from the polymer which occurred to an extent of up to 45% under thermal heating could be suppressed by microwave heating. Aryl halides, triflates, and nonaflates were coupled with various boronic acids successfully to PEG-bound biaryls **31** applying 10 mol % of soluble $Pd(OAc)_2$ as catalyst, 2.5 equiv of K_2CO_3 as base, and water as solvent in a domestic microwave oven (Scheme 13).

5.2. Heck Reactions

Palladium-catalyzed vinylic substitution, also known as the Heck reaction, is generally performed with aryl halides and alkenes. In recent years, development of "ligand-free" palladium-catalyzed protocols has gained much interest. Arvela and Leadbeater reported on Heck couplings of aryl halides with styrene and acrylic acid, respectively, applying their aqueous ultralow palladium protocol developed for Suzuki couplings (Scheme 14).[47,73] Palladium concentrations down to 0.5−1 ppm are sufficient for the coupling at 170 °C for 10−20 min, although a limited substrate scope was observed. Interestingly, better yields were obtained without stirring of the reaction since it is believed that the reaction takes place at the aqueous/organic interface, and with stirring the aryl halide would be exposed to the basic aqueous medium, resulting in faster decomposition.[73] A 10-fold scale up performing the reaction in a stop-flow microwave approach was possible with only a slight change in time (20 vs 10 min) and solvent. Here, a mixture of water/DMF 7:1 proved to be better with respect to pumping the reaction mixture through the lines.[48]

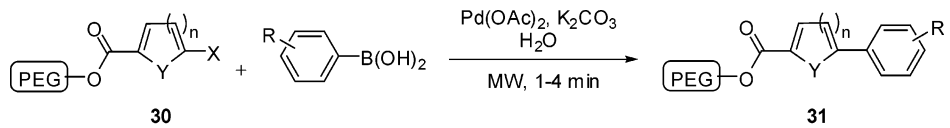
Reactions of aryl iodides with alkenes using slightly different reaction conditions in a domestic microwave oven were conducted by Wang and co-workers.[74] Five mole percent of $Pd(PPh_3)_2Cl_2$ as catalyst, K_2CO_3 as base, and an argon atmosphere had to be employed using microwave irradiation for 10 min in the high-yielding (86−93%) synthesis of aryl styrenes. Microwave heating provided the products 18−42 times faster than under conventional reflux conditions but with comparable yields.

In addition, more complex catalyst/ligand systems for Heck reactions in water were investigated by several groups. Botella and Nájera carried out controlled mono- and β,β-diarylation of terminal alkenes catalyzed by the oxime-derived palladacycle **32** as precatalyst (Scheme 15).[75] When the reaction was conducted at 120 °C with (dicyclohexyl)-methylamine (Cy_2NMe) as base, monoarylated product **33** was obtained in 87% yield in only 10 min with a very high TOF (42 000) (Scheme 15). Standard $Pd(OAc)_2$ could also be applied as catalyst, giving a similar yield. This was not the case for the diarylation process with 1 mol % of $Pd(OAc)_2$ where no conversion was detected. Here catalyst **32** is the better choice; however, only a low yield of 31% of product **34** was isolated. A somewhat better yield (66%) could be obtained under conventional reflux conditions after 13 h.

The same group reported on the preparation of di(2-pyridyl)methylamine−palladium dichloride complex covalently anchored to a poly(styrene-alt-maleic anhydride) resin (**35**, Chart 2) which was used in Heck as well as Suzuki and Sonogashira couplings.[76] Polymeric complex **35** was compared to the monomeric **36**, and for the Heck reaction of 4-bromoacetophenone with styrene a catalyst loading of 0.1 mol %, TBAB as phase-transfer catalyst and diisopropylamine as base were used at 100 °C for 10 min. Catalyst **36** gave slightly higher yields (96% vs 80%), which was also the case under conventional heating at the same temperature, but here a higher catalyst loading (0.5 mol %) and also prolonged reaction times (4.5−6 h) were necessary. However, catalyst **35** could not be recycled after microwave heating due to leaching of palladium and degradation of the polymer.

Another palladacycle which is covalently anchored via the oxime moiety to a glass/polymer composite matrix shaped as Raschig rings was investigated by the group of Kirschning

Scheme 13

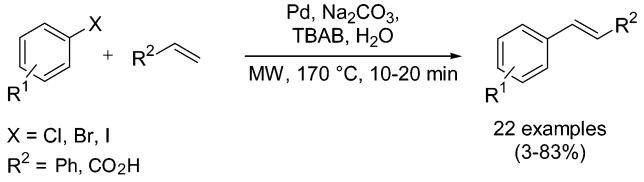


30 31

n = 1, Y = S
n = 2, Y = CH
X = Br, I, OTf, ONf
R = H, 4-CHO, 3-OMe, 3,5-$(CF_3)_2$
1-naphthyl

18 examples
(73 to >95% purity)

Scheme 14



Scheme 15

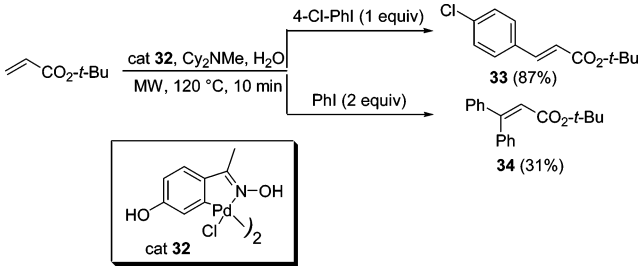
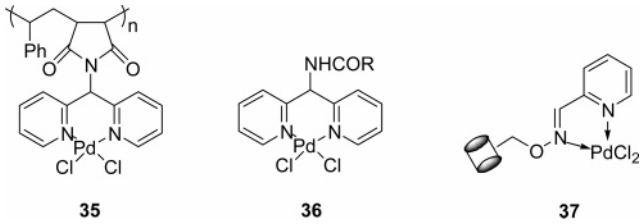


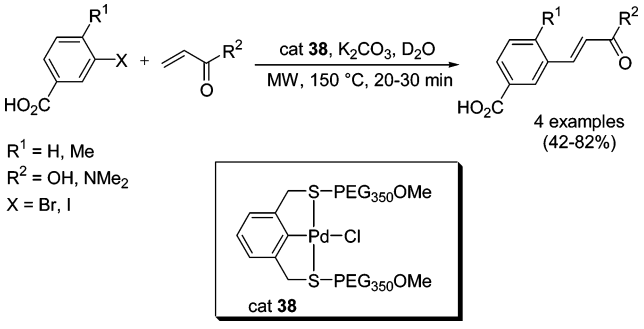
Chart 2



for Mizoroki−Heck and Sonogashira cross-couplings (see Scheme 18).[77] This heterogeneous Pd(II) precatalyst **37** (see Chart 2) was evaluated using water as solvent under both conventional and microwave heating for the coupling of aryl and heteroaryl bromides and iodides, respectively, with *tert*-butylacrylate and styrene. Optimum reaction conditions employ *i*-$PrNH_2$ as base, TBAB, and 0.7 mol % of **37** at 150 °C for 5−20 min under microwave heating, while 5−20 h at 100 °C are necessary under thermal heating, to obtain the coupling products in moderate to excellent yields. If styrene is used as coupling partner NaOH turned out to be superior as base to *i*-$PrNH_2$ for the thermal approach, whereas under microwave heating no difference in yields was observed. Notably, the stability and thus recyclability of Pd complex **37** is diminished under microwave irradiation. Already after the first cycle, Pd complex **37** lost its activity, whereas under conventional heating deactivation was experienced after three runs.

The water-soluble oligo(ethyleneglycol)-bound SCS palladacycle catalyst **38** was developed by Bergbreiter and Furyk for the Heck reaction of water-soluble aryl iodides and bromides with cinnamic acid derivatives (Scheme 16).[78]

Scheme 16

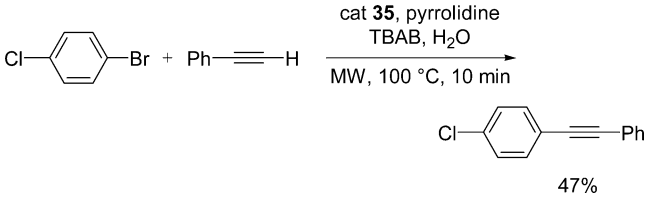


Reaction times could be reduced from several hours to 20−30 min applying microwave heating. Recycling of the catalyst could be accomplished efficiently by performing the reaction in a thermomorphic solvent mixture (1:2 v/v mixture of 10% aqueous DMA/heptane), again under microwave heating. For a new cycle only fresh reagents in heptane had to be added to the aqueous catalyst solution.

5.3. Sonogashira Reactions

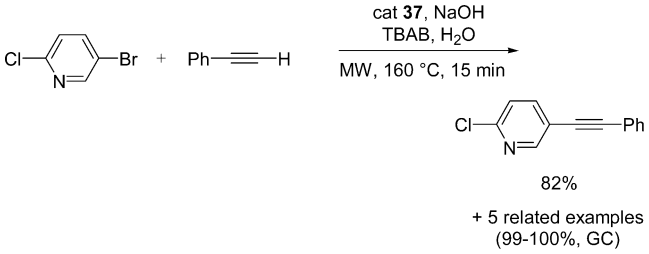
The Sonogashira reaction (palladium and copper cocatalyzed coupling of terminal alkynes with aryl and vinyl halides) is a general method for the preparation of unsymmetrical alkynes. In recent years, investigations toward the design of new catalyst systems or protocols for copper-free reactions have been made. The group of Nájera has performed aqueous copper-free Sonogashira couplings of aryl bromides and iodides with phenylacetylene, applying both polymeric complex **35** and the monomeric **36** as catalyst (see Chart 2), pyrrolidine as base, and TBAB as additive.[76] Under conventional heating better yields in shorter reaction times could be achieved for the polymeric complex; additionally, dimerization of the alkyne was decreased. Applying microwave heating for the reaction of 4-chloro-bromobenzene with phenylacetylene, lower yields were obtained for 0.1 mol % of catalyst **35** than for the monomeric **36** (47 vs 66%) (Scheme 17).

Scheme 17



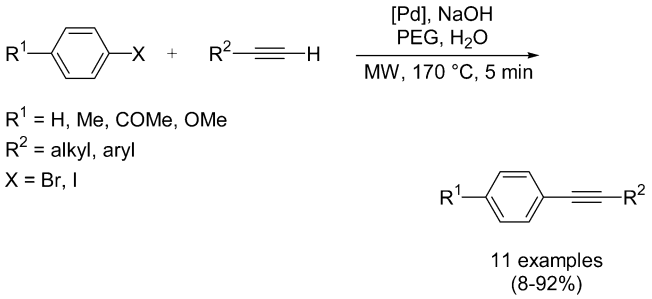
Kirschning and co-workers also succeeded in aqueous copper- and phosphine-free Sonogashira couplings by employing the heterogeneous Pd precatalyst **37** which was already employed in a Heck protocol by the same authors (see Chart 2).[77] Again, the coupling reaction of aryl and heteroaryl bromides and iodides, respectively, with phenylacetylene was studied under both conventional and microwave heating conditions (Scheme 18). The corresponding

Scheme 18



(het)aryl acetylene products were obtained with full conversion according to GC regardless of which heating method was applied; however, under microwave heating the reaction times could be reduced from several hours at 100 °C under thermal heating to only 5−20 min. Compared to the Heck reaction the recyclability of the catalyst **37** could be improved in the Sonogashira coupling; here, the Pd catalyst could be reused for at least five cycles.

Scheme 19



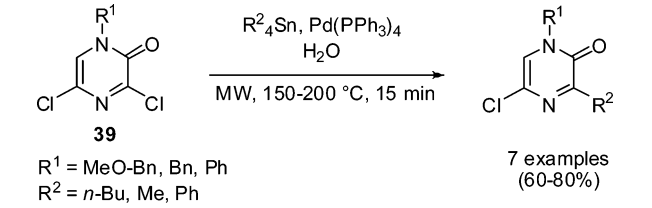
Leadbeater and co-workers were able to successfully perform Sonogashira couplings under "transition-metal-free" conditions,[79] presumably involving ultralow Pd concentrations as contaminations.[47] Key to success is NaOH as base, PEG as phase-transfer catalyst, water as solvent, and microwave heating at 170 °C for 5 min (Scheme 19). Not surprisingly, only substrates which proved to be stable under these highly basic conditions were coupled successfully, e.g., 4-bromobenzaldehyde was destroyed during the reaction. Aryl iodides gave better yields than the corresponding bromides, as did phenylacetylene compared to alkyl acetylenes.

The group of Van der Eycken also reported on Sonogashira couplings without the use of an added transition-metal catalyst.[80] Best conditions proved to be 4 equiv of Na_2CO_3 as base, 1 equiv of TBAB as phase-transfer catalyst, and water as solvent at 175 °C for 10−25 min. No conversion was detected for aryl chlorides under these conditions, allowing complete regioselectivity for 4-bromo-1-chlorobenzene. Under conventional heating conditions, no conversion or lower product yields were obtained.

5.4. Stille Reactions

Very few examples are known of microwave-assisted Stille reactions involving organotin reagents as coupling partners.[12−14] In the course of scaffold decorations of the 2(1*H*)-pyrazinone core **39**, the Stille reaction at the C-3 position was performed by Van der Eycken and co-workers (Scheme 20).[81] For

Scheme 20



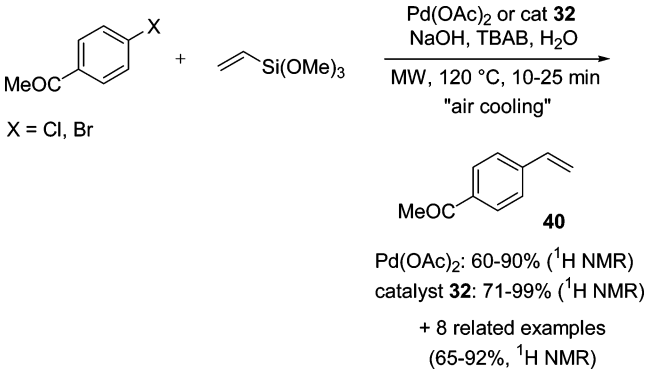
tetraphenyltin a higher temperature (200 °C) had to be applied in order to achieve full conversions. A great acceleration compared to conventional heating in refluxing toluene could be reached (3 days vs 15 min), albeit the yields being somewhat lower for the aqueous microwave synthesis.

5.5. Hiyama Reactions

The Hiyama reaction (palladium-catalyzed cross-coupling of organosilicon compounds with organic halides) has become a good alternative to other coupling reactions which employ different organometallic reagents from an environmental point of view since the organosilicon compounds are attractive because of their stability, ease of handling, and/or low toxicity.[82] Several types of organosilicon reagents have been applied for this carbon−carbon bond-forming reaction such as alkyl-, fluoro-, chloro-, hydroxy-, and alkoxysilanes.[82] In general, Hiyama couplings are promoted by the fluoride anion, usually obtained from tetrabutylammonium fluoride (TBAF), but recently it was found that inorganic bases like KOH, NaOH, and K_2CO_3 are also able to promote the reaction in water as solvent under fluoride-free conditions.[83]

Nájera and Alacid successfully performed the cross-coupling of vinylalkoxysilanes, which are less active than arylsilanes and normally require promotion by fluoride, and aryl bromides or chlorides promoted by aqueous NaOH under fluoride-free conditions.[84] In their study vinyltrimethoxysilane was coupled with aryl or vinyl halides, respectively, under thermal or microwave heating using either $Pd(OAc)_2$ or oxime-derived palladacycle **32** (see Scheme 15) as catalyst, the latter giving somewhat higher yields for the corresponding styrenes **40** (Scheme 21). By employing

Scheme 21



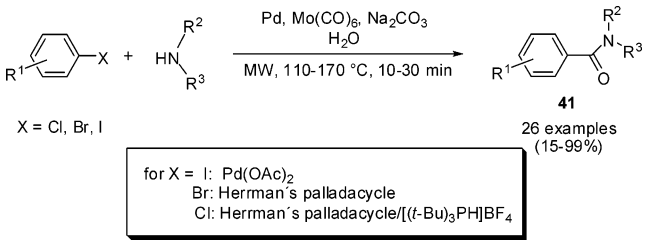
TBAB as additive lower Pd loadings, in the range of 0.5−1 mol % for aryl bromides and 2 mol % for arylchlorides, were possible. The reaction times could be reduced from about 1 day under thermal heating in a pressure tube under the same conditions to 10−25 min by applying microwave irradiation. Importantly, reaction of activated aryl chlorides with vinyltrimethoxysilane to the corresponding styrenes only proceeded under microwave conditions. Since formation of Pd black was observed, the authors assumed that the active catalytic species could be Pd nanoparticles.

5.6. Carbonylation Reactions

For the palladium(0)-catalyzed carbonylations of aryl halides to give aromatic acid derivatives (e.g., acids, amides, esters) the group of Larhed developed a rapid microwave-assisted procedure where solid $Mo(CO)_6$ is used as carbon monoxide source.[85] Very recently the authors additionally showed that aminocarbonylations can also be conducted in water as solvent, the amine being a better nucleophile than water.[86] Aryl iodides, bromides, and even the otherwise unreactive chlorides could be reacted with diverse primary and secondary amines to the aryl amide products **41** in moderate to excellent yields (Scheme 22). The competing hydroxycarbonylation could be inhibited by fine tuning of the reaction parameters; in particular, the stoichiometry of aryl halide to amine was crucial for the successful reaction as well as the proper catalyst. With this general protocol, aryl iodides could be reacted at 110 °C whereas the bromides and chlorides needed the higher temperature of 170 °C and sometimes longer reaction times.

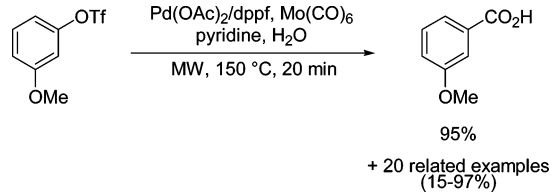
Aqueous hydroxycarbonylations of aryl and vinyl triflates were reported by Silvani and co-workers.[87] A concentration of 0.1 equiv of the catalyst/ligand system $Pd(OAc)_2$/dppf

Scheme 22



(1,1′-bis(diphenylphosphino)ferrocene), pyridine as base, and $Mo(CO)_6$ as CO source proved to be the best conditions (Scheme 23). By heating to 150 °C for 20 min, moderate to

Scheme 23



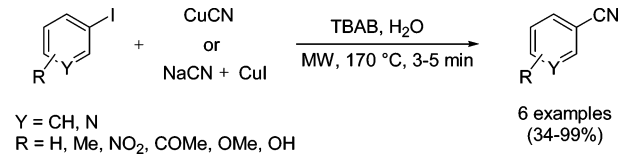
excellent yields for aryl carboxylic acids were achieved. Complete chemoselectivity was obtained for halogenated aryl triflates, affording only the halogenated aryl carboxylic acids.

Recently, Leadbeater and Kormos developed a method for hydroxycarbonylations in water employing gaseous CO in prepressurized vessels using a dedicated microwave autoclave.[88,89] In optimization studies it was demonstrated that a loading of 14 bar with CO, 1 mol % of $Pd(OAc)_2$, and 3.7 equiv of Na_2CO_3 at 165 °C for 20 min gave the highest yield. Reducing the catalyst loading to 0.01 mol %, a 14% reduced product yield was obtained. A range of aryl halides was screened using both 1 and 0.01 mol % Pd concentrations with the result that generally higher yields were obtained with the higher catalyst loading. Disappointingly, only aryl iodides could be converted to the corresponding benzoic acids with aryl bromides remaining completely unreactive.

5.7. Cyanation Reactions

Preparation of aryl nitriles from aryl iodides using CuCN was disclosed by Leadbeater and co-workers (Scheme 24).[90]

Scheme 24

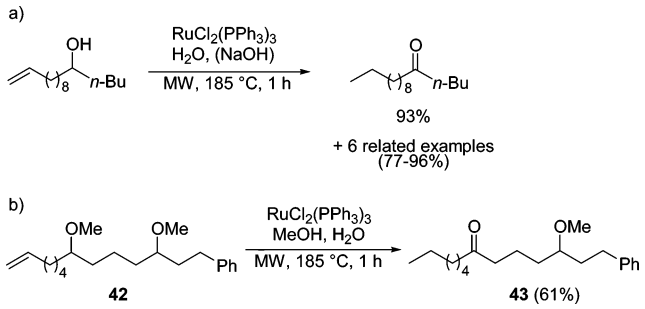


Key to the success of this reaction is the addition of TBAB as phase-transfer agent and a high concentration of cyanide, resulting from a 1:2 ratio of aryl halide/CuCN. Conventional heating under identical conditions resulted in no product; also, activated aryl bromides did not show any conversion. The reaction can also be performed when less expensive NaCN in combination with CuI is employed, forming CuCN in situ.

6. Other Transition-Metal-Mediated Reactions

The efficient ruthenium-catalyzed isomerization of alkenols to alkanones through migration of the C−C double bond

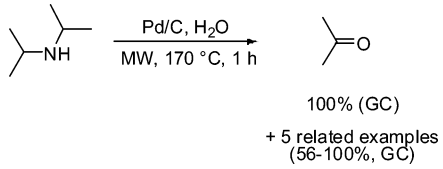
Scheme 25



was developed by the group of Matsubara (Scheme 25).[91] Tris(triphenylphosphine)ruthenium(II) dichloride ($RuCl_2(PPh_3)_3$) proved to be the most active catalyst. Due to HCl formation by hydrolysis of the catalyst, a 0.1 M NaOH solution has to be employed as solvent for acid-sensitive substrates (Scheme 25a). Addition of 10 mol % of MeOH was essential for reaction of protected alcohols. Dimethoxy alkene **42** could be selectively transformed to the methoxyketone **43** via isomerization (Scheme 25b).

The Pd/C-catalyzed synthesis of ketones from amines via a retro-reductive amination pathway using water as an oxygen source was reported by Miyazawa and co-workers (Scheme 26).[92] The product outcome was strongly dependent

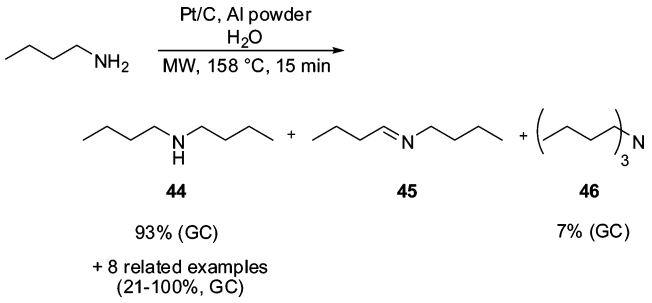
Scheme 26



on the number of hydrogen atoms on the α-carbon of the amine; only amines possessing one hydrogen (mono- or di-*sec*-alkylamines) were converted to the corresponding ketones; those with two hydrogen atoms (e.g., *n*-butylamine) afforded the corresponding imines and secondary alkylamines. The reactions were conducted at constant microwave power which resulted in a maximum temperature of 170 °C. Conventional heating or microwave heating under reflux conditions were less efficient regarding conversion; nonetheless, only the desired ketone was formed.

Because of their findings described above, the same authors further developed this method for transformation of primary amines to secondary amines.[93] They discovered that the catalyst Pt/C worked best, giving the secondary amine **44** as the main product along with imine **45** and tertiary amine **46** (Scheme 27). Addition of aluminum powder to

Scheme 27

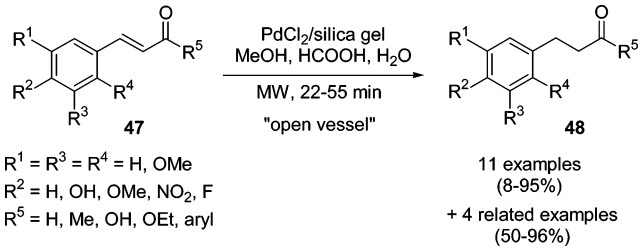


the reaction mixture could prevent formation of **45** since in combination with water additional H_2 for the hydrogenation

of imine **45** to amine **44** is produced. Moreover, the reaction time could be reduced from 1 h to 15 min. Again, the reaction is performed at constant microwave power, reaching a maximum temperature of 158 °C. Moderate to excellent yields of secondary amines were achieved, tertiary amines being the main side products.

The group of Sinha disclosed a chemoselective hydrogenation of α,β-unsaturated carbonyl compounds **47** via a catalytic transfer hydrogenation (CTH) approach in a domestic microwave oven under open-vessel conditions to the corresponding saturated carbonyl derivatives **48** (Scheme 28).[94] The best yields were obtained under heterogeneous

Scheme 28



conditions employing silica-supported $PdCl_2$ as catalyst and a 1:2:3 mixture of MeOH/HCOOH/H_2O as hydrogen source. Use of water plays an important role since it causes the rapid release of hydrogen gas from HCOOH; thus, the reaction proceeds faster and higher yields can be achieved. Interestingly, under conventional heating both the saturated carbonyl compound and its corresponding alcohol were received under the same CTH conditions. Because of the aqueous medium product recovery was facilitated and only required washing steps with the solvent. Additionally, the silica-supported Pd catalyst can be reused at least five times with negligible loss in activity.

Rhodium-catalyzed hydrophosphinylations of propargyl alcohols and ethynyl steroids were investigated by Stockland and co-workers.[95] Whereas reactions involving simple propargyl alcohols generated mixtures of addition and elimination products, addition of P(O)−H bonds to ethynyl steroids (e.g., ethisterone, see Scheme 29) cleanly furnished the addition products **49** or **50**, respectively. Noteworthy, the reactions in aqueous media employing ethynyl steroids showed a very high tolerance to oxygen and could be carried out under an atmosphere of air without removal of oxygen.

7. N-, O-, S-Functionalizations

7.1. N-Acylations

In the transformation of fused succinic anhydrides **51** with hydrazines to the fused *N*-aminosuccinimide derivatives of bicyclo[2.2.2]oct-7-enes **52**, microwave heating in aqueous media proved to be very efficient (Scheme 30).[96] Compared to conventional heating the reaction times could be reduced from several hours to 13−90 min, less hydrazine was necessary (2.2−2.4 vs 10 equiv), and most importantly, cleaner conversions were achieved, giving the products in high yields (80−94%).

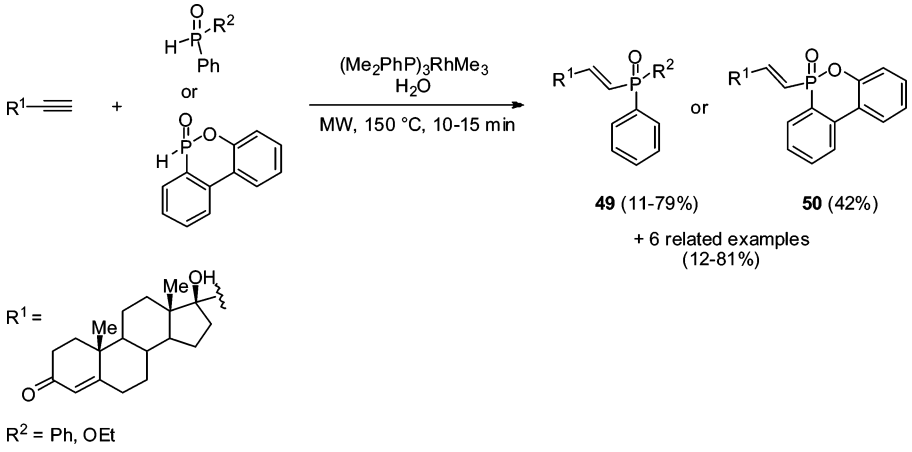
7.2. N-Alkylations

For the synthesis of styrene-based nicotinic acetylcholine receptor (nAChR) antagonists, alkylation product **53** (Scheme 31) was needed as aryl halide starting material for the subsequent Suzuki reaction (see Scheme 4).[56] The otherwise sluggish alkylation reaction under conventional heating could be improved and accelerated with microwave irradiation when protic polar solvents were used. A 99% yield of **53** could be achieved with water as solvent at 160 °C; however, when a MeOH/H_2O mixture or pure MeOH is applied the same result was obtained.

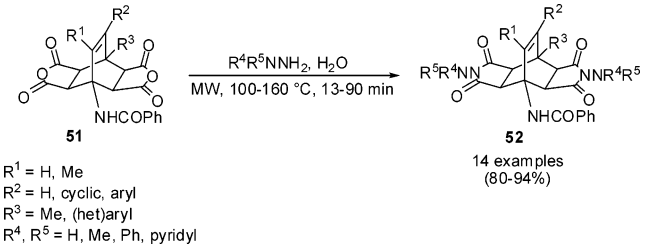
Varma and Ju reported on the synthesis of tertiary amines via *N*-alkylation of primary and secondary amines (aromatic, cyclic, and noncyclic) with alkyl halides (Scheme 32).[97] By applying microwave heating (open vessel, 45−100 °C), not only could the reaction time be reduced from 12 h to 20−30 min but also formation of side products, mainly secondary amines, could be suppressed. Water as solvent, compared to solventless conditions, MeCN and PEG300, proved to be the best choice in regard to product yield and environmental friendliness.

The same authors developed a simple protocol for the synthesis of nitrogen-containing heterocycles from primary amines and hydrazines, respectively, and alkyl dihalides, avoiding otherwise necessary multistep reactions or use of transition-metal catalysts.[98] Again, with microwave irradiation, reaction times could be reduced to 20 min, yields improved, and side reactions eliminated. Double alkylation of primary amines with alkyl dihalides or ditosylates at 120 °C provided azacycloalkanes like pyrrolidines ($n = 4$) or azepanes ($n = 6$) (Scheme 33a), whereas 2,3-dihydro-1*H*-isoindoles could be obtained by reaction of primary amines with α,α-bishalo-*o*-xylenes (10 examples, 61−92%). 4,5-

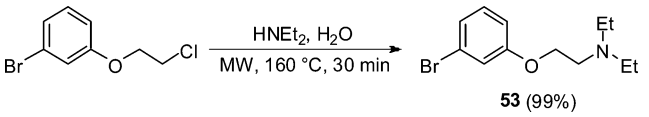
Scheme 29



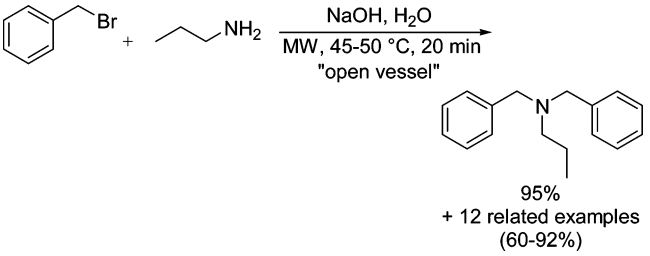
Scheme 30



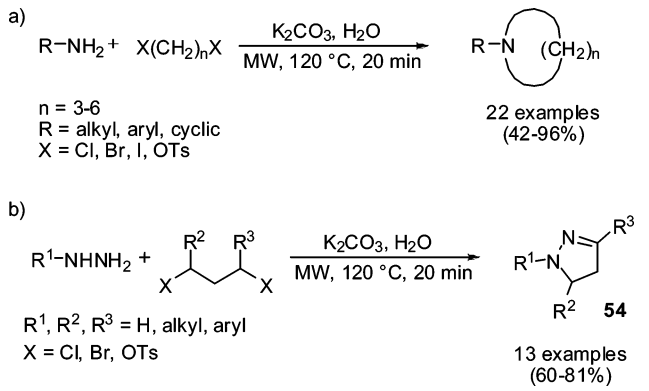
Scheme 31



Scheme 32



Scheme 33

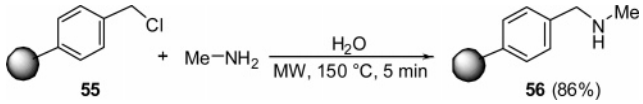


Dihydropyrazoles **54**, pyrazolidines, and 1,2-dihydrophthalazines were obtained via double alkylation of hydrazine derivatives under the same conditions as described above (Scheme 33b). In view of larger scale experiments, this method offers the advantage of simple purification since a phase separation of the product from the aqueous media occurs after the reaction and only a filtration or decantation is required.

By applying the same protocol developed by Varma and Ju for the synthesis of azacycloalkanes and isoindoles (see Scheme 33), Barnard and co-workers performed scale-up experiments starting from 20 mmol and going up to 1 mol under open-vessel conditions.[99] The actual temperatures ranged from 100 to 115 °C, and the reactions needed an overall reaction time of 30 min (ca. 10 min to reach reflux temperature plus 20 min hold time). The yields of the open-vessel experiments were comparable to those under closed-vessel conditions at a 1 mmol scale and also compared well with yields going from a single-mode (20 mmol) to a multimode (0.2−1 mol) instrument. It has to be noted that for all experiments the same reaction conditions were applied. As already mentioned above, using water as solvent the purification step is facilitated, and since no byproducts occurred the resulting *N*-heterocycles could be isolated by simple extraction or filtration.

In one of the rare solid-phase syntheses in aqueous media, Westman and Lundin described the amination of Merrifield resin (**55**, chloromethylated polystyrene resin) with aqueous methylamine as the initial reaction step in the synthesis of heterocycles (Scheme 34).[100] The solid-supported benzylmethylamine product **56** was obtained in 86% via microwave heating at 150 °C for 5 min and is further reacted to polymer-bound aminopropenones which are released from the resin by cyclative cleavage with the appropriate dinucleophile to give heterocycles in pure form.

Scheme 34

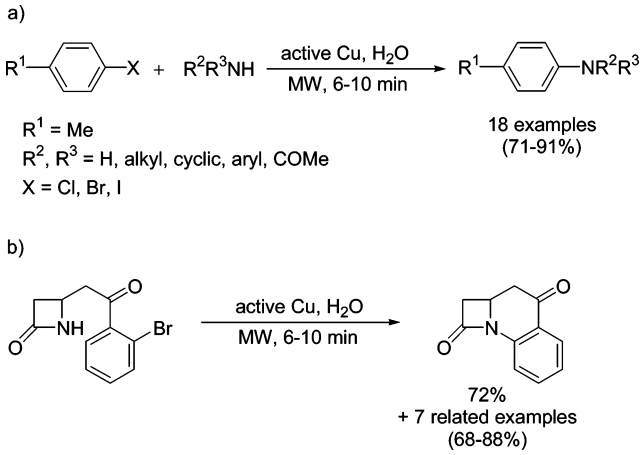


A scale-up (ca. 15 fold) of this solid-phase methylamination was performed by Kappe and co-workers in a dedicated large-scale microwave instrument.[89] Under the same reaction conditions as in the small-scale experiment (150 °C, 5 min), a similar yield could be achieved, demonstrating the successful direct scalability from small to large scale.

7.3. *N*-Arylations

Yadav and co-workers disclosed base-free inter- and intramolecular *N*-arylations promoted by active copper.[101] Reactions of aryl halides with amines, amides, imides (Scheme 35a), and β-lactams (Scheme 35b) proceeded under very mild conditions. Key to the successful intramolecular *N*-arylations of β-lactams is the absence of a base since decomposition of the starting material is otherwise observed. Interestingly, a protocol with irradiation for 2 min at 85−90 °C and subsequent mixing for 2 min outside the microwave instrument was applied (this irradiation−mixing cycle was repeated until completion of the reaction was detected; times given in Scheme 35 correspond to total irradiation times). Similar or lower yields, especially in the case of β-lactam derivatives, were achieved by performing the reaction under solvent-free microwave conditions.

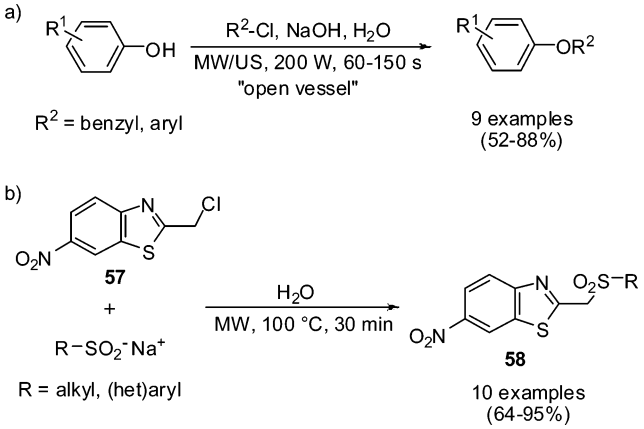
Scheme 35



7.4. *O*- and *S*-Functionalizations

A combined microwave and ultrasound (US) protocol for the Williamson ether synthesis from phenols and aryl or alkyl

Scheme 36



chlorides, respectively, was disclosed by Song and Peng (Scheme 36a).[102] This rather uncommon combination, which is performed in a custom-built instrument, proved to give higher yields in much shorter reaction times compared to only microwave heating or sonication.[103] With an ultrasound power of 50 W and a microwave power of 200 W, diphenyl and benzyl phenylethers were obtained in moderate to good yields very rapidly in 60−150 s. A second "green" aspect in this heterogeneous synthesis is the absence of an otherwise required phase-transfer catalyst.

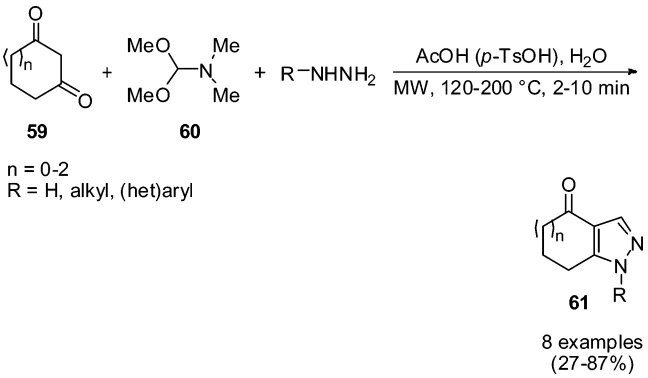
The group of Vanelle reported formation of new sulfonylmethylbenzothiazole derivatives **58** which show significant cytotoxic activity.[104] The synthesis proceeds via aqueous *S*-alkylation of sodium salts of diverse substituted sulfinic acids with 2-chloromethyl-6-nitrobenzothiazole **57** (Scheme 36b). All experiments were also conducted under conventional heating at the same temperature (100 °C), affording products **58** in similar or lower yields in 24 h. Hence, the authors assumed that specific microwave effects due to a more polar transition state are responsible for the higher yields achieved by microwave heating.

8. Heterocycle Synthesis

8.1. Five-Membered N-Heterocycles

Molteni and co-workers described the three-component, aqueous one-pot synthesis of fused pyrazoles (**61**) by reacting cyclic 1,3-diketones (**59**) with *N*,*N*-dimethylformamide dimethyl acetal **60** (DMFDMA) and a suitable bidentate nucleophile like a hydrazine derivative (Scheme 37).[105] The reaction

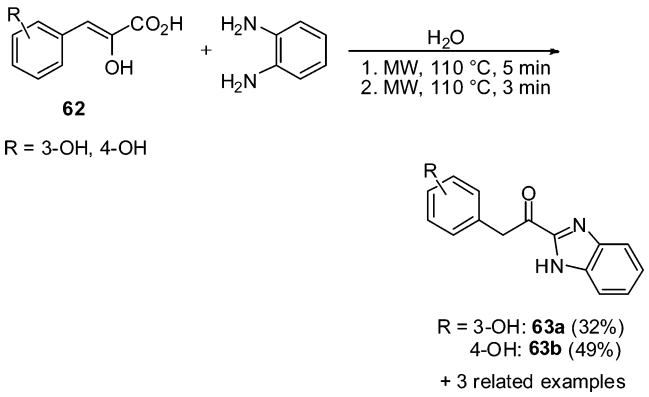
Scheme 37



proceeds via initial formation of an enaminoketone in situ followed by a tandem addition−elimination/cyclodehydration step. An amount of 2.6 equiv of acetic acid is necessary to ensure a clean conversion at 200 °C within 2 min. For 1,3-cyclopentanedione ($n = 0$), *p*-toluenesulfonic acid has to be used instead of AcOH at lower temperatures but with longer irradiation time (120 °C, 10 min) to afford the corresponding pyrazole in 27% yield. Pyrimidines and isoxazoles could be synthesized as well applying the same protocol employing amidines and hydroxylamine as nucleophiles.

The synthesis of benzimidazoles **63a,b** as potential HIV-1 integrase inhibitors by condensation of α-hydroxycinnamic acids **62** with 1,2-phenylenediamine in water was performed by the group of Monforte (Scheme 38).[106] Two irradiation

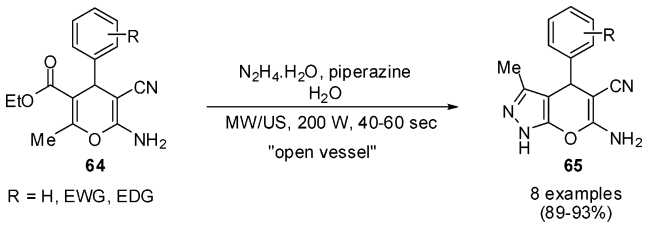
Scheme 38



cycles of 5 and 3 min at 110 °C proved to be the method of choice to generate the desired heterocyclic products in moderate yields. Compared to conventional heating at 120 °C the reaction time was significantly reduced under microwave conditions (2 h vs 8 min). Benzimidazole **63a** was found to prevent the cytophatic effect of HIV-1 III_B with an EC_{50} of 27 μM but did not inhibit the HIV-1 integrase enzymatic activity.

Investigations toward the combined microwave and ultrasound irradiation (CMUI) in the synthesis of 4*H*-pyrano-[2,3-*c*]pyrazoles **65** as a "proof-of-concept" reaction in aqueous media were presented by Song and co-workers (Scheme 39).[107,103] In a model reaction of pyran **64** (R = H;

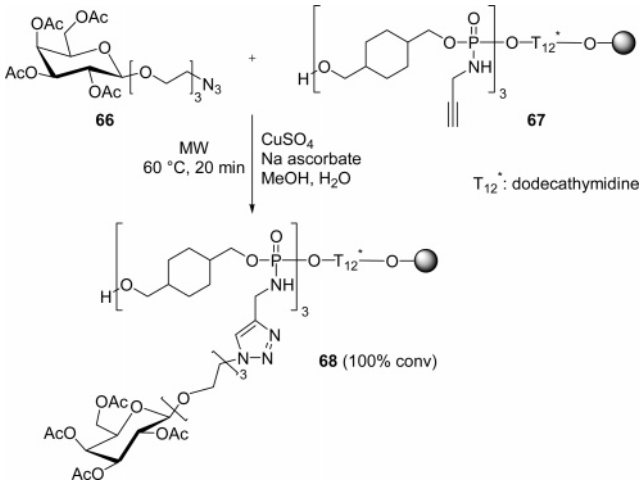
Scheme 39



see Scheme 39) with hydrazine monohydrate and a catalytic amount of piperazine it turned out that the highest conversion in the shortest reaction time could be obtained by the CMUI approach (100%, 1 min) in comparison to microwave irradiation only (48%, 20 min) or the combination of oil-bath heating and ultrasound irradiation (99%, 20 min). An explanation for this rate acceleration by applying ultrasound irradiation could be that a passivation coating on the surface on the substrate particles, which occurs due to poor water solubility of the products, is removed by sonication. This method proved to be very general for the synthesis of a set of pyranopyrazoles in a very fast manner (40−60 s) and excellent yields (Scheme 39).

For the multiple labeling of oligonucleotides with carbohydrates Morvan and co-workers developed a "click" chemistry approach on solid support.[108] Azide-functionalized galactoside **66** was reacted with solid-supported alkyne-functionalized oligonucleotide **67** via a 1,3-dipolar cycloaddition with in situ generation of Cu(I) and a 1:1 mixture of MeOH/water as solvent, at 60 °C within 20 min to give the triazole-linked trigalactosylated oligonucleotide **68** in 100% conversion (Scheme 40). Compared to the reaction at 20 °C

Scheme 40

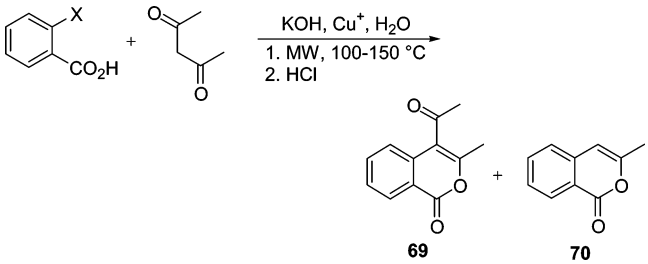


under the same conditions a ~30% higher conversion and 20-times acceleration could be achieved by microwave irradiation. The cycloaddition was performed in solution phase as well; however, here hydrolysis of one phosphoramidate bond occurred which was not observed in the solid-phase synthesis.

8.2. Six-Membered O-Heterocycles

Aromatic substitution by activated methylene compounds (1,3-diketones) with base and stoichiometric amounts of a copper(I) catalyst leads to different isochromenone derivates depending on the temperature, pressure, and nature of the activating methylene groups which was shown by the Bryson group (Scheme 41).[109] Under standard reflux conditions

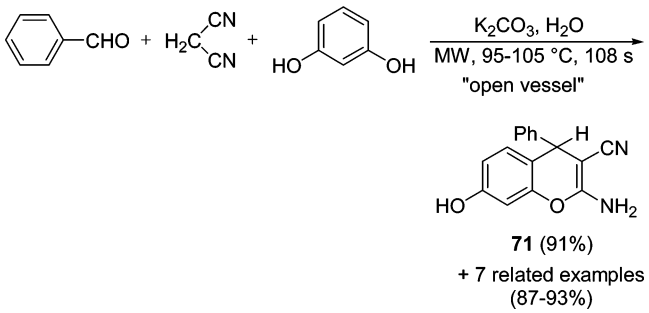
Scheme 41



(NaH, Cu^+) in THF, isochromene **69** is obtained as the main product after acidification, whereas under microwave irradiation (KOH, Cu^+) in water at 100−150 °C (3−14 bar) it is the minor product and deacylated isochromene **70** the main product (55−70%) due to cleavage of the acyl group in the high-temperature water media.

Kidwai and co-workers described the rapid three-component one-pot reaction of an aldehyde, malononitrile, and resorcinol as phenol component to 2-amino-4*H*-chromenes **71** (Scheme 42).[110] By performing the synthesis in a domestic

Scheme 42

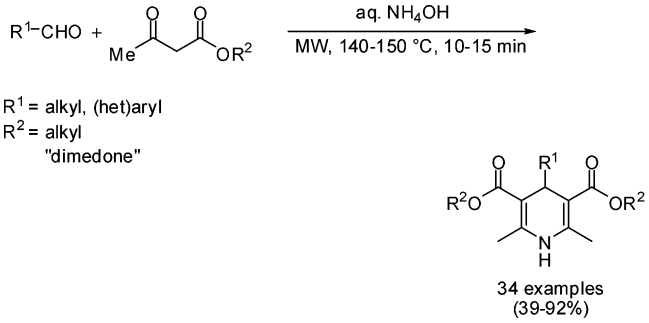


microwave oven under open-vessel conditions at 95−105 °C, otherwise used organic bases like piperidine and solvents could be replaced by a saturated solution of K_2CO_3 in water. Substituted 2-amino-benzo[*e*]chromenes were additionally prepared by applying the same protocol.

8.3. Six-Membered N-Heterocycles

A well-known method for the preparation of heterocycles is the Hantzsch dihydropyridine (DHP) synthesis. Öhberg and Westman presented a fast procedure for this multicomponent, one-pot condensation of an aldehyde, β-ketoester, and aqueous ammonium hydroxide, which was used as both reagent and solvent (Scheme 43).[111] Best yields were

Scheme 43

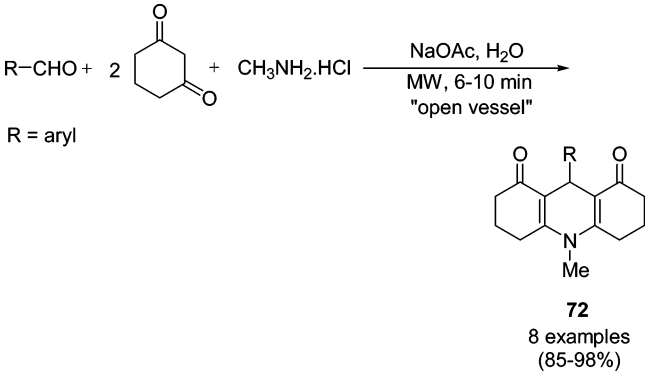


obtained by exposing the reaction mixture to microwave heating at 140−150 °C for 10−15 min. Additionally, a small library of 24 compounds was prepared by applying a fully automated microwave instrument within hours. In a very recent publication, Bagley and Lubinu applied the same conditions reported by Öhberg and Westman for the synthesis of related dihydropyridines.[112] These DHPs were further aromatized in only 1 min at 100 °C, again under microwave irradiation, by oxidation with manganese dioxide to generate the corresponding pyridines in excellent yields (91−99%). In a somewhat modified method, aqueous ammonium acetate instead of ammonium hydroxide and TBAB as phase-transfer catalyst were used by Salehi and Guo to prepare DHPs in a domestic microwave oven under reflux conditions in very good yields (21 examples, 77−92%).[113]

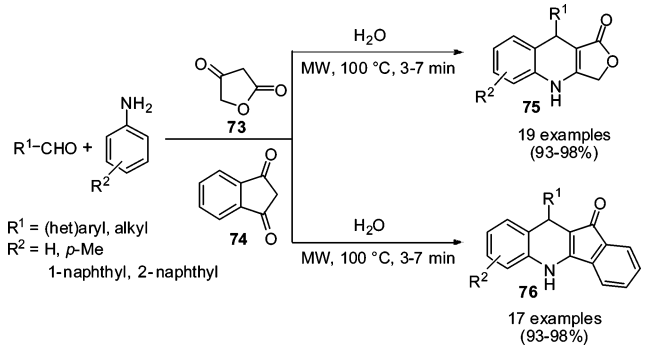
The Hantzsch-related one-pot synthesis of *N*-substituted acridine derivatives **72** by condensation of an aldehyde, 2 equiv of 1,3-cyclohexanedione, and methylamine under open-vessel reflux conditions in a domestic microwave oven was reported by Tu and co-workers (Scheme 44).[114] When 1,3-cyclohexanedione is employed as dicarbonyl substrate, water was used as solvent. On the other hand, the reaction with dimedone only proceeded in glycol with high yields.

Recently, the same authors described the synthesis of 4-aza-podophyllotoxin derivatives **75** and **76** via the three-

Scheme 44



Scheme 45

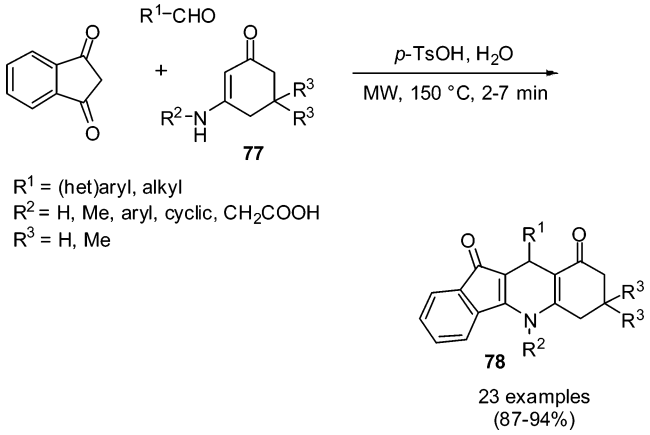


component reaction of an aldehyde, aromatic amine, and tetronic acid (**73**) or 1,3-indanedione (**74**), respectively (Scheme 45).[115] The proposed reaction mechanism includes, first, the condensation of the aldehyde with the amine, subsequent addition of **73** or **74**, respectively, cyclization, and dehydration. After optimization studies they found that a reaction temperature of 100 °C and an initial power of 150 W (with lower power the time to reach the set temperature was too long) gave the best results. Also, the volume of water as solvent turned out to be crucial for the outcome of the reaction, highest yields being achieved using 2 mL of water for a 1 mmol scale. With this general method a set of 4-aza-podophyllotoxin derivatives **75** and **76** could be prepared in very short times and excellent yields.

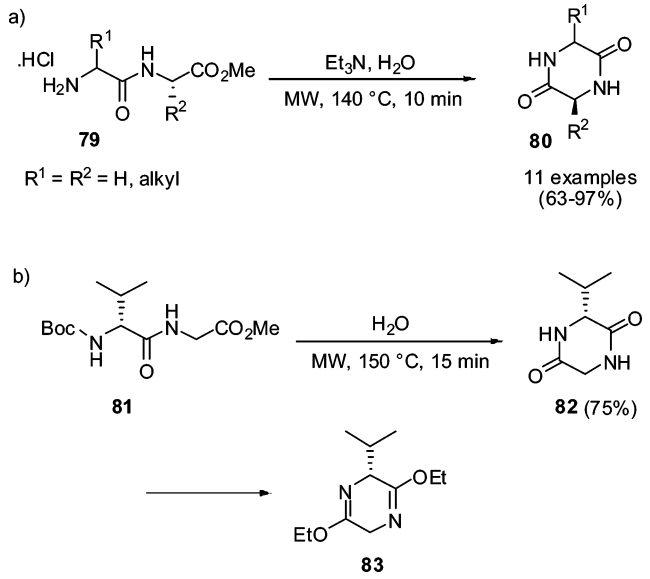
In a subsequent publication the authors presented a similar approach to poly-substitued indeno[1,2-*b*]quinolines **78**, again via a three-component reaction of 1,3-indanedione, (het)-aryl or alkyl aldehydes, and various substituted enaminones (**77**) employing *p*-toluenesulfonic acid (*p*-TsOH) as catalyst (Scheme 46).[116] While aryl aldehydes with electron-withdrawing groups reacted within 2−3 min, electron-donating substituted aldehydes had a decreased reactivity, requiring ca. twice the reaction time. Additionally, some reactions were also performed using conventional heating at the same temperature, providing the products in somewhat lower yields and longer reaction time (2 h). Due to the aqueous conditions the purification was simplified; only neutralization and subsequent filtration of the solid products was necessary.

For development of a general and environmentally benign synthesis of 2,5-diketopiperazines **80** Luthman and co-workers performed several studies to identify optimum reaction conditions.[117] Eleven dipeptide methyl esters as their hydrochloride salts (**79**, see Scheme 47a) served as starting materials which were obtained by removal of the Boc-protecting group with HCl/MeOH. Investigations were

Scheme 46



Scheme 47



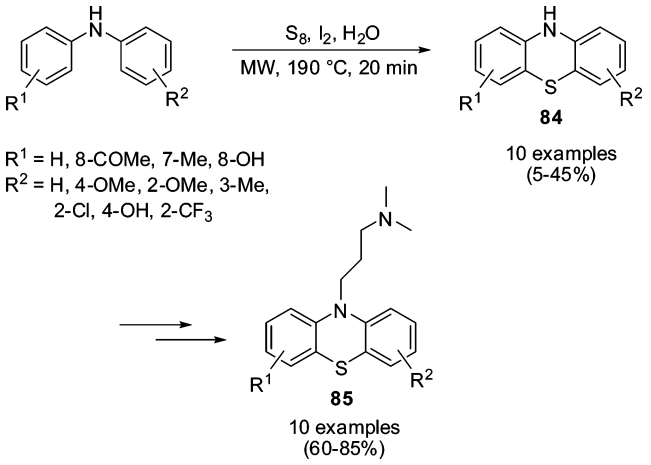
conducted toward the amino acid sequence, solvent, time, and temperature under both conventional and microwave heating. The most efficient and general method was found to employ water as solvent at 140 °C for 10 min under microwave irradiation. Product precipitation occurred in most of the cases during the reaction, so that only a simple workup was necessary.

The key step in the synthesis of the Schöllkopf bis-lactim ether chiral auxiliary **83** is the conversion of dipeptide **81** to the 2,5-diketopiperazine **82** (Scheme 47b).[118] As described above, normally the synthesis proceeds in two steps: removal of the Boc group from **81** followed by cyclization to the piperazine. Recently, the same authors succeeded in a one-step transformation, which was not possible in the synthesis described above (see Scheme 47a), by heating dipeptide **81** in water under microwave conditions to 150 °C for 15 min to obtain **82** in 75% yield.[118] In a 6-fold scale-up experiment, 12 g of **81** could be converted to the piperazine **82** at 200 °C within 15 min in a large-scale microwave instrument in a similar yield.

8.4. Six-Membered N,S-Heterocycles

In order to evaluate the structure−activity relationship for the binding of phenothiazine derivatives to HIV-1 TAR RNA the group of James synthesized a small focused library of

Scheme 48

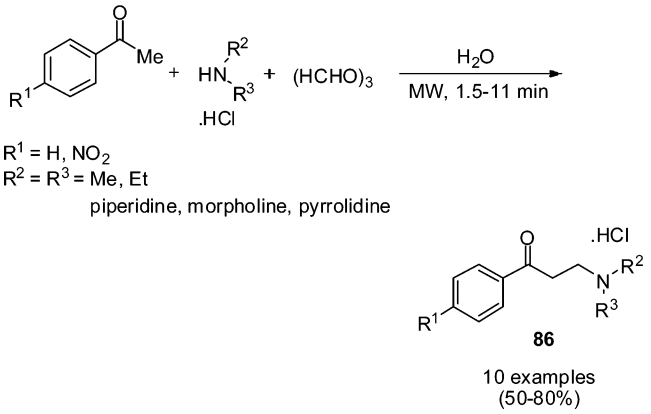


10*H*-phenothiazines **84** with novel substitution patterns around the ring system (Scheme 48).[119] The synthesis proceeded by an iodine-catalyzed reaction of diarylamines with sulfur in doubly distilled water at 190 °C within 20 min in acceptable to moderate yields. Due to the hydrophobicity of the 10*H*-phenothiazine products, they directly precipitated upon cooling and could be isolated by filtration. Further alkylation at the NH and subsequent amination (MW, 100 °C, 40 min) delivered scaffolds **85** which contain an aliphatic amine functionality at the side chain and were screened for binding to HIV-1 TAR RNA.

9. Mannich-Type Multicomponent Reactions

The Mannich reaction is one of the most important transformations leading to β-aminoketones. Although the reaction is powerful, it suffers from some disadvantages, such as the need for drastic conditions, long reaction times, and sometimes low yields of products. The group of Song reported on the Mannich reaction of acetophenones, secondary amines in the form of their hydrochloride salt, and trioxymethylene as formaldehyde source (Scheme 49).[120]

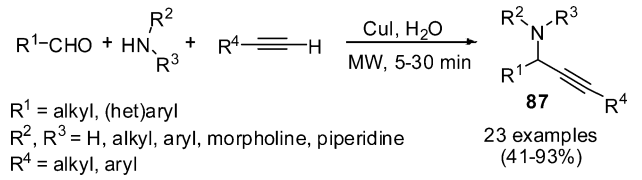
Scheme 49



Applying microwave heating, β-aminoketones **86** were obtained in 1.5−11 min in moderate to good yields. Slightly higher yields in shorter reaction times (20−50 s) could be achieved by performing the reaction under combined microwave and ultrasound conditions.[103]

A different type of Mannich reaction which involves condensation of an aldehyde, a primary or secondary amine, and a terminal alkyne in the presence of Cu(I) iodide, which promotes activation of the C−H bond of the alkyne, was disclosed by Tu (Scheme 50).[121] Propargylamines **87** were obtained in moderate to high yields by irradiation under closed-vessel conditions in a domestic microwave oven with irradiation cycles of 1 min each with subsequent cooling in between. Additionally, an asymmetric synthesis of propargylamines was developed by employing (*S*)-proline methyl ester as chiral amine, affording **87** with high diastereoselectivity (95:5 for $R^1 = R^4 = Ph$; see Scheme 50).

Scheme 50



10. Nucleophilic Substitutions

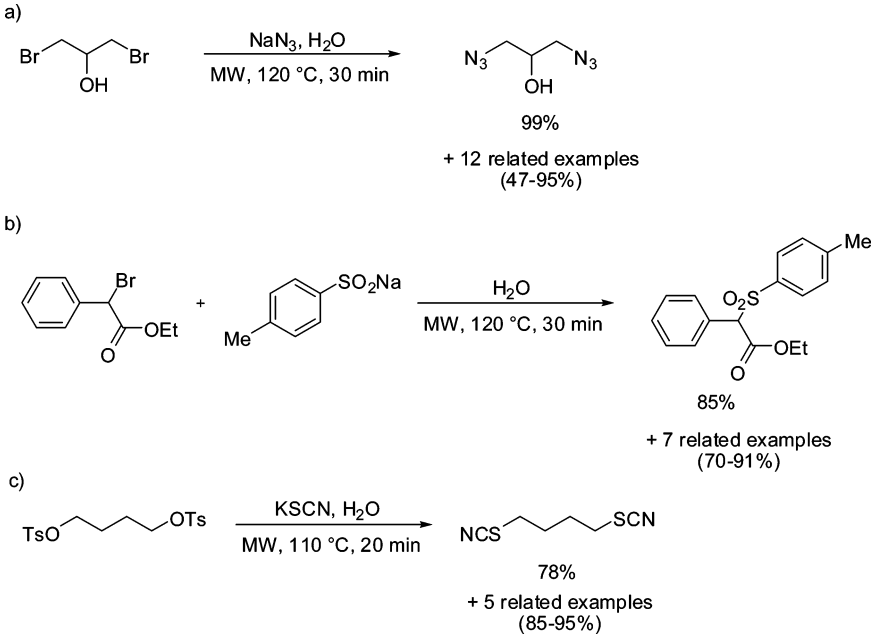
Varma and co-workers developed a rapid and general protocol for the synthesis of a variety of azides, sulfones, and thiocyanates (Scheme 51) which are known to be key intermediates in various organic transformations.[122] Easily accessible alkyl halides or tosylates are reacted with ready available alkali azides, sulfinates, and thiocyanates (Scheme 51a, b, and c) in an aqueous medium without the need for a phase-transfer catalyst. The reactions of halides and tosylates with sodium azide (Scheme 51a) or sodium sulfinates (Scheme 51b), respectively, are conducted at 120 °C for 30 min, whereas the nucleophilic substitutions with potassium thiocyanate (Scheme 51c) required 110 °C and 20 min. By applying these protocols all products are prepared in good to excellent yields, a variety of functional groups is tolerated, and moreover product isolation is simplified.

10.1. Nucleophilic Aromatic Substitutions

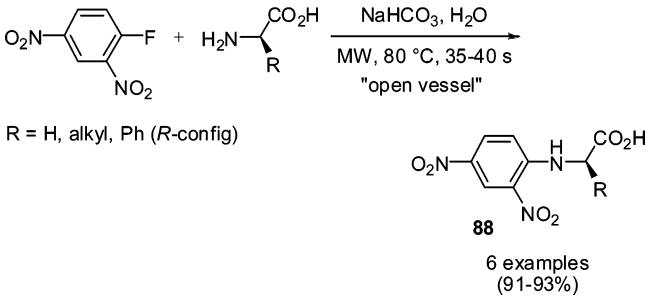
Conducted under conventional heating, nucleophilic aromatic substitutions (S_NAr) are relatively difficult to perform requiring high temperatures and long reaction times. Additionally, the aryl component which is reacted with various nucleophiles like amines or alcohols must bear an electron-withdrawing group. One example is shown by Cherng, where the reactivity of the aryl halide is improved by NO_2 groups in both the ortho and para positions.[123] 2,4-Dinitrofluorobenzene (Sanger's reagent) is reacted with amino acids to afford *N*-aryl-α-amino acid derivatives **88** in excellent yields in very short reaction times (35 s, Scheme 52). To increase the nucleophilicity of the amino acids, 2 equiv of $NaHCO_3$ have to be added to the reaction mixture. Under conventional heating at 95 °C, no product was detected within 1 min. The bromo and chloro derivatives of 2,4-dinitrobenzene reacted at a much slower rate and gave inferior yields (6−15 min, 48−64%).

The group of Van der Eycken explored the synthesis of pyrido-fused heterocycles which was performed in *n*-BuOH as solvent under microwave irradiation and usually consists of three steps: nucleophilic substitution, Knoevenagel condensation, and ring closure applying the *tert*-amino effect.[124] In a case study, the authors were successful in performing all three reactions in water as solvent. Nucleophilic substitution of *o*-fluoro-benzaldehyde with pyrrolidine at 130 °C for 3 min gave intermediate **89**, which was found to be converted

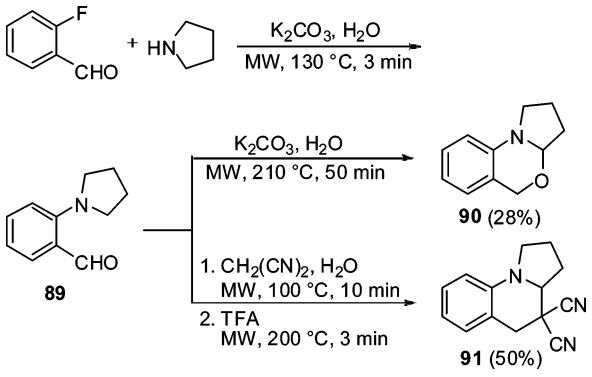
Scheme 51



Scheme 52



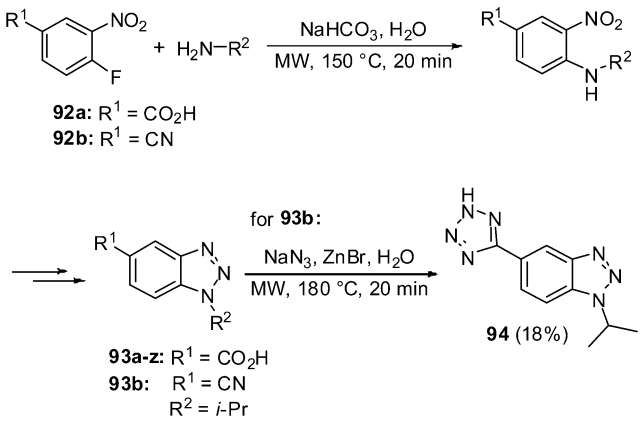
Scheme 53



to the pyrrolobenzoxazine **90** by further heating at 210 °C for 50 min in 28% yield (Scheme 53). To obtain the tricyclic pyrido-fused product **91**, the Knoevenagel condensation with malononitrile and the subsequent cyclization could be performed in one pot (Scheme 53).

For structure−activity relationship (SAR) investigation purposes a small library of *N*1-alkyl benzotriazole-5-carboxylic acids (**93a**−**z**) was prepared by Semple and coworkers in a three-step synthesis.[125] 4-Fluoro-3-nitrobenzoic acid (**92a**) is reacted with diversely substituted amines in the first step via nucleophilic substitution under microwave conditions (Scheme 54). Use of water was highly beneficial because of purification issues: upon cooling the amine precipitated from the reaction mixture and was easily

Scheme 54

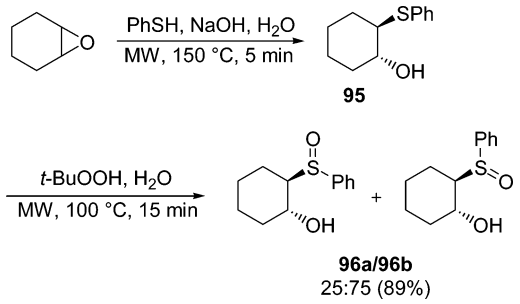


separated. A series of the synthesized benzotriazole carboxylic acids showed good in vitro agonist activity for the human orphan G-protein-coupled receptor GPR109b and excellent selectivity for GPR109b versus the closely related GPR109a. To further determine the effect of the size of the ligand on activity and explore the limits of the binding pocket, 1-isopropyl-benzotriazole-5-tetrazole **94** was synthesized, starting from 4-fluoro-3-nitro-benzonitrile (**92b**). The last step in this synthesis was conversion of **93b** to the tetrazole **94** by treatment with NaN_3 in water at 180 °C under microwave irradiation (Scheme 54). It turned out that **94** did not show any activity for GPR109b, leading to the assumption that the bicyclic acid scaffold was close to the size limit and that a further enlargement of the ligand is not tolerated.

11. Epoxide Ring-Opening Reactions

Recently, Pironti and Colonna described the synthesis of β-hydroxy sulfides **95** via the aqueous thiolysis of epoxides with thiophenol in the presence of a catalytic amount of NaOH (Scheme 55).[126] The ring opening proved to be completely anti stereoselective, and the trans products **95** were obtained in excellent yields (six examples, 85−98%). Additionally, a one-pot procedure was developed for the synthesis of β-hydroxy sulfoxide **96**. Addition of 2 equiv of

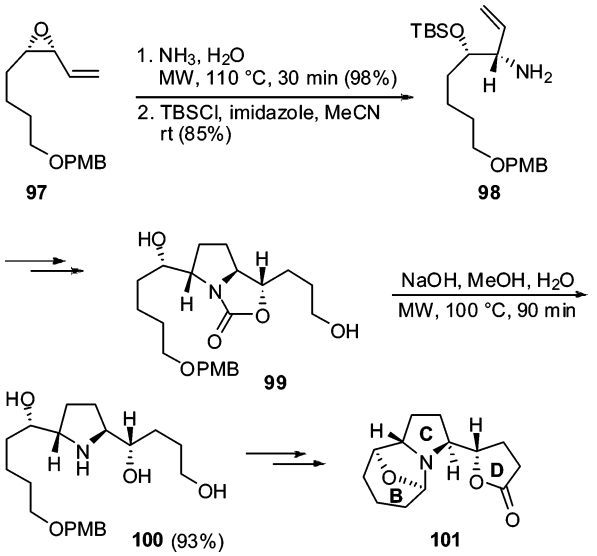
Scheme 55



tert-butyl hydroperoxide to the reaction mixture of already formed β-hydroxy sulfide **95** and subsequent irradiation at 100 °C generated the oxidized product in 89% yield as a 25:75 mixture of diastereomers **96a** and **96b** (Scheme 55).

In the course of the asymmetric synthesis of the tricyclic B,C,D-ring core structure of croomine (**101**), Lindsay and Pyne reported on the epoxide ring opening of chiral *cis*-epoxide **97** via aminolysis with aqueous ammonia at 110 °C for 30 min (Scheme 56).[127] The aminoalcohol could be

Scheme 56



obtained regioselectively in 98% yield and was further converted to the protected *O*-TBS ether **98**, which served as starting material in the synthesis of **101**. Microwave heating under aqueous conditions was also applied in another synthesis step on the way to the natural product **101**. The base-catalyzed hydrolysis of the oxazolidine group of **99** was performed at 100 °C for 90 min, and triol **100** was received in 93% yield (Scheme 56).

Epoxide ring opening via aminolysis was one synthetic step in the generation of the cyclic β-aminoalcohol building block in the course of the generation of a series of cyclic ketone inhibitors **104** of the serine protease plasmin, which was reported by Seto and Xue (Scheme 57).[128] If aqueous ammonium hydroxide is employed for the ring opening, irradiation at 85 °C for 30 min is required to obtain β-aminoalcohols **102** in good to excellent yields. In a second series, *N*-Boc-protected diamines (**103**) in water as solvent are applied for the ring opening; here a somewhat higher temperature of 105 °C and longer reaction times are required. In the plasmin inhibition studies it turned out that two compounds with attached alkylamino substituents with a spacer length of six carbon atoms (**104**, R^1 = Cbz, R^2 = $(CH_2)_6$-NH_2, X = O, SO_2; see Scheme 57) showed a significant activity against plasmin due to an optimal length for binding in the S1 subsite of plasmin.

12. Diels–Alder Cycloadditions

Enhanced rate accelerations in Diels−Alder cycloadditions due to the combined effects of a water-soluble organotungsten Lewis acid catalyst (**105**), water as solvent, and microwave heating were observed by Yu and co-workers.[129] All reactions were completed in less than 1 min at 50 °C employing 3 mol % of the Lewis acid catalyst **105** (Scheme 58). When the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6) is employed as solvent, even higher accelerations were possible, the reactions being completed within 30 s. Another advantage of the ionic liquid medium is the higher degree of catalyst recovery. Lewis acid **105** can be reused up to 10 times without significant activity loss, whereas a 20% decrease in conversion after the sixth cycle was obtained for the water recovery.

A key step in the synthesis of oroidin-derived alkaloids like palau'amine is the Diels−Alder cycloaddition of dienophile **106** and diene **107** which was recently reported by Romo and his group.[130] Best conditions were found to employ water as solvent, $LiClO_4$ as weak Lewis acid, 0.6 equiv of 2,6-lutidine, and 3 equiv of diene **107** at 170 °C for 45 min to generate a 1:6 ratio of dienophile to product **108** (Scheme 59). The Diels−Alder product **108** was obtained in an overall yield of 48% after TBDPS protection. Unfortunately, dimerization of the tosylvinyl (Tsv) protected diene was determined as a major side product due to the excess diene employed, which limited the use of this substrate for the palau'amine synthesis. The diene bearing Tse (*p*-tolylsulfonylethyl) as protecting group proved to give higher yields of the corresponding products; however, for this substrate the Diels−Alder reaction was not performed under aqueous conditions.

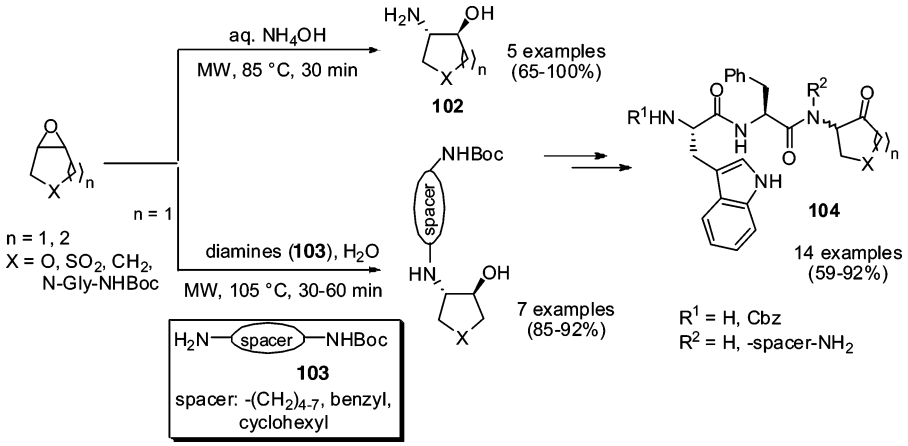
Diels−Alder reactions without any additive were investigated by Kočevar, Parvulescu, and Michelet.[131] Formation of bicyclo[2.2.2]octenes **111** via cycloaddition of 2*H*-pyran-2-ones **109** and maleimides **110** was possible in very high yields (Scheme 60). Heating the reaction mixture conventionally, longer reaction times (1.5−2 h) and higher temperatures (refluxing decalin, 190 °C) were needed. With water as solvent under reflux conditions (2 h), a 30% decrease in yield was observed.

13. Decarboxylations and Hydrolyses

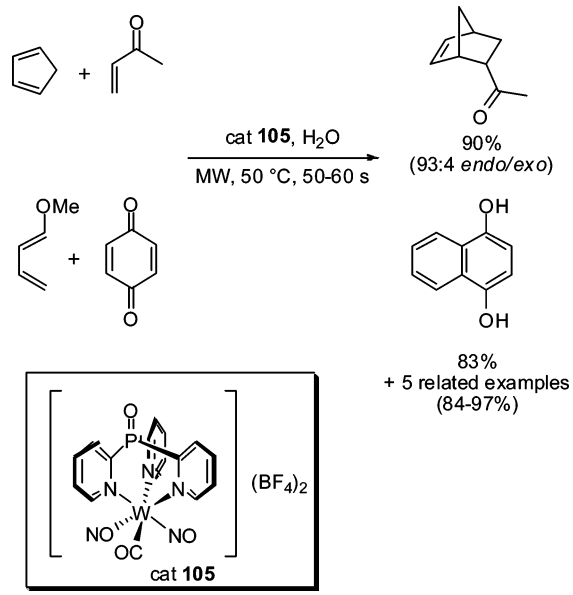
In the context of the preparation of a library of pyrazole-based cyclooxygenase II (COX-II) inhibitors, the Organ group described the microwave-assisted decarboxylation of pyrazole carboxylic ester **112** with 20% sulfuric acid (Scheme 61a).[56] While the conventional protocol (reflux, 100 °C) required 96 h to provide a yield of 86%, full conversion could be achieved within 5 min at 200 °C under microwave heating, leading to an 88% isolated product yield.

Decarboxylation of malonic acid derivatives **113** performed in water was reported by Giguere and co-workers (Scheme 61b).[132] In order to achieve the rather high temperature of 190 °C more easily and stay within the pressure limit of the instrument, a Weflon-coated (graphite-doped Teflon) stirring bar was used which is a strongly microwave-absorbing passive heating source.[40]

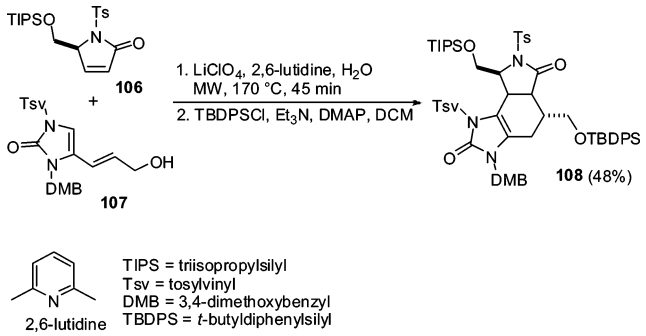
Scheme 57



Scheme 58

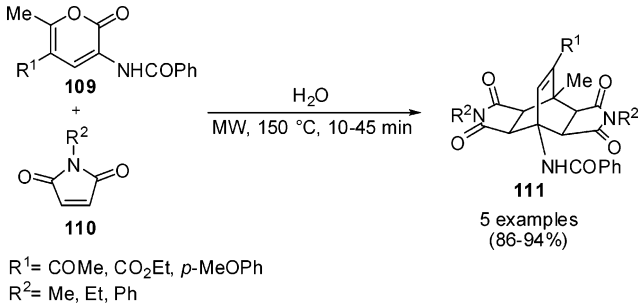


Scheme 59

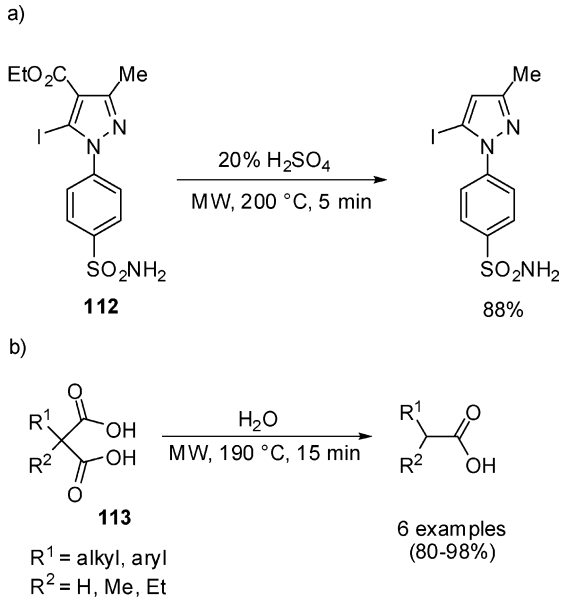


Hydrolysis of chloromethyl thiazole hydrochloride under continuous-flow (CF) conditions in a dedicated microwave flow reactor[16,37] was reported by the Bagley group (Scheme 62).[133] A standard pressure-rated glass tube (10 mL) filled with sand (ca. 12 g) acted as CF reactor which was connected to an HPLC flow system. A sample of 1.5 g of alcohol **114** could be prepared at 150 °C in 15−30 min at a flow rate of 1 mL/min (Scheme 62). Somewhat higher conversions were obtained by conducting the reaction in batch under microwave or conventional heating at the same temperature for 10 or for 12 min, respectively.

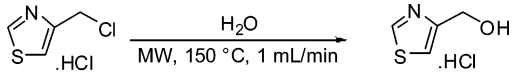
Scheme 60



Scheme 61

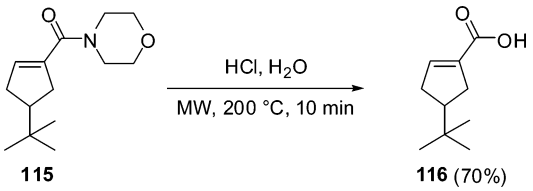


Scheme 62



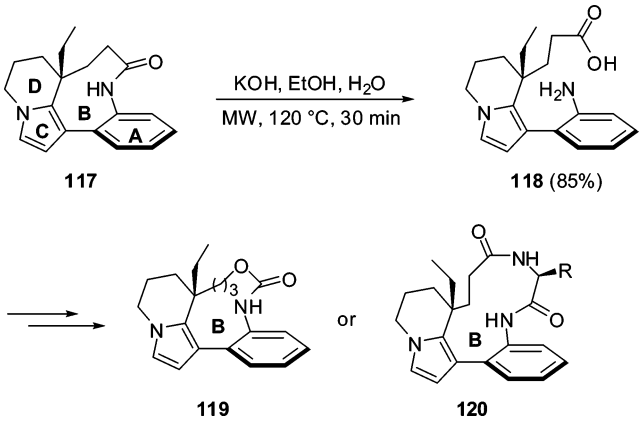
4-*tert*-Butylcyclopentene-1-carboxylic acid **116** was obtained upon hydrolysis from its morpholide derivative **115**, which was disclosed by Strauss and co-workers (Scheme 63).[134] Performing the reaction under reflux conditions for 4 h in an aqueous 2 M HCl solution only 48% of the acid could be obtained. Raising the temperature to 200 °C, an increase in yield to 70% was possible after 10 min.

Scheme 63



The synthesis and biological evaluation of B-ring analogues of (−)-rhazinilam (**117**), which is known to possess unique antimitotic properties with in vitro inhibition of both microtubule assembly and disassembly, was depicted by the Baudoin group.[135] The first step in the synthesis of derivatives with an enlarged B-ring was hydrolysis of the lactam group of rhazinilam (**117**) with a large excess of KOH in a 1:1 mixture of EtOH/H_2O at 120 °C for 30 min (Scheme 64).

Scheme 64

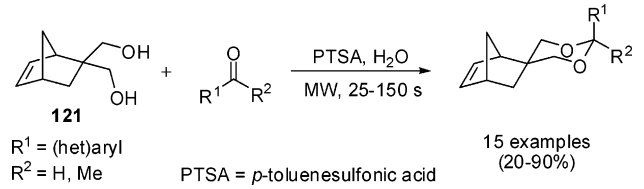


The hydrolysis product **118** could be obtained under thermal heating as well in refluxing EtOH and water after 23 h in 82% yield. Amino-acid **118** was further reacted to the 11- and 12-membered macrocycles **119** and **120** (Scheme 64) which showed very weak activity on the assembly and disassembly of microtubules possibly due to the high flexibility of the enlarged B-ring compared to that of rhazinilam.

14. Protection/Deprotection Reactions

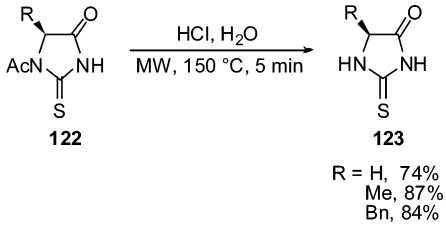
One of the most commonly used protection methods for carbonyl compounds is acetal formation. In 1999, Pourjavadi and Mirjalili described the synthesis of ketals and acetals, respectively, from 2,2′-bis-(hydroxymethyl)norborn-5-ene **121** and various aromatic aldehydes or ketones applying microwave heating in a domestic microwave oven under sealed-vessel conditions (Scheme 65).[136] In general, aldehydes were more reactive than the corresponding ketones as well as aldehydes with electron-withdrawing groups at the aryl moiety. Acetalizations conducted with conventional heating gave similar yields, but prolonged reaction times were necessary (up to 5 h), whereas decreased yields (10−65%) were observed for reactions under solventless microwave conditions.

Scheme 65



In the course of a re-evaluation study of the synthesis of 1-acetyl-thiohydantoins **122**, which can be obtained by reaction of unprotected amino acids with acetic anhydride and ammonium thiocyanate, Reyes and Burgess disclosed the deacylation at the *N*1-position of **122** (Scheme 66).[137]

Scheme 66

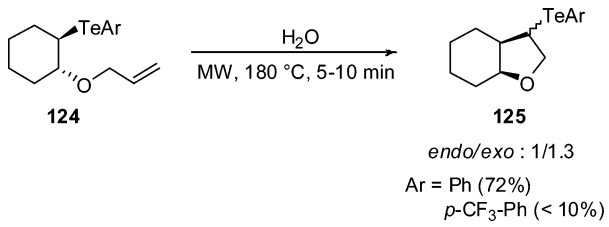


The deprotection step was performed in a 3 M aqueous HCl solution and furnished products **123** in high yields.

15. Miscellaneous Reactions

In 2004, Ericsson and Engman developed radical group-transfer cyclizations of organotellurium compounds.[138] They found that secondary alkyl aryl tellurides **124** underwent rapid cyclization (5−10 min) to afford tetrahydrofuran derivatives **125** (Scheme 67). Disappointingly, primary alkyl aryl tellurides showed low conversions for the group-transfer cyclization when heated in water at 180 °C, whereas the reaction went to completion when heated in ethylene glycol at 250 °C (<10% vs 74% isolated yield). However, due to the higher temperatures a loss in diastereoselectivity was obtained when applying these higher temperatures.

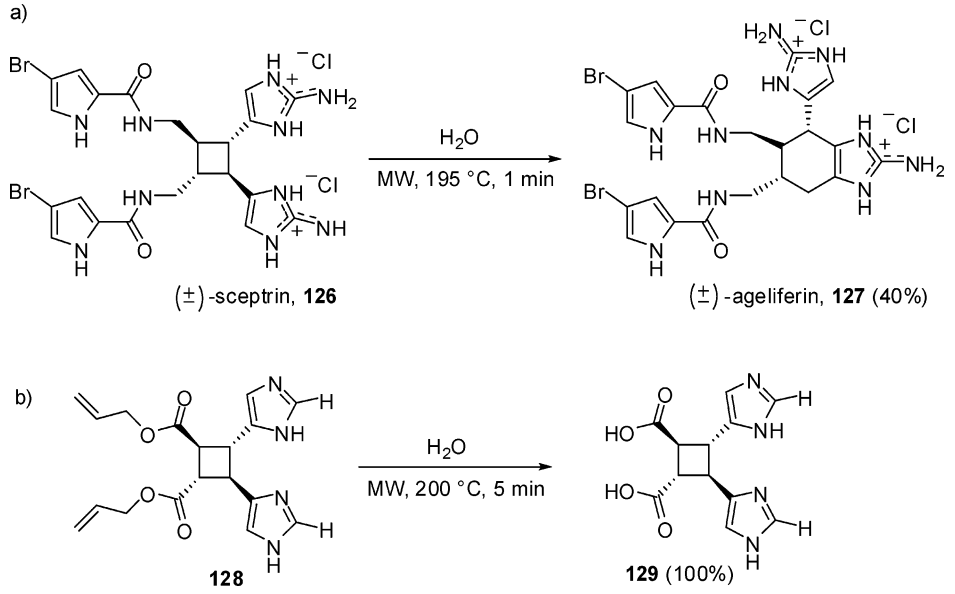
Scheme 67



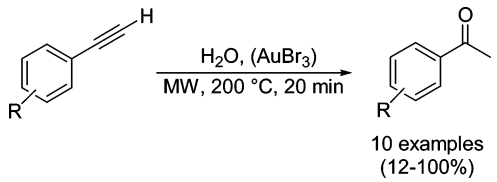
The total synthesis of ageliferin, a natural product with antiviral activity, via vinylcyclobutane rearrangement was published by the group of Baran.[139] Microwave irradiation of sceptrin (**126**) for 1 min at 195 °C provided ageliferin (**127**) in 40% yield along with 52% of recovered starting material (Scheme 68a). When the reaction was conducted at the same temperature without microwaves, only sceptrin and decomposition products were observed. Interestingly, only the hydrolysis product **129** was quantitatively obtained when cyclobutane **128** was irradiated at 200 °C for 5 min, indicating the requirement of the 2-aminoimidazole subunit (Scheme 68b).

Vasudevan and Verzal were successful in the hydration of terminal alkynes to form the corresponding ketones under acid-free conditions in water at 200 °C (Scheme 69).[140] Alkynes possessing electron-donating groups showed high conversions without any catalyst; however, the outcome of sluggish alkynes with electron-withdrawing substituents could be improved by addition of 2 mol % of $AuBr_3$. Hydration of 4-ethynyl anisole (R = OMe) by heating in an

Scheme 68



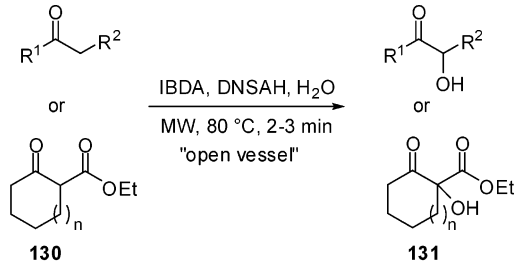
Scheme 69



oil bath under the same conditions depicted in Scheme 69 without $AuBr_3$ resulted in very low yields (<5% vs 94%), whereas a 60% yield was obtained with $AuBr_3$. Extension of this method led to a one-pot conversion of alkynes to imines via hydroamination.

The direct conversion of ketones to α-hydroxyketones is usually performed under acidic conditions in the presence of hypervalent iodine compounds. Lee and co-workers reported on the rapid α-hydroxylation of various ketones with iodobenzene diacetate and 2,4-dinitrobenzenesulfonic acid hydrate under microwave open-vessel reflux conditions at 80 °C for only 2−3 min (Scheme 70).[141] Cyclic *β*-keto esters

Scheme 70

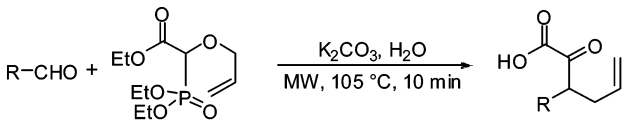


IBDA = iodobenzene diacetate
DNSAH = 2,4-dinitrobenzenesulfonic acid hydrate

130 were converted to the corresponding α-hydroxy-*β*-keto esters **131** in good yields applying the same conditions.

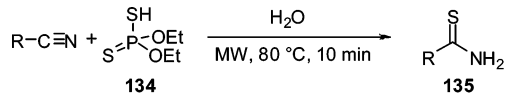
A tandem three-step, one-pot protocol involving Horner−Wadsworth−Emmons (HWE) olefination, Claisen rearrangement, and a hydrolysis sequence in the synthesis of α-keto acids **133** was developed by Quesada and Taylor.[142] Aldehydes are reacted with allyl phosphonate **132** in aqueous K_2CO_3 at 105 °C for 10 min to furnish the products **133** in good to excellent yields (Scheme 71). Interestingly, the outcome of the tandem process could be tuned by the temperature. If the reaction is performed at 55 °C for 30 min under microwave heating the sequence stops after the HWE-olefination which proceeded quantitatively. A 70-fold overall enhancement could be reached by applying microwave irradiation compared to conventional heating.

Scheme 71



The parallel synthesis of thioamides **135** as first step in the course of a three-step preparation of 2,4-disubstituted 5-aminoimidazoles was recently shown by the group of Lam.[143] Aryl and alkyl nitriles were converted with diethyldithiophosphoric acid **134** to the corresponding thioamides in excellent yields employing a multivessel rotor system (Scheme 72). The overall reaction time was reduced from

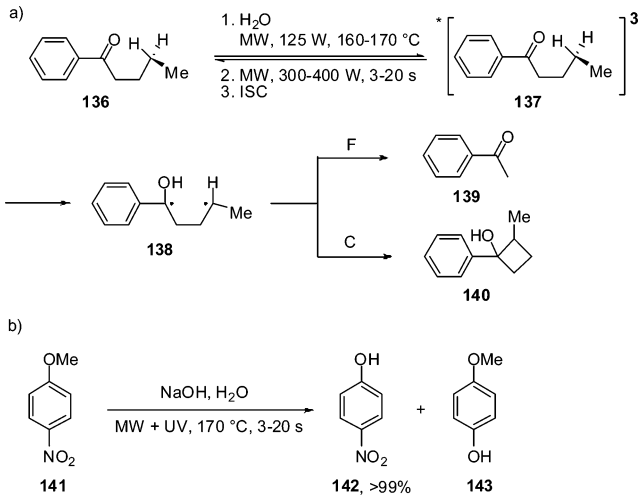
Scheme 72



days to 25 min when microwave heating was employed for all three steps.

Photochemical reactions can sometimes also be performed with microwave assistance. Toward this end, electrodeless discharge lamps, which are able to generate UV radiation when placed into the microwave field, can be applied.[144] Klán and co-workers reported recently on the Norrish Type II

Scheme 73



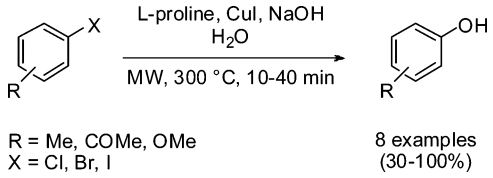
reaction and photochemical nucleophilic substitutions under high-temperature water conditions.[145] In the Norrish Type II reaction, the short-lived singlet biradical **138**, which is formed by intersystem crossing of valerophenone triplet 1,4-biradical **137**, can fragment (F) to give acetophenone **139**, cyclize (C) to the cyclobutanol derivative **140**, or disproportionate back to the starting ketone **136** (Scheme 73a). In the first step, the mixture was heated with low power (125 W) which was too low to induce a discharge in the lamp but sufficient to reach temperatures of 160−170 °C. Then, the microwave power was increased to 300−400 W, which resulted in an ignition of the lamp. It was shown that fragmentation to acetophenone was the preferred pathway, even at 200 °C. For the second reaction, photosubstitution of 4-nitroanisole (**141**), the authors discovered that it is a mainly thermally driven process. The main products obtained under photochemical conditions are 4-nitrophenol (**142**) and 4-methoxyphenol (**143**). However, microwave heating at 170 °C with and without the discharge lamp furnished only 4-nitrophenol (Scheme 73b).

16. Reactions in Near-Critical Water

Only a small number of publications that deal with microwave-assisted organic chemistry in water above 200 °C exist due to the pressure limit of ca. 20 bar for most of the commercially available microwave instruments. Pure water, for example, reaches an autogenic pressure of 50 bar at 250 °C. Reactions in the near-critical water (NCW) region between 200 and 300 °C that are presented in this section of the review have to be performed in one of the few accessible dedicated instruments with higher pressure limits (80−100 bar). The examples shown here are conducted in two different multimode microwave instruments with temperature and pressure limits of 260 °C/100 bar and 300 °C/80 bar, respectively.[134,89]

Leadbeater and Kormos reported on the direct conversion of aryl halides to the corresponding phenols at 300 °C (Scheme 74).[146] The combination of 10 mol % CuI as catalyst and 5 mol % L-proline as additive was found to be the optimum catalyst system and NaOH to be the best base. If aryl iodides are employed the reaction mixture is ramped to 300 °C within 10 min. However, the reactions could also be conducted at 200 °C under the same conditions, resulting in a small decrease in yield and slightly longer reaction times (30 min). In the case of aryl bromides and chlorides,

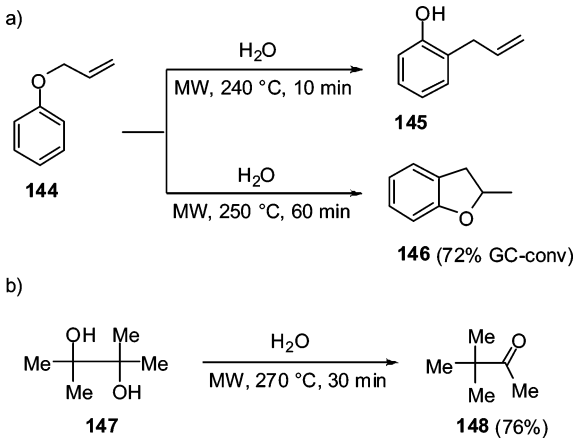
Scheme 74



10−40% higher yields are possible when the reactions are heated to 300 °C (10 min ramp, 30 min hold time).

The Claisen rearrangement of allyl phenyl ether **144** to 2-allyl phenol **145** was successfully performed by the Strauss group at 240 °C to give the product in 84% isolated yield, whereas only 10% conversion was achieved when **144** was heated at 200 °C (Scheme 75a).[134,147] In a further study the

Scheme 75



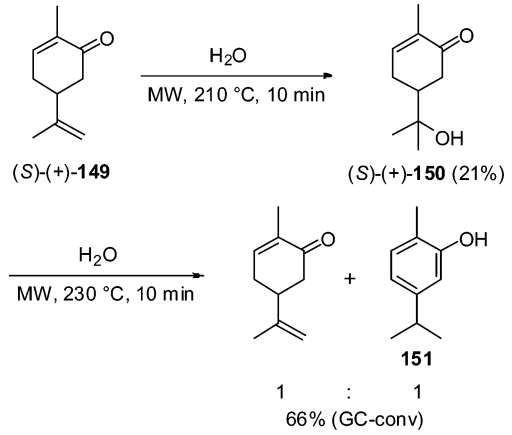
authors showed that by increasing the temperature and time to 250 °C and 1 h, dihydrobenzofuran **146** was produced in 72% GC conversion due to involvement of water into the reaction pathway. This product was identified as the thermodynamic product (Scheme 75a).[148]

Kremsner and Kappe disclosed the rearrangement of pinacol **147** to pinacolone **148** in water at 270 °C (Scheme 75b).[38] At this temperature, full conversion was achieved and the product was isolated in a 76% yield by transformation of the ketone into the corresponding hydrazone by treatment with 2-(2,4-dinitrophenyl)hydrazine. Attempted transformation to the ketone at 200 °C for 20 min yielded a 14% product yield only. This rearrangement normally proceeds under acid catalysis, leading the authors to assume that here NCW acts as an acid catalyst itself.

Investigations toward the hydration of alkenes were conducted by Strauss and co-workers.[147] On the pathway to the synthesis of carvacrol (**151**), (*S*)-(+)-8-hydroxy-*p*-6-menthen-2-one (**150**) was found as an intermediate, which could be isolated in a 21% yield, upon heating of the (*S*)-(+)-isomer of carvone (**149**) at 210 °C for 10 min (Scheme 76). Addition of water to the 8,9-double bond of (*S*)-(+)-**149** proceeded at lower temperatures than did aromatization; thus, (*S*)-(+)-**149** isomerizes quantitatively (95% yield) to **151** at 250 °C within 10 min.

Hydration of alkynes by Vasudevan and Verzal at 200 °C within 20 min was already described above (see Scheme 69).[140] In a re-evaluation, Kremsner and Kappe were unsuccessful to transform phenylacetylene to acetophenone under the conditions described by Vasudevan and Verzal, mainly because the temperature of 200 °C could not be reached under the single-mode microwave conditions specified by

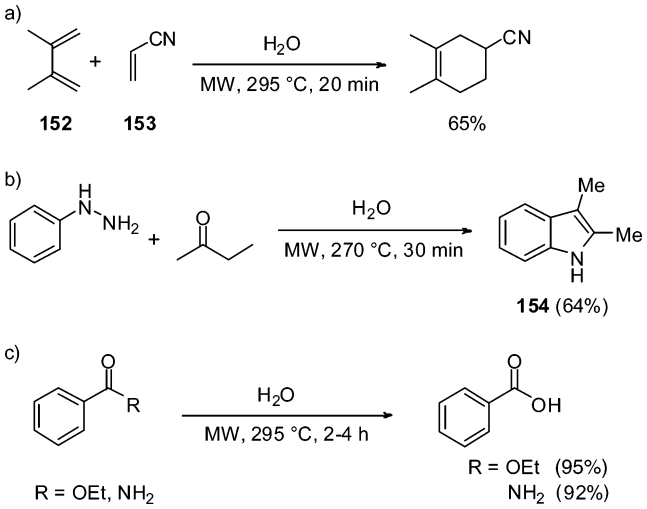
Scheme 76



the authors.[38] However, by applying a temperature of 295 °C for 150 min it was possible to obtain acetophenone as the corresponding hydrazone in 78% isolated yield.

Kappe and Kremsner also reported on Diels−Alder cycloadditions (Scheme 77a, see also Section 12), Fischer

Scheme 77



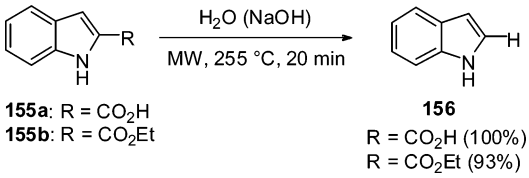
indole synthesis (Scheme 77b), and hydrolysis of ethyl benzoate and benzamide (Scheme 77c) using microwave-generated NCW.[38] In the Diels−Alder cycloaddition of 2,3-dimethylbutadiene (**152**) and acrylonitrile (**153**), full conversion was achieved at 295 °C within 20 min (Scheme 77a).

By applying the conditions for the Fischer indole synthesis reported by Strauss and co-workers (222 °C, 30 min, 67% isolated yield),[20,21] full conversion of phenylhydrazine was obtained but a 28% HPLC yield of an unknown byproduct was detected. Conducting the reaction at 270 °C for 30 min, clean and quantitative HPLC conversion was observed and 2,3-dimethylindole (**154**) was isolated in 64% yield (Scheme 77b).

In general, hydrolysis of esters and amides is only possible in the presence of strong mineral acids or bases, whereas in the NCW region no addition of any catalyst is necessary since an autocatalytic $A_{ac}2$ mechanism is assumed.[26] Complete hydrolysis of ethyl benzoate (R = OEt) to benzoic acid was detected after 2 h at 295 °C, and upon cooling most of the benzoic acid precipitated from the aqueous reaction medium (Scheme 77c). In previous work on the benzamide hydrolysis (R = NH_2, Scheme 77c) the authors demonstrated that sulfuric acid as catalyst is necessary to achieve any benzoic acid product at 180 °C.[149] Performing the reaction in 20% aqueous H_2SO_4, complete hydrolysis was accomplished in 2 min at 180 °C and in 7 min when a 5% aqueous H_2SO_4 solution is employed. Under NCW conditions (295 °C) full conversion was detected after 4 h without the need of a catalyst (Scheme 77c) since it is supposed that the formed ammonium hydroxide autocatalyzes this reaction.[38]

A simple protocol for the decarboxylation of indole-2-carboxylic acid (**155a**) to indole (**156**) was established by the group of Strauss (Scheme 78).[147] Heating at 255 °C for

Scheme 78



20 min furnished product **156** in quantitative yield, whereas 2-carbethoxyindole (**155b**) showed only 20% GC conversion under these conditions. This problem could be overcome by performing the reaction in a 0.2 M aqueous NaOH solution: now ester **155b** is first hydrolyzed to the acid **155a** which further undergoes decarboxylation to indole (93% yield).

17. Future Prospects and Challenges

The combined use of microwave irradiation as a heating source and water as solvent for synthetic organic transformations is a relatively new field. In this review we summarized the results reported mainly within the last 5 years in ∼100 publications. The authors have not commented specifically on the benefits of using water as a solvent or on the benefits of using microwave heating technology in all cases. In most cases, comparison studies with standard organic solvents and/or conventional heating were not performed. Despite this, it is quite clear from the growing number of emerging publications in this field that the possibility to rapidly superheat water to far above its boiling point utilizing sealed-vessel microwave technology allows reaction conditions to be accessed that are very valuable for organic synthesis. This is particularly true for water at near-critical conditions (ca. 200−300 °C), which can relatively easily be generated using modern microwave reactors. It remains to be seen if microwave technology can be developed that one day will also allow supercritical water at >374 °C and >221 bar to be generated.

Another important issue is the question of scale-up. Most of the reactions described in this review were performed in <1 g scale, which reflects the current limitation of this technology when it comes to processing larger volumes.[16] In order for microwave chemistry to be a valuable tool for the process chemist, new microwave scale-up technology needs to be developed, which is both economically viable and environmentally sustainable if one considers the energy balance. Till then the question if microwave chemistry is truly green chemistry cannot be answered.

18. Acknowledgments

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Promotion Agency (FFG), the "Jubiläumsfonds der Österreichischen Nationalbank", the European Union COST program, the Austrian Academic Exchange Service (OeAD), the University of Graz, and various industrial contributors. We wish to thank all members of the Microwave Synthesis Lab in Graz for their essential contributions to microwave chemistry.

19. References

(1) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1988.

(2) (a) Matlack, A. S. *Introduction to Green Chemistry*; Marcel Dekker Inc.: New York, 2001. (b) Lancester, M. *Green Chemistry: An Introductory Text*; Royal Society of Chemistry: Cambridge, 2002. (c) Clark, J. H.; Macquarrie, D. *Handbook of Green Chemistry & Technology;* Blackwell Publishers: Oxford, 2002.

(3) The 12 principles are as follows: prevention, atom economy, less hazardous chemical synthesis, designing safer chemicals, safer solvents, design for energy efficiency, use of renewable feedstocks, reduce derivatives, catalysis, design for degradation, real-time analysis for pollution prevention, inherently safer chemistry for accident prevention.

(4) Adams, D. J.; Dyson, P. J.; Tavener, S. J. *Chemistry in Alternative Reaction Media*; Wiley: Chichester, 2004.

(5) *Solvent-free Organic Synthesis*; Tanaka, K., Ed.; Wiley-VCH: Weinheim, 2003.

(6) (a) *Supercritical Carbon Dioxide in Polymer Reaction Engineering*; Kemmere, M. F., Meyer, T., Eds.; Wiley-VCH: Weinheim, 2005. (b) *Green Chemistry Using Liquid and Supercritical Carbon Dioxide*: DeSimone, J. M., Tumas, W., Eds.; Oxford University Press: Oxford, 2003. (c) *Supercritical Carbon Dioxide: Separations and Processes*: Gopalan, A. S., Wai, C. M., Jacobs, H. K., Eds.; ACS Symposium Series 860; American Chemical Society: Washington, DC, 2003.

(7) (a) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2002. (b) *Ionic Liquids as Green Solvents. Progress and Prospects*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symposium Series 856; American Chemical Society: Washington, DC, 2003. (c) *Green Industrial Applications of Ionic Liquids*; Rogers, R. D., Seddon, K. R., Volkov, S., Eds.; Kluwer Academic Publishers: Dordrecht, 2003.

(8) *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004.

(9) (a) *Organic Synthesis in Water*; Grieco, P.A., Ed.; Blackie: London, 1998. (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (c) *Organic Reactions in Water*; Lindström, U., Ed.; Blackwell Publishing: Oxford, 2007. (d) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. (e) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (f) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (g) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (h) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68.

(10) (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (b) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471. (c) Pirrung, M. C. *Chem. Eur. J.* **2006**, *12*, 1312.

(11) The release of contaminated wastewater resulting from a chemical or manufacturing process, however, is a serious environmental problem, and there is typically a high cost associated with the recycling/purification of contaminated water, see: Wei, W.; Keh, C. C. K.; Li, C.-J.; Varma, R. S. *Clean Techn. Environ. Policy* **2004**, *6*, 250 and references therein.

(12) (a) *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation and Applications*; Kingston, H. M., Haswell, S. J., Eds.; American Chemical Society, Washington, DC, 1997. (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002. (c) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (d) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell Publishing: Oxford, 2005. (e) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry;* Wiley-VCH: Weinheim, 2005. (f) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006. (g) *Microwave Methods in Organic Synthesis*; Larhed, M., Olofsson, K., Eds.; Springer: Berlin, 2006.

(13) (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66.

(14) (a) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (c) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863. (d) Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589.

(15) Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Process Res. Dev.* **2005**, *9*, 516.

(16) (a) Kremsner, J. M.; Stadler, A.; Kappe, C. O. *Top. Curr. Chem.* **2006**, *266*, 233. (b) Glasnov, T. N.; Kappe, C. O. *Macromol. Rapid Commun.* **2007**, *28*, 395. (c) Ondruschka, B.; Bonrath, W.; Stuerga, D.In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 2, p 62.

(17) (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (b) Varma, R. S. *Green Chem.* **1999**, 43. (c) Kidwai, M. *Pure Appl. Chem.* **2001**, *73*, 147. (d) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193. (e) Varma, R. S. *Tetrahedron* **2002**, *58*, 1235.

(18) (a) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Comb. Chem. High Throughput Screen.* **2004**, *7*, 511. (b) Habermann, J.; Ponzi, S.; Ley, S. V. *Mini-Rev. Org. Chem.* **2005**, *2*, 125. (c) Leadbeater, N. E.; Torenius, H. M. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 7, p 327.

(19) Zhang, W. *Top. Curr. Chem.* **2006**, *266*, 145.

(20) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665.

(21) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83.

(22) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653.

(23) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881.

(24) The American Chemical Society journals *Organic Letters* and the *Journal of Organic Chemistry*, for example, will allow work performed with domestic microwave ovens to be published only if the experiments were conducted at atmospheric pressure and the temperature profiles have been recorded. For more details, see the corresponding Instructions for Authors.

(25) (a) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545. (b) Widom, B.; Bhimalapuram, P.; Koga, K. *Phys. Chem. Chem. Phys.* **2003**, *5*, 3085. (c) Sijbren, O.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809. (d) Lindström, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548.

(26) (a) Krammer, P.; Vogel, H. *J. Supercrit. Fluids* **2000**, *16*, 189. (b) Krammer, P.; Mittelstädt, S.; Vogel, H. *Chem. Eng. Technol.* **1999**, *22*, 126.

(27) (a) Bröll, D.; Kaul, C.; Krämer, A.; Krammer, P.; Richter, T.; Jung, M.; Vogel, H.; Zehner, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2998. (b) Savage, P. E. *Chem. Rev.* **1999**, *99*, 603. (c) Siskin, M.; Katritzky, A. R. *Chem. Rev.* **2001**, *101*, 825. (d) Katritzky, A. R.; Nichols, D. A.; Siskin, M.; Murugan, R.; Balasubramanian, M. *Chem. Rev.* **2001**, *101*, 837. (e) Watanabe, M.; Sato, T.; Inomata, H.; Smith, R. L., Jr.; Arai, K.; Kruse, A.; Dinjus, E. *Chem. Rev.* **2004**, *104*, 5803. (f) Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725. (g) Weingärtner, H.; Franck, E. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2672.

(28) (a) Minett, S.; Fenwick, K.; Stenmark, L. *Speciality Chem. Mag.* **2001**, *21*, 30. (b) Qi, X.-H.; Zhuang, Y.-Y.; Yuan, Y.-C.; Gu, W.-X. *J. Hazard. Mater.* **2002**, *90*, 51. (c) Del Re, G.; Di Giacomo, G. *Desalination* **2001**, *138*, 61. (d) Baur, S.; Schmidt, H.; Kraemer, A.; Gerber, J. *J. Supercrit. Fluids* **2005**, *33*, 149.

(29) (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, R. *Tetrahedron Lett.* **1986**, *27*, 279. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.

(30) (a) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406. (b) Wathey, B.; Tierney, J.; Lidström, P.; Westman, J. *Drug Discovery Today* **2002**, *7*, 373. (c) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. *Mini-Rev. Med. Chem.* **2003**, *3*, 449. (d) Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. *Drug Discovery Today: Technol.* **2005**, *2*, 155. (e) Kappe, C. O.; Dallinger, D. *Nature Rev. Drug Discovery* **2006**, *5*, 51.

(31) (a) Bogdal, D.; Penczek, P.; Pielichowski, J.; Prociak, A. *Adv. Pol. Sci.* **2003**, *163*, 193. (b) Wiesbrock, F.; Hoogenboom, R.; Schubert, U. S. *Macromol. Rapid Commun.* **2004**, *25*, 1739.

(32) (a) Barlow, S.; Marder, S. R. *Adv. Funct. Mater.* **2003**, *13*, 517. (b) Zhu, Y.-J.; Wang, W. W.; Qi, R.-J.; Hu, X.-L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1410.

(33) Tsuji, M.; Hashimoto, M.; Nishizawa, Y.; Kubokawa, M.; Tsuji, T. *Chem. Eur. J.* **2005**, *11*, 440.

(34) (a) Orrling, K.; Nilsson, P.; Gullberg, M.; Larhed, M. *Chem. Commun.* **2004**, 790. (b) Zhong, H.; Zhang, Y.; Wen, Z.; Li, L. *Nature Biotechnol.* **2004**, *22*, 1291. (c) Zhong, H.; Marcus, S. L.; Li, L. *J. Am. Soc. Mass Spectrom.* **2005**, *16*, 471.

(35) (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213. (b) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1.

(36) Kappe, C. O. *Chimia* **2006**, *60*, 308.

(37) For a detailed review of commercially available microwave reactors for organic synthesis, see ref 12e, Chapter 3, p 29.

(38) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672.

(39) Neas, E. D.; Collins, M. J. In *Introduction to Microwave Sample Preparation: Theory and Practice*; Kingston, H. M., Jassie, L. B., Eds.; American Chemical Society: Washington, DC, 1988; Chapter 2, p 7.
(40) Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651.
(41) Torry, L. A.; Kaminsky, R.; Klein, M. T.; Klotz, M. R. *J. Supercrit. Fluids* **1992**, *5*, 163.
(42) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(43) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.
(44) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888.
(45) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407.
(46) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660.
(47) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.
(48) Arvela, R. K.; Leadbeater, N. E.; Collins, M. J., Jr. *Tetrahedron* **2005**, *61*, 9349.
(49) Leadbeater, N. E.; Williams, V. A.; Barnard, T. M.; Collins, M. J., Jr. *Org. Process Res. Dev.* **2006**, *10*, 833.
(50) Chanthavong, F.; Leadbeater, N. E. *Tetrahedron Lett.* **2006**, *47*, 1909.
(51) Leadbeater, N. E.; Smith, R. J. *Org. Lett.* **2006**, *8*, 4589.
(52) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101.
(53) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.
(54) Čapek, P.; Pohl, R.; Hocek, M. *Org. Biomol. Chem.* **2006**, *4*, 2278.
(55) Čapek, P.; Vrábel, M.; Hasník, Z.; Pohl, R.; Hocek, M. *Synthesis* **2006**, 3515.
(56) Organ, M. G.; Mayer, S.: Lepifre, F.; N′Zemba, B.; Khatri, J. *Mol. Diversity* **2003**, *7*, 211.
(57) Freundlich, J. S.; Landis, H. E. *Tetrahedron Lett.* **2006**, *47*, 4275.
(58) Appukkuttan, P.; Orts, A. B.; Chandran, R. P.; Goeman, J. L.; Van der Eycken, J.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2004**, 3277.
(59) Mei, X.; Martin, R. M.; Wolf, C. *J. Org. Chem.* **2006**, *71*, 2854.
(60) Crozet, M. D.; Castera-Ducros, C.; Vanelle, P. *Tetrahedron Lett.* **2006**, *47*, 7061.
(61) (a) Maes, B. U. W.; R'kyek, O.; Košmrlj, J.; Lemière, G. L. F.; Esmans, E.; Rozenski, J.; Dommisse, R. A.; Haemers, A. *Tetrahedron* **2001**, *57*, 1323. (b) Maes, B. U. W.; Košmrlj, J.; Lemière, G. L. F. *J. Heterocycl. Chem.* **2002**, *39*, 535.
(62) Gong, Y.; He, W. *Heterocycles* **2004**, *62*, 851.
(63) Gong, Y.; Barbay, J. K.; Dyatkin, A. B.; Miskowski, T. A.; Kimball, E. S.; Prouty, S. M.; Fisher, M. C.; Santulli, R. J.; Schneider, C. R.; Wallace, N. H.; Ballentine, S. A.; Hageman, W. E.; Masucci, J. A.; Maryanoff, B. E.; Damiano, B. P.; Andrade-Gordon, P.; Hlasta, D. J.; Hornby, P. J.; He, W. *J. Med. Chem.* **2006**, *49*, 3402.
(64) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803.
(65) Aquino, M.; Bruno, I.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2006**, *8*, 4831.
(66) Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C. M. *Tetrahedron Lett.* **2006**, *47*, 217.
(67) Villemin, D.; Gómez-Escalonilla, M. J.; Saint-Clair, J.-F. *Tetrahedron Lett.* **2001**, *42*, 635.
(68) Yan, J.; Zhu, M.; Zhou, Z. *Eur. J. Org. Chem.* **2006**, 2060.
(69) Solodenko, W.; Schön, U.; Messinger, J.; Glinschert, A.; Kirschning, A. *Synlett* **2004**, 1699.
(70) Solodenko, W.; Mennecke, K.; Vogt, C.; Gruhl, S.; Kirschning, A. *Synthesis* **2006**, 1873.
(71) Cho, J. K.; Najman, R.; Dean, T. W.; Ichihara, O.; Muller, C.; Bradley, M. *J. Am. Chem. Soc.* **2006**, *128*, 6276.
(72) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885.
(73) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2005**, *70*, 1786.
(74) Wang, J. X.; Liu, Z.; Hu, Y.; Wei, B.; Bai, L. *Synth. Commun.* **2002**, *32*, 1607.
(75) Botella, L.; Nájera, C. *Tetrahedron Lett.* **2004**, *45*, 1833.
(76) Gil-Moltó, J.; Karlström, S.; Nájera, C. *Tetrahedron* **2005**, *61*, 12168.
(77) (a) Dawood, K. M.; Solodenko, W.; Kirschning, A. *ARKIVOC* **2007**, (*v*), 104. (b) For the use of the Pd precatalyst in Suzuki couplings, see: Dawood, K. M.; Kirschning, A. *Tetrahedron* **2005**, *61*, 12121.
(78) Bergbreiter, D. E.; Furyk, S. *Green Chem.* **2004**, *6*, 280.
(79) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919.
(80) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2003**, 4713.
(81) Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125.
(82) (a) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 10, p 421. (b) Denmark, S. E.; Ober, M. H. *Aldrichim. Acta* **2003**, *36*, 75. (c) Handy, C. J.; Manoso, A. S.; McElroy, W. T.; Seganish, W. M., DeShong, P. *Tetrahedron* **2005**, *61*, 12201.
(83) (a) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 403. (b) Koike, T.; Mori, A. *Synlett* **2003**, 1850. (c) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147. (d) Wolf, C.; Lerebours, R. *Synthesis* **2005**, 2287.
(84) Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2006**, *348*, 2085.
(85) (a) Kaiser, N. F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109. (b) Georgsson, J.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2003**, *5*, 350. (c) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750.
(86) (a) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327. (b) Wu, X.; Ekegren, J. K.; Larhed, M. *Organometallics* **2006**, *25*, 1434.
(87) Lesma, G.; Sacchetti, A.; Silvani, A. *Synthesis* **2006**, 594.
(88) Kormos, C. M.; Leadbeater, N. E. *Synlett* **2006**, 1663.
(89) Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Process Res. Dev.* **2003**, *7*, 707.
(90) Arvela, R. K.; Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Org. Biomol. Chem.* **2003**, *1*, 1119.
(91) Ishibashi, K.; Takahashi, M.; Yokota, Y.; Oshima, K.; Matsubara, S. *Chem. Lett.* **2005**, *34*, 664.
(92) Miyazawa, A.; Tanaka, K.; Sakakura, T.; Tashiro, M.; Tashiro, H.; Prakash, G. K. S.; Olah, G. A. *Chem. Commun.* **2005**, 2104.
(93) Miyazawa, A.; Saitou, K.; Tanaka, K.; Gädda, T. M.; Tashiro, M.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron Lett.* **2006**, *47*, 1437.
(94) Sharma, A.; Kumar, V.; Sinha, A. K. *Adv. Synth. Catal.* **2006**, *348*, 354.
(95) Stockland, R. A., Jr.; Lipman, A. J.; Bawiec, J. A., III; Morrison, P. E.; Guzei, I. A.; Findeis, P. M.; Tamblin, J. F. *J. Organomet. Chem.* **2006**, *691*, 4042.
(96) Martelanc, M.; Kranjc, K.; Polanc, S.; Kočevar, M. *Green Chem.* **2005**, *7*, 737.
(97) Ju, Y.; Varma, R. S. *Green Chem.* **2004**, *6*, 219.
(98) (a) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135. (b) Ju, Y.; Varma, R. S. *Tetrahedron Lett.* **2005**, *46*, 6011. (c) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409.
(99) Barnard, T. M.; Vanier, G. S.; Collins, M. J., Jr. *Org. Process Res. Dev.* **2006**, *10*, 1233.
(100) Westman, J.; Lundin, R. *Synthesis* **2003**, 1025.
(101) Yadav, L. D. S.; Yadav, B. S.; Rai, V. K. *Synthesis* **2006**, 1868.
(102) Peng, Y.; Song, G. *Green Chem.* **2002**, *4*, 349.
(103) For information on the combined microwave/ultrasound instrument, see: Peng, Y.; Song, G. *Green Chem.* **2001**, *3*, 302.
(104) Gellis, A.; Boufatah, N.; Vanelle, P. *Green Chem.* **2006**, *8*, 483.
(105) Molteni, V.; Hamilton, M. M.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. *Synthesis* **2002**, 1669.
(106) Ferro, S.; Rao, A.; Zappalà, M.; Chimirri, A.; Barreca, M. L.; Witvrouw, M.; Debyser, Z.; Monforte, P. *Heterocycles* **2004**, *63*, 2727.
(107) Peng, Y.; Song, G.; Dou, R. *Green Chem.* **2006**, *8*, 573.
(108) Bouillon, C.; Meyer, A.; Vidal, S.; Jochum, A.; Chevolot, Y.; Cloarec, J. P.; Praly, J. P.; Vasseur, J. J.; Morvan, F. *J. Org. Chem.* **2006**, *71*, 4700.
(109) Bryson, T. A.; Stewart, J. J.; Gibson, J. M.; Thomas, P. S.; Berch, J. K. *Green Chem.* **2003**, *5*, 174.
(110) Kidwai, M.; Saxena, S.; Khan, M. K. R.; Thukral, S. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4295.
(111) Öhberg, L.; Westman, J. *Synlett* **2001**, 1296.
(112) Bagley, M. C.; Lubinu, M. C. *Synthesis* **2006**, 1283.
(113) Salehi, H.; Guo, Q. X. *Synth. Commun.* **2004**, *34*, 4349.
(114) Hua, G. P.; Tu, S. J.; Zhu, X. T.; Zhang, X. J.; Xu, J. N.; Zhang, J. P.; Shi, F.; Wang, Q.; Ji, S. J. *Chin. J. Chem.* **2005**, *23*, 1646.
(115) Tu, S.; Zhang, Y.; Zhang, J.; Jiang, B.; Jia, R.; Zhang, J.; Ji, S. *Synlett* **2006**, 2785.
(116) Tu, S. J.; Jiang, B.; Zhang, J. Y.; Jia, R. H.; Zhang, Y.; Yao, C. S. *Org. Biomol. Chem.* **2006**, *4*, 3980.
(117) Tullberg, M.; Grøtli, M.; Luthman, K. *Tetrahedron* **2006**, *62*, 7484.
(118) Carlsson, A. C.; Jam, F.; Tullberg, M.; Pilotti, Å.; Ioannidis, P.; Luthman, K.; Grøtli, M. *Tetrahedron Lett.* **2006**, *47*, 5199.
(119) Mayer, M.; Lang, P. T.; Gerber, S.; Madrid, P. B.; Gómez Pinto, I.; Guy, R. K.; James, T. L. *Chem. Biol.* **2006**, *13*, 993.
(120) Peng, Y.; Dou, R.; Song, G.; Jiang, J. *Synlett* **2005**, 2245.
(121) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001.
(122) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697.
(123) Cherng, Y. J. *Tetrahedron* **2000**, *56*, 8287.
(124) Kaval, N.; Dehaen, W.; Mátyus, P.; Van der Eycken, E. *Green Chem.* **2004**, *6*, 125.
(125) Semple, G.; Skinner, P. J.; Cherrier, M. C.; Webb, P. J.; Sage, C. R.; Tamura, S. Y.; Chen, R.; Richman, J. G.; Connolly, D. T. *J. Med. Chem.* **2006**, *49*, 1227.
(126) Pironti, V.; Colonna, S. *Green Chem.* **2005**, *7*, 43.
(127) Lindsay, K. B.; Pyne, S. G. *Synlett* **2004**, 779.
(128) Xue, F.; Seto, C. T. *Bioorg. Med. Chem.* **2006**, *14*, 8467.
(129) Chen, I. H.; Young, J. N.; Yu, S. J. *Tetrahedron* **2004**, *60*, 11903.

(130) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223.
(131) Kranjc, K.; Kočevar, M.; Iosif, F.; Coman, S. M.; Parvulescu, V. I.; Genin, E.; Genêt, J.-P.; Michelet, V. *Synlett* **2006**, 1075.
(132) Zara, C. L.; Jin, T.; Giguere, R. J. *Synth. Commun.* **2000**, *30*, 2099.
(133) Bagley, M. C.; Jenkins, R. L.; Lubinu, M. C.; Mason, C.; Wood, R. *J. Org. Chem.* **2005**, *70*, 7003.
(134) Raner, K. D.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1995**, *60*, 2456.
(135) Décor, A.; Monse, B.; Martin, M. T.; Chiaroni, A.; Thoret, S.; Guénard, D.; Guéritte, F.; Baudoin, O. *Bioorg. Med. Chem.* **2006**, *14*, 2314.
(136) Pourjavadi, A.; Mirjalili, B. F. *J. Chem. Res. (S)* **1999**, 562.
(137) Reyes, S.; Burgess, K. *J. Org. Chem.* **2006**, *71*, 2507.
(138) Ericsson, C.; Engman, L. *J. Org. Chem.* **2004**, *69*, 5143.
(139) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674.
(140) Vasudevan, A.; Verzal, M. K. *Synlett* **2004**, 631.
(141) Lee, J. C.; Yoo, E. S.; Park, J. Y. *Bull Korean Chem. Soc.* **2004**, *25*, 1457.
(142) Quesada, E.; Taylor, R. J. K. *Synthesis* **2005**, 3193.
(143) Soh, C. H.; Chui, W. K.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 464.
(144) Klán, P.; Cirkva V. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 19, p 860.
(145) Müller, P.; Loupy, A.; Klán, P. *J. Photochem. Photobiol., A* **2005**, *172*, 146.
(146) Kormos, C. M.; Leadbeater, N. E. *Tetrahedron* **2006**, *62*, 4728.
(147) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505.
(148) Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1996**, *61*, 7355.
(149) Stadler, A.; Pichler, S.; Horeis, G.; Kappe, C. O. *Tetrahedron* **2002**, *58*, 3177.

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