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New Microwave-Promoted Synthesis of Heterocyclic Derivatives without Added Metal Catalysts

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Abstract

Abstract. *New Microwave-Promoted Synthesis of Heterocyclic Derivatives without Added Metal Catalysts*

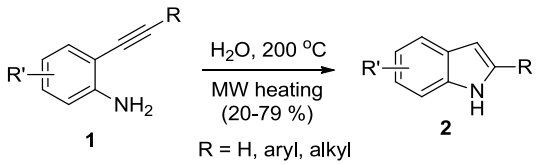
The indole ring system is a structural component of a vast number of biologically active natural and unnatural compounds and it can be found in many pharmaceutical agents. The synthesis and functionalization of indoles have been a major area of focus for synthetic organic chemists and numerous methods have been developed. Among the many described approaches, the cyclization reaction of both *N*-substituted and *N*-unsubstituted-2-alkynylaniline derivatives is a major procedure for the construction 2,3-disubstituted and 2-substituted indoles.

In fact, there is the significant advantage of ready availability of the starting 2-alkynylanilines which can be prepared easily by Sonogashira-type alkynylation from a large variety of commercially available substrates. Typically, the cyclization is achieved using strong bases (like metal alkoxides, metal hydrides and metal amides) or transition metals. However, most of the cited methods require the use of moisture sensitive bases, harsh or strongly basic conditions which are incompatible with a wide range of functional groups. As regards the use of transition metals, the cyclization of 2-alkynylanilines and 2-alkynylanilides typically takes place in the presence of catalytic amounts of Pd(II) salts or Pd(0) complexes, stoichiometric or catalytic Cu(I) and Cu(II) salts or complexes, and catalytic Au(III) salts. In addition, also the use of platinum, molybdenum, iridium, rhodium, zinc, mercury, iron and indium have been recently described for preparing substituted indoles. Nonetheless, only a small number of these methods deal with *N*-un-protected 2-alkynylanilines, which cyclize in the presence of expensive metal-sources and/or with high catalyst loadings, with the additional drawback of potential metal-contamination of the products.

Curiously, a very few examples describe the application of microwave irradiation in this type of cyclization. On the other hand, the need for cleaner and more benign processes is becoming ever more urgent. In this novel perception, reactions conducted in aqueous

media as well as the application of microwaves for reaction mixtures heating have been receiving increasing attention. Recently, microwave irradiation was applied with significant advantages in heterocyclic synthesis, allowing to reach quickly higher temperatures and to obtain faster reactions than by conventional heating. Particularly worthy of note are synthetic organic reactions run in water and under superheated conditions. An interesting example is represented by the hydration of terminal alkynes in superheated water at 200 °C under microwave irradiation described by Vasudevan et al. In 2006 Alami and coworkers expanded the scope of hydration of alkynes and demonstrated the positive effect of microwave heating toward the hydration of arylalkynes, diarylalkynes as well as arylpropargylic alcohols performed in ethanol with *p*-toluenesulfonic acid. Recently, the same authors showed that this methodology can successfully afford 2-arylsubstituted benzofurans and benzothiophenes from diarylalkynes.

Bearing in mind all these considerations, we put forward the idea that a microwave-assisted cycloisomerization of 2-alkynylanilines, taking place *via* an intramolecular hydroamination, might be a feasible way to prepare substituted indoles. In particular, we wanted to explore the use of water as solvent and apply microwave irradiation to reach the water "near critical" region. Our investigations demonstrated that 1*H*-indole and 2-substituted indoles can be obtained by a straightforward methodology which involved a microwave-promoted cycloisomerization in water, taking place *via* intramolecular hydroamination of the corresponding 2-alkynylanilines. The cyclization proceeded without any additive, either acid or basic, and without any added metal catalyst.



For the preparation of the required alkyne substrates without significant metal-contamination, we developed during this Doctorate Thesis an *ad hoc* efficient copper-free Sonogashira protocol with Pd EnCat^{TM} catalysts. The products were obtained with Pd

contents lower than 0.1 ppm by AAS. In order to avoid potential metal contaminants during the cyclization, we used ACS UltraTrace water, where most common transition and non transition metals are present at a 10^{-5} ppm level.

Moderate to good yields were achieved for a variety of substrates, however, the methodology presented clear limitations especially in terms of applicability. In fact, if high yields were obtained for compounds bearing electron-donating substituents, the introduction of electron-withdrawing groups caused a significant decrease in yields. Moreover, when we tried to increase the concentration of the substrates above 0.1 mmol/ml, the yield dropped in most cases, and, after significant efforts, it appeared clear that a further improvement of these conditions was not straightforward.

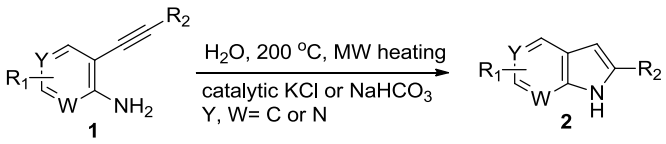
In the search for more efficient cyclization conditions, with the aim of developing a more general method suitable for higher substrate loadings and for diversified starting materials, we tried to find species that, if added to water, could help the cyclization, enhance the interaction of the substrates with microwaves and/or possibly increase the solubility in water of the less reactive substrates.

Our first intent was to explore the effect of the addition of inorganic salts. Our idea arose from the well known principle that microwave absorbance of water is improved by the addition of inorganic salts. Thus, we screened neutral, basic and acid salts as additives, and eventually demonstrated that even catalytic amounts facilitated the cycloisomerization. Moreover, the use of aqueous salt solutions proved extremely effective to overcome limitation encountered in terms of low substrate loading.

However, the presence of the salt, even if beneficial for the yield, was accompanied by a significant increase of the pressure which was developed during the heating to 200 °C inside the reaction vials. In our equipment, this caused leakages from the reaction caps with loss of water and compounds, especially at the higher substrate concentrations. The application of short cycles of microwave-heating circumvented the problem and provided

the same irradiation times in conditions less stressful for the equipment (reaction vials are cooled and de-pressurized between one cycle of heating and the other).

The reactivity of different substrates was studied and we were able to show that differently substituted indoles and azaindoles could be prepared by microwave-promoted cycloisomerization of 2-alkynylanilines and alkynylpyridinamines in water, expedited by the use of catalytic amounts of inorganic salts such as KCl and $NaHCO_3$.



We obtained good to very good yields for a variety of both electron-rich and electron-poor substrates, even bearing labile functional groups. In some instances, also the addition of 1 or 2 equiv of pyrrolidine instead of the salt gave good yields.

In conclusion, the ambitious objectives we fixed at the beginning of this work were thus reached, since we developed efficient procedures for the cycloisomerization to (aza)indole derivatives. We even collected data obtained under thermal heating conditions, to show that microwave heating was necessary to obtain significant yields in short reaction times.

As a natural extension of our studies, we were interested in verifying the behaviour of *N*-protected anilines and pyridinamines in the cycloisomerization to (aza)indoles, since these substrates are described as being more reactive in such reactions. Moreover, a further expansion would be represented by the inclusion of oxygen- or sulfur-bearing substrates, and, in particular, (2-methoxyaryl)alkynes and/or (2-carboxylaryl)alkynes. Unfortunately, our work program could not be extended enough to include in-depth experimental data sets acquisition within the deadlines established for this Doctorate Thesis. As a consequence, only preliminary results could be collected.

Chapter 1

Introduction to microwaves in organic synthesis

1.1 A short introduction to microwaves

In recent years, microwave-assisted organic synthesis has developed into an established tool both for academic and industrial chemists. The growing interest in this new technology has been highlighted by a dramatic increase in the number of publications in this area.[1,2] The driving force has been the remarkable rate acceleration observed in many reactions heated using microwave irradiation instead of conventional heating, frequently accompanied by increased yields and diminished side-product formation. Not surprisingly, the adoption of microwave technology has been most widespread in areas where time savings are most valued, in particular within the pharmaceutical industry.

It is enough to mention that the consumption of energy for heating and cooling, which represents a major adverse effect to the environment in many chemical processes, could be overcome through the development of efficient methods which make use of alternative energy sources, such as microwave irradiation, to facilitate chemical reactions. A recent study compared the energy efficiency of conventional oil bath synthesis (heating by conduction and convection currents) to microwave-assisted synthesis (direct "molecular" heating of the reaction mixture). The outcome was 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.[3] Moreover, early indications from studies on multigram scale microwave reactions are promising, especially with the observation that conditions are directly scalable and do not require significant re-optimisation upon scale-up (for additional considerations and bibliography, see following paragraph 1.2.3).

In addition, the growing importance of microwave-assisted synthesis is well in accordance with the principles of green chemistry, an area under paramount development in recent years. In particular, the aim of green chemistry is to perform clean organic reactions under conditions which reduce the use of toxic reagents, solvents and wastes, and maximize, where possible, the use of aqueous environments and of solvent-free processes. A more detailed and referenced discussion on the use of water in microwave-assisted

reactions will be presented in paragraph 1.3.1, while solvent-free processes will be commented on and referenced in paragraph 1.3.2.

1.1.1 General characteristics of the interaction between microwaves and matter[1,2]

Microwaves represent only a small part of the electromagnetic spectrum, and are conventionally described as electromagnetic waves with wavelengths ranging between 1 mm and 1 m, with corresponding frequencies set between 300 GHz and 0.3 GHz. However, microwaves display some singular characteristics that determine their interaction with matter and enable their application to organic synthesis. In fact, reaction mixtures which contain at least one component that is able to interact with microwaves are rapidly heated, as the radiation is applied, with a much faster temperature increase than with conventional heating. Moreover, since different interactions exist between microwaves and different materials, there is also the possibility of creating a differential heating. As a result, microwave energy is directly delivered to the reaction mixture, without any heating of the vessel walls (typically made of quartz glass, which is nearly transparent to microwaves). Furthermore, heat is not primarily spread by convection and other heat transport phenomena, as it happens for conventional heating, where walls are heated first and then heat moves to the inner parts of the reaction mixture. Instead, microwaves generate heat *in situ* and quite homogeneously throughout the reaction mixture. Therefore, at least in principle, changed reaction profiles, selectivity, and reaction times could be expected. As a part of the electromagnetic spectrum, microwaves are composed of two field components, the electric and the magnetic one. The electric component is important for the purpose of heating, as it results in a force being applied to all the polar or charged molecules. Those molecules, in response to the oscillating electric field, start to move or rotate and cause additional polarization of the neighbouring polar molecules. The frequency selected for

general customer applications (including dedicated, synthetic microwave instruments) is 2.45 GHz, corresponding to a wavelength of 12.25 cm.

1.1.2 Microwave heating mechanisms[1,2]

In general, when matter interacts with microwaves, three different heating mechanisms[1,2] are encountered: *(i)* dielectric (dipolar) heating caused by dipole rotation, *(ii)* ionic conduction, and *(iii)* resistance heating.

(i) Dielectric (dipolar) heating. Assemblies of polar molecules (such as those encountered in typical reaction mixtures), which represent dipoles, cannot respond to the change in the orientation of the electric component of the microwave radiation sufficiently quickly. As a result, when dipoles try to re-orient themselves following the field direction changes, a phase difference develops. This dipole movement generates heat as a result of molecular friction and dielectric losses with a consequent temperature increase. This heating mechanism is generally known as dielectric (or dipolar) heating. The energy of the microwave radiation is transferred to the medium and the electric energy is converted into thermal (and kinetic) energy. Also, matter physical properties profoundly affect its ability to heat with microwaves. For example, ice is approximately 180 times less susceptible to microwave heating than water, which means it is essentially microwave transparent. It is also obvious why polar molecules in the gaseous phase cannot be heated with microwave irradiation.

(ii) Ionic conduction. The second relevant heating mechanism *via* microwave irradiation is the so-called ionic conduction mechanism. When charged particles (ions) in a solution are subjected to the electric component of a microwave radiation, they start to move in a back-and-forth fashion, following the movement of the electric field. During such movements, charged particles collide with neighbouring particles (charged or neutral) and such collisions create heat. This mechanism nicely illustrates the heating differences between distilled and tap water, the latter warming up much faster under otherwise identical

conditions. It is also important to point out that the ability to generate heat is much greater *via* ionic conduction than *via* dielectric heating.

(iii) Resistance heating. The third mechanism is only encountered in strongly conducting materials, such as metals and semiconductors. When a material possessing loosely bonded electrons is irradiated with microwaves, the electrons start to flow like an electric current, generating heat because of the material resistance. This mechanism is important when elementary metals (in the form of thin foils or films), graphite supports or passive heating elements (made of silicon carbide) are employed during a synthesis. On the other hand, larger metal parts reflect most of the microwave energy and thus do not tend to heat up.

According to the microwave heating mechanisms described above, the dielectric properties of the material in use are of paramount importance. Three different properties, combined together, describe well the ability of a material to be heated under the effect of microwave irradiation. The first is the relative permittivity (ε'), which describes the aptitude of a molecule (or an assembly of molecules on a macroscopic level) to be polarized by the application of an electric field. The other property is the dielectric loss (ε''), which describes the capacity of a material to convert dielectric energy into heat. For approximate chemical applications, if we combine the two values into a single equation, a new property is obtained, the so-called dielectric loss tangent ($\tan \delta = \varepsilon''/\varepsilon'$). At low values, $\tan \delta$ corresponds well to the ability of a bulk material to convert the energy of the electromagnetic field into thermal energy. Even though $\tan \delta$ is a valuable parameter for comparing the heating rates of a series of substances with comparable chemical and physical characteristics (with similar ε'), a more general and refined approach exists which includes the electric field pattern, the heat capacity of the compound, its density, viscosity, *etc*. However, being a general property of each material, $\tan \delta$ includes two factors: the polarity, *i.e.*, how efficiently the material will absorb the microwaves, and the ability of the material to transform the absorbed microwave energy into heat. Very polar materials may

not be very efficient in transforming the absorbed microwave energy into heat, but may absorb microwave energy well. Therefore, it is not surprising that for water heat up a higher microwave power is required than the less polar ethanol. Moreover, ε' decreases for pure water when the microwave frequency increases, whereas ε'' grows. As a consequence, the addition to water of an ionic electrolyte, like NaCl, significantly increases tan δ at 2.45 GHz, whereas at other frequencies the change is negligible.[4] It is also important to stress that ε' and ε'', and thus tan δ, depend on the temperature. Water can be heated relatively rapidly under microwaves; however, in its supercritical state (at 374 °C) tan δ decreases so much that becomes nearly microwave transparent.

1.1.3 Penetration depth[1,2]

Another important factor pertaining to microwave irradiation heating is the penetration depth, which represents a considerably limiting factor when trying to scale up microwave-assisted synthesis. The penetration depth is defined as the depth at which the energy of the microwave irradiation decreases to 1/e of its initial value and depends on tan δ and on the frequency of the microwave irradiation. Materials with large tan δ offer relatively short penetration depths and represent significant obstacles, especially with regard to those materials that are well heated by microwave irradiation. As an example, for pure water the penetration depth of microwave irradiation at a frequency of 3 GHz is around 1.4 cm at 25 °C and 5.7 cm at 95 °C. The importance of the penetration depth will be further discussed in paragraph 1.2.3 when the issues related to the scale−up of microwave-assisted processes are specifically presented.

1.1.4 Microwave effects[1,2,5]

The problems associated with reaction temperature measuring (see also paragraph 1.2.1) show how troublesome it is to compare and evaluate the results obtained with different microwave reactors, not to mention the older results produced in domestic

microwave ovens. The consequence is a still on-going debate about the various effects that are (or might be) responsible for the results obtained under microwave irradiation, especially when different results are obtained for the same reaction conducted under conventional heating.

In general, the effects observed when microwaves are applied to heat up a reaction mixture can be distinguished between *(i)* ***thermal***, *(ii)* ***specific*** and *(iii)* ***non-thermal microwave effects***.[5] From the very beginning of microwave irradiation application to organic synthesis, some authors have observed rate accelerations and different selectivity when compared to conventional heating. A possible explanation for this has included the so-called *specific* and *non-thermal* microwave effects. Such effects were invoked when the results of a reaction conducted under microwave irradiation were different from those obtained under conventional heating for the same measured reaction temperature. However, today, it is clear that in the majority of cases, the discrepancies were a mere consequence of inaccurate temperature measurements, the differences purely owed to thermal effects. The most notable specific effects are: *i*) the superheating effects of the solvents in open vessels; *ii)* the selective heating of more polar molecules in homogeneous or heterogeneous mixtures; *iii)* the inversed thermal flux through the wall of the reaction vessel and the consequent elimination of wall effects; *iv)* the volumetric *in-situ* heating, *i.e.*, the rapid and homogeneous heating of the whole reaction mixture. A large influence is also played by the heterogeneity of the reaction mixtures, leading to specific interactions on solid-liquid interface, and consequently to enhanced reaction rates.[6] All the other effects are often called *non-thermal* microwave effects. Reported studies show that rotationally excited diatomic molecules experience altered statistics of collision with other molecules upon microwave irradiation and also support the existence of a microwave catalytic effect, as verified through a computer simulation of a realistic chemical reaction.[7] Moreover, further reports argued that the presence of an electric field leads to orientation effect of dipolar molecules and thus changes the pre-exponential factor A[8] or the activation energy[9] in the Arrhenius equation. Furthermore, such an effect should be mostly observed for polar

reaction mechanisms where the polarity is increased going from the ground state to the transition state, resulting in an enhancement of reactivity through a lowering of the activation energy. A recent study by Loupy and co-workers illustrates this point.[2f,5a,10] The application of the technique of simultaneous cooling during the irradiation of the reaction mixture with microwaves ("cooling while heating") proved helpful to study the possible existence of non-thermal microwave effects, because it enables researchers to compare microwave-assisted reactions run at different power settings, this being more reliable than comparing microwave-assisted reactions with those executed under conventional heating.[11] When "cooling while heating" technique is applied, the reaction is cooled from the outside with compressed air, while being irradiated by microwaves. This allows a higher level of microwave power to be administered directly to the reaction mixture, but prevents over-heating by continuously removing latent heat. The more power is applied, the higher will be the "instantaneous" temperature, relative to the measured bulk temperature.[1c] However, care must be taken not to misinterpret the results coming from the simultaneous cooling approach. In fact, unless an internal probe is used (the more useful one being the fiber-optic probe), the actual reaction temperature is not known. In fact, the compressed air supplied to cool the vessel will interfere with a standard external IP pyrometer, which only provides a measure of the vessel surface temperature[5c,11a] (see following section 1.2.1 for details on temperature measure techniques).

1.2 Equipments for microwave-assisted reactions

All microwave equipments contain a source of microwave irradiation, which in most cases is a magnetron. The microwave irradiation produced is then transmitted *via* a waveguide into the resonant cavity in which the reaction vessel is placed. The waveguides are, in general, metal tubes with a circular or rectangular cross-section. The microwave electromagnetic waves then travel through the waveguide as alternating electric and magnetic fields. When the microwaves enter the waveguide, many different modes can be excited. However, only modes above the cut-off, which depends on the dimension and the shape of the waveguide, can be attenuated at a short distance typical for the microwave equipment. There are also an infinite number of different possible modes in the cavity; however, with a careful choice of geometry and size, single- or multi-mode cavities can be obtained.

When microwaves reach the end of the waveguide and enter into the cavity where the reaction vessel is positioned, oblique microwaves are reflected back toward their source (reflected waves), while the incident waves reach the reaction vessel. The microwave equipment should be designed to minimize the quantity of reflected waves, in order to ensure that the most part of the microwave irradiation is transmitted into the reaction vessel. To achieve this, the resonant frequency of the cavity, together with the reaction vessel (and its contents), should be similar to the frequency of the microwave irradiation (*i.e.*, 2.45 GHz). If this is not the case, the reflected microwaves could travel back to the source and damage the magnetron.

The electric field pattern of microwaves inside the cavity can be extremely complex, with higher and lower energy spots. In multi-mode instruments microwave energy homogeneity is achieved by special rotating prisms. However, the use of single-mode cavities is preferred for laboratory applications, since the position of the sample is well-defined and at the exact spot where the electric field strength is at its maximum. Nevertheless, the design of single-mode cavities is more complicated and, consequently, this type of equipment is

more expensive. The most obvious difference between the two systems is that in single-mode just one reaction vessel at a time can be irradiated, whereas in multi-mode systems, at least generally, more reaction vessels can be irradiated at the same time with the help of rotors. Notably, there are also efforts among researchers to combine the advantages of single-mode and multi-mode instruments in one microwave device.[12]

These dedicated microwave reactors should include precise temperature and pressure monitoring, various safety features with regard to over-heating or the generation of excessive pressure in the case of closed reaction vessels, the possibility of stirring and of rapid cooling after the reaction is completed, the interactive change of operating parameters, various levels of automation, *etc*. All these and many other characteristics can be found in the equipments available on the market.

1.2.1 Temperature measuring in microwave equipment

Temperature measure is the most important issue in microwave-assisted reactions.[5c] Classical thermometers are not suitable, as their fillings (mercury, alcohol) interact with microwaves and therefore do not operate correctly. Metal-based thermocouples are also inappropriate. Generally, one of the two possibilities is used, *i.e.*, external infrared sensors or internal fiber-optic sensors.[1]

(i) External infrared temperature sensors. Modern microwave systems intended for laboratory use most often include a calibrated external infrared sensor integrated into the cavity as the temperature-measuring device. Such sensors detect the surface temperature of the reaction vessel (either from the bottom or from the side of the vessel) and are normally inexpensive. However, they can introduce a systematic error as they measure a somewhat lower temperature than the reaction mixture temperature. Their operation range is, in general, between −40 °C and 400 °C.

(ii) Internal fiber-optic temperature sensors. This second option is more accurate, but also far more expensive. Fiber-optic sensors also have a slightly narrower operating range

(between 0 °C and 300 °C), suffer from a permanent aging phenomenon (already after a few hours at 250 °C), are mechanically very sensitive, and are therefore not usually practical for routine use.

1.2.2 Open *versus* closed vessels

When starting a microwave-assisted reaction, there is the possibility to choose between open- and closed-vessel protocols.[13] The open-vessel protocol, where the maximum temperature achievable is limited by the boiling point of the reaction mixture, is closer to the conventional reflux conditions in an oil bath. However, with microwave irradiation the final reflux temperature can be reached faster. In certain cases, the open-vessel procedure might be the best choice since it enables the simultaneous removal of volatile side products, thus providing a driving force for the reaction completion.[14] For the other possibility, it is necessary to use dedicated closed-vessel equipment with a pressure-monitoring facility. Closed-vessel protocols are the most common ways to perform microwave-assisted reactions as the operating temperatures are far above the boiling point of the reaction mixture. Moreover, rate increases are much higher than with open vessels. However, closed vessels are in general smaller and might represent a safety hazard, especially when employed on a larger scale.

1.2.3 Scale up of microwave-assisted reactions[15]

An important issue pertaining to microwave-assisted reactions is related to the process scale-up. Regarding the relatively shallow penetration depth (as already discussed in section 1.1.3), a direct scale-up into larger volume reaction vessels would not be practical and efficient, unless special and dedicated equipments were designed. Therefore, other options were proposed, like parallel reactors and flow-through systems.

Leadbeater and coworkers[15c,d,f] evaluated a large range of reaction classes in parallel (batch) open and closed reactors. They found that open reactors are applicable in most

cases, unless particularly volatile or toxic reagents are used, in which case closed reactors are preferable. They also proved that continuous-flow processes are suitable and that the homogeneity of the reaction mixture is of crucial importance. Moreover, during some very recent experiments made with a prototype microwave unit designed by AccelBeam Synthesis, Leadbeater and coll. demonstrated that reactions from 2000 to 12000 ml can be run in a single batch.[15c] The authors claim the unit will be commercially available soon with three interchangeable reaction glass vessels of 5, 9 and 13 L capacity (working volumes of 2–4 L, 4–8 L and 7–12 L, respectively). The desired reaction vessel is placed in a mechanically sealed stainless steel chamber which is pressurized to 250–300 psi (17.2–20.7 bar) by nitrogen *via* a high pressure cylinder. Three 2.45 GHz water-cooled magnetrons supply the reactor with a total maximum power of 7.5 kW. Parameters such as reaction time, temperature, pressure and magnetron power are monitored and collected. To check the effectiveness of the magnetron, the authors tested a selection of solvents under microwave heating by using the 5 L vessel, clearly expecting that, while DMSO, DMF, EtOH would heat well, DCM or THF, that interact poorly with microwave, would require significantly more power input to reach elevate temperatures. Quite surprisingly, however, solvent regarded as "poor" microwave absorbers performed best in their study, while "good" solvents for microwave chemistry took more time to heat up (*e.g.*, 4 L of DCM, ACN and THF reached 150 °C in around 4 minutes, 4 L of EtOH took almost 6 minutes and 4 L of water over 9 minutes). In fact, the depth to which microwave energy can penetrate the contents of the vessel is different at larger scales, and this observation explains the reason why less absorbent solvents such as DCM or THF have a larger cross-section that is absorbing microwave energy, as compared to more absorbing solvents such as water or ethanol. Hence, the authors conclude that microwave absorption and heating cross section are interlinked and inversely proportional and that, with efficient stirring and properly sized magnetrons, it should be possible to design batch reactors capable of effectively heating reactions on significantly large scales. A range of reactions was tested

successfully inside the unit, which proved a promising prototype tool for the development of kilo-scale microwave chemistry.

The group of Kappe recently reported[15a,16a] a high-temperature organic reaction under continuous-flow conditions in a stainless steel, microtubular flow reactor, capable of achieving temperatures of 350 °C and pressures up to 200 bar. Such extreme reaction conditions enabled the authors to efficiently conduct transformations that are otherwise carried out in high-boiling point solvents at reflux temperatures (or in sealed vessels) in a flow-through regime by using low-boiling point solvents at, or near, their supercritical conditions. Furthermore, the same authors showed that the heterogeneous hydrogenation of substituted pyridines can be accomplished by a continuous-flow hydrogenation device that incorporates *in-situ* hydrogen generation (*via* the electrolysis of water) and a pre-packed catalyst.[16b] However, the authors stressed that, because catalyst loadings and hydrogen pressures are vastly different between microwave batch and flow hydrogenations, a direct comparison is not feasible.

In spite of all the above-mentioned activity in the field of scale-up, there is still no general solution for large scale microwave synthesis. At the present time, none of the three strategies that have evolved for scale-up (batch, stop-flow, and continuous flow) offers solutions to all the scale-up-related problems that chemists face. For a microwave batch reactor, the penetration depth is still a limiting factor, and the reaction volume of commercially available microwave reactors does not exceed the 1-2 L range. With regard to a stop-flow or continuous flow regime, the handling of suspensions and precipitating products which may block the lines and valves, is still a severe limitation that hinders the broad use of these tools for the scale-up of organic reactions.

1.3 Selection of the appropriate solvent

It is a noticeable trend in organic synthesis to change the reaction protocols to fulfil as many as possible of the "twelve principles of green chemistry".[17] One of these is to use safer solvents and reaction conditions.[2h,18] In many cases microwave-assisted conditions allow the replacement of a conventional solvent, which is typically toxic, with a more benign one, simplifying, in addition, isolation procedures and increasing yields. In connection with this, as it is already introduced in section 1.1, it is beneficial to use water or another green reaction medium or to work under solvent-free conditions.

1.3.1 Water as a solvent of choice in microwave-assisted reactions

Water offers many advantages, since it is non toxic, non flammable, readily available and very cheap and hence it has attracted great interest as a solvent for organic reactions.[19] In fact, it retains unique reactivity and selectivity, exploiting, for example, the so-called hydrophobic effects.[19a,b,e] In particular, significant advantages have been observed in this area, since the selectivity of synthetic organic reactions run in water can be directed through the interaction of non-polar, and since hydrophobic, regions of the reactants. In organic solvents, these forces are normally too weak to compete with any steric and electronic effects. In water, on the other hand, hydrophobic surfaces associate strongly as a result of its tendency to exclude non-polar species and thus minimize the Gibbs energy of solvation, a phenomenon known as the hydrophobic effect. It is important to stress that for an efficient chemical transformation, the solubility of the reactants in water is not a prerequisite for its successful use in synthesis.

There are many recent examples of efficient microwave-assisted syntheses performed in aqueous media.[20] In particular, homogeneous and heterogeneous transition metal-catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions represent one of the most important reaction types performed under microwaves assistance.[21] Hence, Suzuki, Heck, Sonogashira, Stille and Hiyama reactions have been conducted with the application of

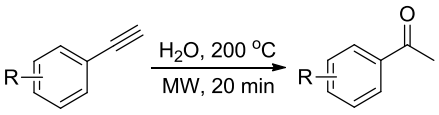
microwaves and in water as a solvent. Also in the field of heterocycle synthesis a large variety of conditions are described in the literature.[22]

Water in the near critical region deserves a particular discussion in organic synthesis.[23] In fact, when water is heated to temperatures in the range of 200–300 °C, favourable changes occur in its chemical and physical properties.[24] The dielectric constant drops rapidly from 78 at 25 °C to 20 at 275 °C, while its density goes from 1 to 0.7 g/cm^3, values typical for most organic solvents at ambient temperature, thus allowing the dissolution of many organic molecules. Most importantly, its ionic product changes as a function of the temperature reaching a maximum near 250 °C and resulting in a three-fold increase between 25 and 250 °C. Not surprisingly, we found that acid- or base-catalyzed reactions can be performed without the addition of extra acids or bases.[23b] Moreover, the need for post reaction neutralization is skipped, as well as the extraction/isolation procedure, since a facile separation of the organic products from water is possible due to the natural phase separation which occurs upon cooling from the reaction temperature to the ambient conditions.

The majority of microwave-assisted organic reactions today are performed in single-mode reactors, which have a pressure limit of 20 bar, thereby limiting the reaction temperature for water as a solvent to 200-220 °C. Moreover, since water dielectric constant drastically decreases with temperature, the dielectric loss ε'' and therefore the loss tangent are also reduced.[4] For that reason it is not easy 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 under microwave dielectric heating.[23a] However, the use of dedicated multi-mode reactors reported by Kappe[23a] allows the investigation of a variety of transformations to study the general feasibility of microwave-assisted near-critical water chemistry in the temperature range between 200 and 300 °C. In addition, it is well known that the dielectric loss of a solvent like water can be significantly increased by

the addition of small amounts of inorganic salts[4,23a] and that relatively low salt concentrations (0.03 M–0.001 M) are able to improve microwave absorbance by ionic conduction. It should also be stressed that the above-mentioned problems associated with the use of water as a solvent in microwave-assisted reactions are only experienced under high dilution conditions and/or in the high temperature region (> 200 °C), where an 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.

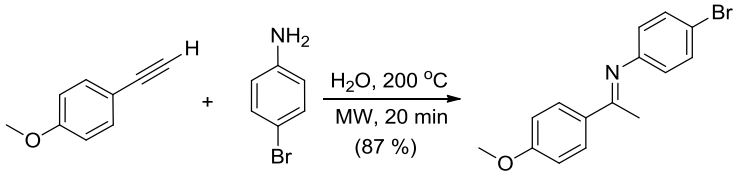
A very interesting example of synthetic organic reactions run in water and under superheated conditions is represented by the hydration of terminal alkynes in superheated water at 200 °C under microwave irradiation described by Vasudevan *et al.* in 2004.[25] Alkynes containing both electron-withdrawing and electron-donating groups were examined and proved able to afford the corresponding acetophenones with moderate to good yields, as reported in Scheme 1.



R	Yield %
4-OMe	94
2-OMe	100
4-NH_2	96
H	75
3-OH	12
4-OEt	27
3-NH_2	90
4-Cl	20
4-Me	98
4-Br	—

Scheme 1. MW-assisted hydration of terminal alkynes in superheated water.

In the same paper the authors present a very interesting example of intermolecular hydroamination run under the same conditions, thus demonstrating that terminal alkynes undergo hydroamination when heated in water alone and in the absence of any catalyst (Scheme 2).



Scheme 2

1.3.2 Solvent-free conditions, phase-transfer catalysis, ionic liquids and PEG

The combination of solvent-free reaction conditions and microwave irradiation was often used as an eco-friendly approach for the synthesis of a variety of products, since it generally offered a number of advantages such as large reductions in reaction times, enhancements of conversions, changes in selectivity, *etc*.[26a,b] In fact, solvent-free methods offer the advantages of an enhancement of reactivity because of increased concentrations, and of a specific selectivity, because of restricted mobility. Moreover, environmentally benign synthesis could be easily designed, without using large volumes of solvents, with considerably simplified work-up procedures and shortened reaction times. In particular, the use of "dry media" as solid supports in solvent-free processes is particularly interesting, since many mineral oxides are poor heat conductors, yet good microwave absorbents. These recyclable solid supports (*e.g.* silica, alumina, clays, zeolites, *etc.*) can be acidic or basic and thus represent useful replacements to mineral acids and oxidants.[1]

There are three main types of solvent-free reactions: *(i) reaction mixtures adsorbed on a solid support* (dry media),[27] *(ii) neat reactions*, where liquid or solid reagents are used directly without dilution or any solid support and *(iii) phase-transfer catalysis* under certain

conditions.[26c] There is an extensive amount of research on microwave-assisted, solvent-free reactions in numerous areas, including oxidations, reductions, condensations, bond cleavages, rearrangements, cycloadditions, protections, deprotections, *etc*.[1,2] However, even though reactions under solvent-free conditions have good potentials and are environmentally benign, nonetheless solvents might be necessary during the isolation steps. Moreover, neat reaction conditions are sometimes accompanied by a problem observed when one of the reactants is prone to sublimation at the reaction temperature and therefore tends to deposit on the upper, colder parts of the reaction vessel, thus becoming unavailable for the reaction. To avoid the use of unnecessarily large excesses of such reactants, it was shown that in such cases the addition of a small amount of an appropriate liquid (typically 1-butanol or toluene) that acts as a rinsing agent can prove very beneficial.

It is also of interest to note that solvent-free conditions are especially appropriate for observing specific microwave effects (and non-thermal microwave effects, if they exist), as they allow the greatest interactions between microwaves and materials, without any detrimental solvent absorption. Polar solvents should be avoided for such purposes, because they absorb microwaves and could mask specific microwave effects. On the other hand, non-polar solvents, which are more or less transparent to microwaves, are also applicable for the potential observation of specific microwave effects.

Finally, we will only mention, without discussing in details, other alternative green-reaction media, like poly(ethylene glycol) and ionic liquids, which have attracted interest as novel solvents in catalytic processes and in many microwave-assisted reactions.[1,2,28]

1.4 Setting our objectives

A primary driver of pharmaceutical green chemistry is the development of efficient and environmentally benign synthetic protocols. As we already highlighted in the previous sections, there are many examples of the successful application of green chemistry to drug discovery. These include *i)* the use of alternative heating systems such as microwave irradiation, *ii)* the use of water as a reaction medium, and *iii)* the application of solid-supported, reusable catalysts.

The advent of microwave technology enabled organic and medicinal chemists to accelerate both synthesis and screening of substances in order to generate diverse arrays of complex targets in short periods of time. In particular, microwave-induced heterocyclic chemistry has been extensively examined in the preparation of different classes of compounds of considerable interest for the pharmaceutical industry, like indoles, azaindoles, furans, benzofurans, pyridines, furopyridines, thiophenes, pyrazines, pyrrolopyrazines, imidazoles, pyrazoles, pyrazolopyrimidines, phtalides and isocoumarins.[1,22] Often heterocyclic synthesis, which requires harsh conditions, high temperature and long reaction times, can take advantage of microwave irradiation to easily reach higher temperatures than conventional heating and to implement less stressful conditions which could be applied also to compounds with lower stability. Frequently, in fact, suppressed formation of side-products and improved yields have been observed under microwave heating conditions.

Moreover, in this scenario, water plays a considerable role as an alternative benign solvent and has found a wide range of application in microwave-assisted heterocyclic synthesis. Its significance in microwave-assisted reaction has been extensively discussed in section 1.3.1. In virtue of its characteristics, the use of water will be an important feature in our research program.

1.4.1 Synthesis of heterocycles *via* heterofunctionalization of alkynes: our objectives

The carbon-carbon triple bond is among the most important functional groups in organic chemistry and has been used extensively in the production of functionalized molecules.[29] In particular, the synthesis of heterocycles *via* heteroannulation of alkynyl derivatives represents one of the most efficient and best described methodologies[30] since a variety of functionalized starting materials are available and can be obtained typically *via* a Sonogashira approach (Figure 1).

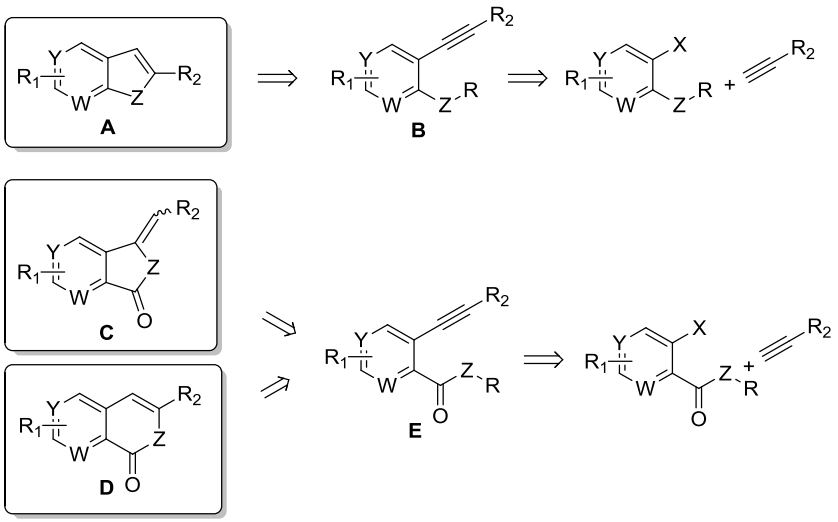
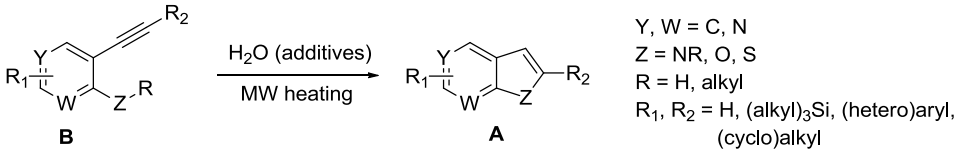


Figure 1. Retrosynthetic approach to heterocyclic compounds A, C and D.

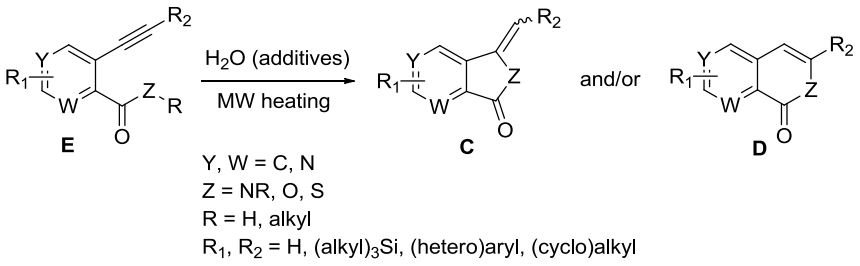
As a primary objective of this Doctorate Thesis, we have identified the feasibility assessment of microwave-assisted heterocyclic synthesis *via* cyclization through hetero-functionalization of alkynes. Moreover, considering the numerous advantages offered by the application of aqueous media and microwave irradiation, we established that water would be our preferred solvent and microwaves our elected way to heat reaction mixtures. In the choice of our starting materials, we mainly focused on simple and readily available (hetero)arylacetylenic derivatives to prepare heterocyclic compounds through simple and

straightforward cyclizations. During our investigations, we would be assessing feasibility, validity, limits, regioselectivity and generalization of this novel carbon-heteroatom bond-forming methodology, with the main purpose to set up very simple reaction conditions, solventless or in water as a solvent, with weakly acidic or basic additives, thus circumventing, if possible, the use of transition metal catalysts and of harsh conditions.

In the broad field of heterocyclic chemistry we identified some general structures of interest, mainly because of their biological activity. In particular, our attention focused on well-known scaffolds like **A**, **C** and **D** depicted in Scheme 3 and Scheme 4, where the conditions of choice for our investigations are reported.



Scheme 3



Scheme 4

It is worth underlining the strong novelty contained in this idea which is, as far as we know, unprecedented for many aspects (like the preparation of indoles and aza-analogues) and not completely explored for others, as it is confirmed by the existence of really limited literature evidence.

In the instance of compounds of general formula **A** in Scheme 3, the cyclization of the corresponding starting materials **B** is typically achieved under basic conditions or by applying transition metal catalysis.[30a] A more detailed analysis of the most commonly

described synthetic methodologies can be found in the following paragraphs 1.4.2.1 and 1.4.2.2, where substituent Z of different type are considered. As for the preparation of compounds of general formula **C** or **D** (Scheme 4), the intramolecular cyclization of enynecarboxylic acids, esters or amides of general formula **E** represents one of the preferred pathways for heterocyclic ring construction. The selectivity of the ring closure, which can generate phtalides (Z = O) or isoindolones (Z = NR) of general formula **C**, and/or isocoumarins (Z = O) or isoquinolinones (Z = NR) of general formula **D**, has been the object of extensive studies. A more detailed analysis including a literature evaluation can be found in the following paragraph 1.4.2.3.

Moreover, as already pointed out, what particularly deserves attention is the general consideration that the cyclization of compounds of general formula **B** and **E** has not been extensively explored with microwave assistance. Only a very small number of examples exist, even if it represents a powerful and well established methodology to obtain heterocyclic derivatives.[30e] What is more, the vast majority of the examples of microwave application show the use of transition metals (typically Cu, Pd salts and complexes) or of strong bases to achieve cyclization, as we will better elucidate in the following paragraphs.

1.4.2 Literature review of heterocyclic synthesis *via* heterofunctionalization of alkynes under microwave heating

In the following sections 1.4.2.1-1.4.2.3 a review of the most relevant examples of microwave-assisted synthesis of heterocycles *via* heteroannulation of alkynes is reported. Notably, the number of publications we could find in the field was rather narrow.

1.4.2.1 Microwave-assisted synthesis of indole and azaindole derivatives *via* cyclization and annulation of alkynes

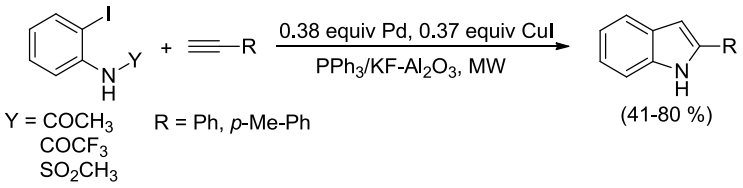
The indole and azaindole ring systems are common moieties in a vast number of biologically active natural and unnatural compounds and in pharmaceutically important molecules.[31] The synthesis and functionalization of (aza)indoles has been a major area of

focus for synthetic organic chemists and numerous methods have been developed. Among the many approaches described for their synthesis and functionalization, the cyclization of 2-alkynylanilines and alkynylpyridinamines represents a major procedure to obtain 2-substituted and 2,3-disubstituted indoles[32] and their aza-analogues[33]. In fact, the starting 2-alkynylanilines and aminopyridines can be easily prepared by a Sonogashira-type alkynylation from a large variety of commercially available substrates.[34] Typically, the cyclization of the alkynes is achieved using strong bases[33e,35] (like metal alkoxides, metal hydrides and metal amides) or transition metal catalysts[32,36-45]. Moreover, most of the cited methods require the use of moisture-sensitive bases, harsh or strong basic conditions which are incompatible with a wide range of functional groups. As regards the use of transition metals, the cyclization of 2-alkynylanilines and 2-alkynylanilides typically takes place in the presence of catalytic amounts of Pd(II) salts or Pd(0) complexes,[32g,36] stoichiometric or catalytic Cu(I) and Cu(II) salts or complexes,[37] and catalytic Au(III) salts[38]. In addition, also the use of platinum,[39] molybdenum,[40] iridium,[41] rhodium,[32f,42] zinc,[43] mercury,[44] iron,[45] and indium,[46] has recently been described for preparing substituted (aza)indoles. Notably, recent but isolated examples of metal-free procedures describe the electrochemical-mediated cyclization of 2-alkynylanilines to indoles[47] and the cyclization of 1-[2-(phenylethynyl)phenyl]urea to form 2-phenylindole in 71 % yield, promoted by 2 equiv of triflic acid in refluxing 1,2-dichloroethane[48].

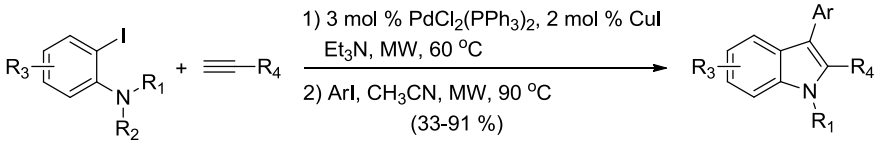
Moreover, it is not negligible that only a small number of these methods deal with *N*-unprotected 2-alkynylanilines or pyridinamines, thus avoiding additional protection/deprotection steps. However, the cyclization occurs in the presence of expensive metal sources and/or with high catalyst loadings, with the additional drawback of potential metal contamination of the products.[36g,h,43a]

As already mentioned in section 1.4.1, a very few examples describe the application of microwave irradiation in this type of cyclization[49] and, anyway, the majority of them

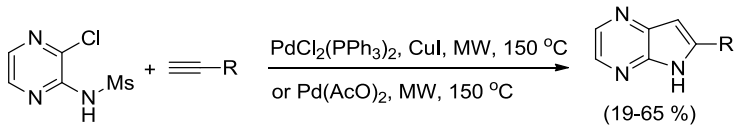
involve the use of transition metal catalysts. Typically, Pd complexes[49a-c] have been applied with and without copper co-catalysts (Scheme 5, Scheme 6 and Scheme 7).



Scheme 5

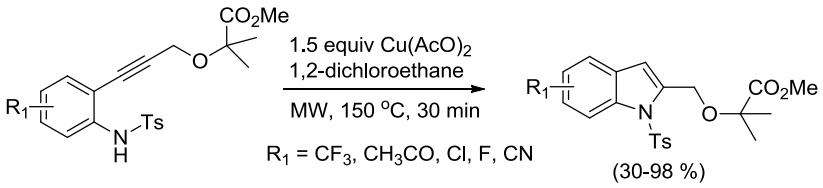


Scheme 6

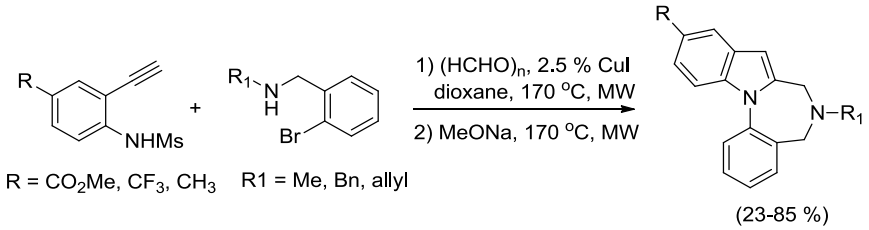


Scheme 7

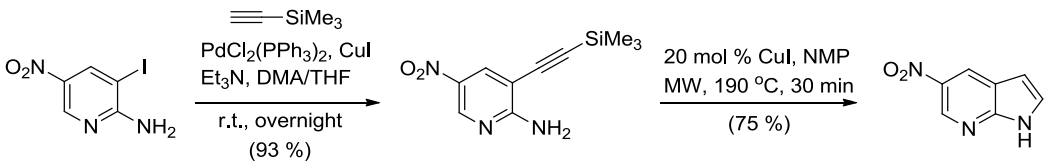
However, also Cu salts[49d-f] have been employed in microwave-assisted cyclizations of both *N*-protected anilines (Scheme 8 and Scheme 9) and *N*-unprotected amino-pyridines (Scheme 10).



Scheme 8

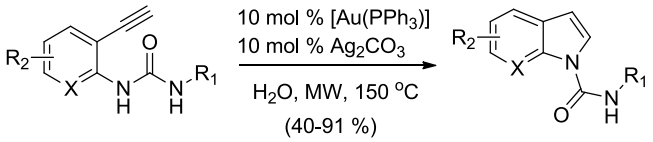


Scheme 9



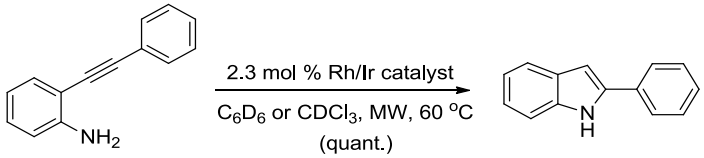
Scheme 10

Moreover, one example describes the use of an Au/Ag catalytic system in water[49g] (Scheme 11).



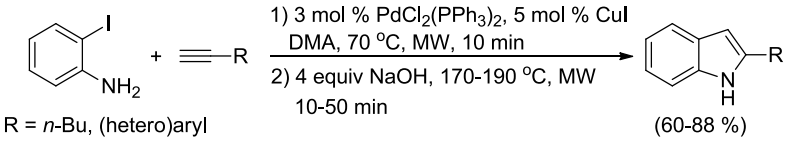
Scheme 11

Finally, few examples report the application of Ir and Rh catalysts[49h] (Scheme 12).



Scheme 12

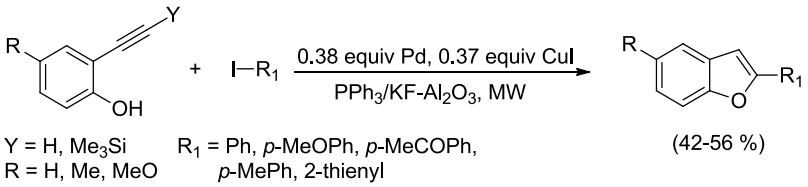
Interestingly, in one instance NaOH is employed to promote the cyclization in a two-step Sonogashira coupling-cyclization procedure (Scheme 13).[49i] However, the use of significant amounts of palladium and copper in the Sonogashira coupling does not allow to classify the procedure as "metal-free", since no isolation nor purification occurred before the NaOH-promoted cyclization. Therefore, it is highly likely to think about a heavy metal participation in the indole formation step.



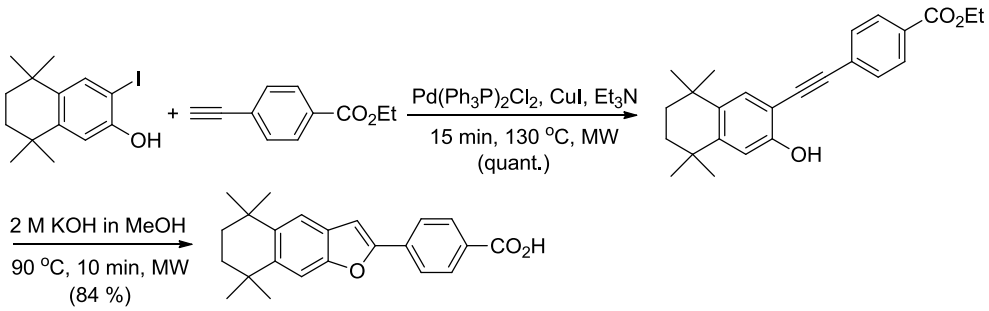
Scheme 13

1.4.2.2 Microwave-assisted synthesis of benzofurans, benzothiophenes and furopyridines *via* cyclization and annulation of alkynes

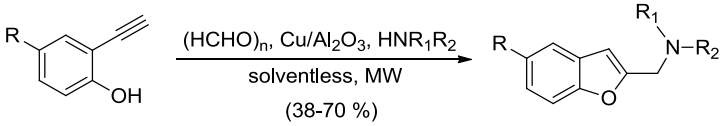
As already pointed out in section 1.4.1, the cyclization reaction of 2-alkynylphenols, 2-alkynylhydroxypyridines and 2-alkynylbenzenethiols represents a major procedure to obtain 2-substituted and 2,3-disubstituted benzofurans,[50] benzothiophenes[51] and their aza-analogues[52], with the majority of examples making use of transition metal catalysts for the triple bond activation. Only a small number of instances describe the use of microwave heating and an even smaller group of examples are concerned with microwave-assisted metal-free protocols.[53] A quick overview is reported in the following schemes. As already discussed for the preparation of (aza)indoles, the one-pot Sonogashira coupling-cyclization procedure is described as an efficient methodology to prepare benzofurans and has been studied under microwave heating conditions (Scheme 14,[49a] Scheme 15[53a] and Scheme 16[53b]).



Scheme 14

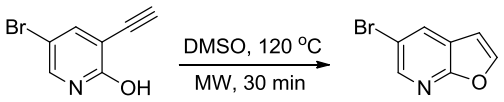


Scheme 15



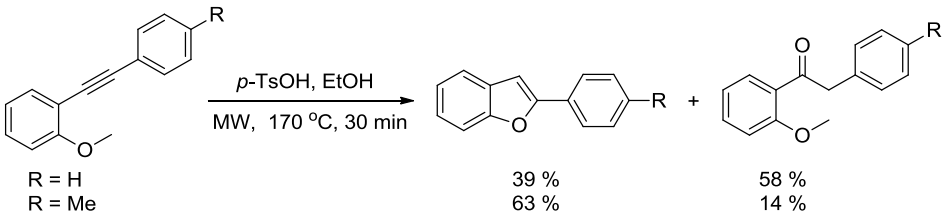
Scheme 16

Interestingly, no catalyst is required in the instance of an electron-poor substrate such as 5-bromo-3-ethynylpyridin-2-ol depicted in Scheme 17, which cyclizes by heating a DMSO solution at 120 °C under microwave irradiation.[53c]



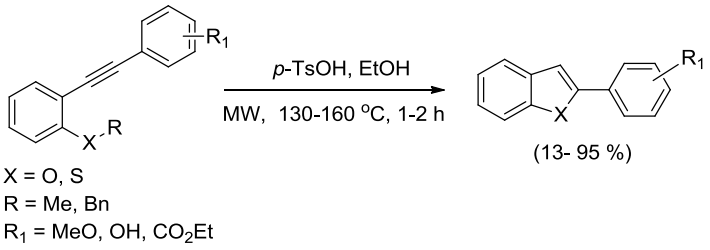
Scheme 17

In 2004 Alami and co-workers demonstrated the positive effect of microwave heating toward the hydration of arylalkynes, diarylalkynes as well as arylpropargylic alcohols performed in ethanol with 1 equiv of *p*-toluenesulfonic acid.[53d,e] In two instances, when 2-methoxyphenyl alkynes were used as starting materials, the authors were surprised to find that significant amounts of the corresponding 2-arylbenzofurans were generated (Scheme 18).



Scheme 18

More recently, in 2009, the same authors expanded their previous studies and showed that this methodology represents a general way to afford 2-arylsubstituted benzofurans and benzothiophenes from diarylalkynes, as described in Scheme 19.[53f]

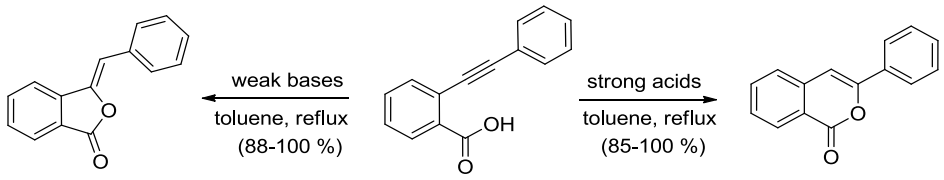


Scheme 19

1.4.2.3 Microwave-assisted synthesis of isocoumarins *via* 6-endo-dig cyclization and/or phtalides *via* 5-exo-dig cyclization of (hetero)aryl acids and esters to alkynes

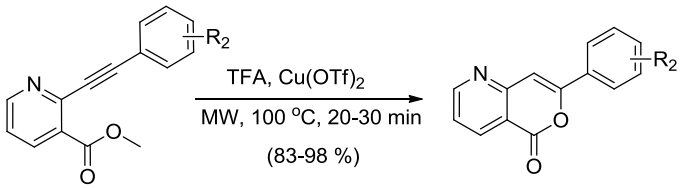
The synthesis of phtalides and isocoumarins *via* intramolecular cyclization of enynecarboxylic acid/ester systems is a well known and described approach.[54,55] However, the regioselectivity can vary and is not always high. Moreover, most of the described procedures involve the use of metal catalysts, typically Pd or Ag.[54] In one example $InBr_3$ is used.[46b]

Recently, an attracting metal-free procedure was disclosed almost contemporary by Uchiyama[55a] and Terada[55b]. They identified efficient conditions for the regiocontrolled intramolecular cyclization of carboxylic acids to carbon-carbon triple bonds promoted by acid or base catalysts. In particular, they demonstrated that when weak bases such as triethylamine, pyridine or DMAP were used, (*Z*)-3-benzylideneisobenzofuran-1(3*H*)-one could be obtained with a 97/3 ratio *vs*. 3-phenylisocumarin. On the other hand, when strong acids like trifluoroacetic acid, 97% sulfuric acid or triflic acid were applied, 3-phenylisocumarin was obtained with a 99/1 selectivity (Scheme 20).[55]



Scheme 20

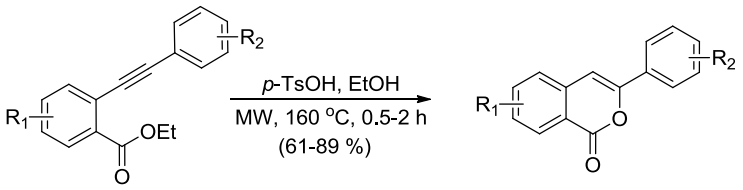
In 2008 Bihel *et al.* expanded the scope of the 6-*endo*-dig cyclization reported by Uchiyama in 2006 to prepare isocoumarins by including heteroaryl esters as starting materials (Scheme 21).[56]



Scheme 21

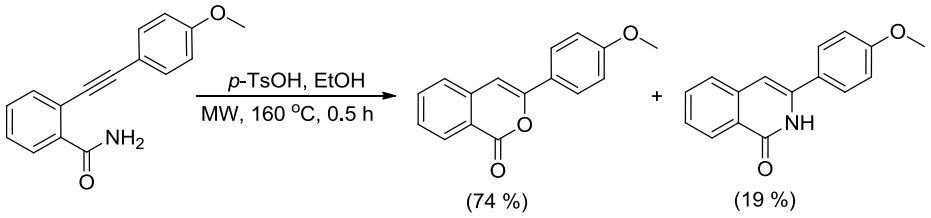
However, they demonstrated that a Lewis acid such as $Cu(OTf)_2$ was required in order to obtain efficient yields. Notably, they conducted their cyclizations under microwave irradiation.

Another very interesting example of microwave application in the acid-catalysed regioselective synthesis of isocoumarins from aryl esters was presented by Alami *et al.* in 2008.[57,53f] This metal-free procedure employed *p*-toluenesulfonic acid in ethanol as a solvent to promote the intramolecular cyclization (Scheme 22).



Scheme 22

In one example 2-[(4-methoxyphenyl)ethynyl]benzamide is transformed into the corresponding isoquinolone even if in low yield (19 %) and in mixture with the corresponding isocoumarin, which is the main product (Scheme 23).[57] To the best of our knowledge, this is the only example where microwaves are used to promote the cyclization of an alkynylbenzamide.



Scheme 23

1.5 Our research objectives and work plan

As we stated in the project objective section 1.4, our research interests were mainly directed towards exploring the microwave-assisted cyclization of alkynyl derivatives to obtain heterocyclic compounds. To outline a plan for our research project, we identified a series of compounds that we were interested in studying under microwave-assisted cyclization conditions. In the following Figure 2, we illustrate the classes of compounds that we selected. Indoles **2**, benzofurans **4**, isocoumarins **6**, phtalides **7**, and all their aza-analogues, appeared as the most attracting classes of compounds to run our studies.

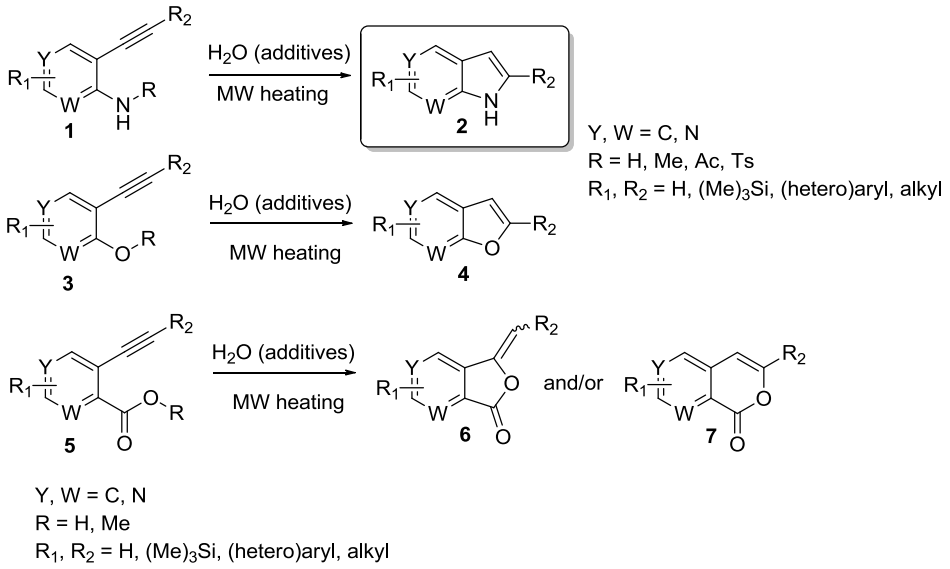


Figure 2

In particular, indoles and azaindoles of general formula **2** appeared as especially interesting compounds to start out our investigation. In fact, the (aza)indole ring system has been intensively studied by the pharmaceutical industry, being a structural component of a vast number of biologically active natural and unnatural compounds that can be found in many pharmaceutical agents. The synthesis and functionalization of (aza)indoles has been a major area of focus for synthetic organic chemists and numerous methods have been developed. Moreover, as already discussed in section 1.4.2, while for benzofurans, isocoumarins and phtalides efficient, but limited in number, metal-free synthetic methods

already exist also with microwave assistance, the same does not stand true for (aza)indoles. In fact, when our research was started, to the best of our knowledge, the literature did not show any report on metal-free synthetic trials to prepare compounds of general formula **2**, especially under microwave irradiation. Therefore, the study of this class of compounds opened up for novelty and, in our opinion, for a new and promising research area. The results of the efforts spent towards the development of an efficient and green methodology are presented and discussed in chapters 3-6.

However, before starting to discuss about heterocycle synthesis, we first present in chapter 2 the work conducted to identify and develop a suitable and efficient methodology to prepare the required alkynyl derivatives.

As already pointed out in section 1.4.2.1, the retrosynthetic approach which identifies 2-ethynylanilines and pyridines of general formula **1** as the starting materials to (aza)indoles of general formula **2**, is well described. However, since our main objective was to verify that the cyclization of suitably functionalized alkynes proceeded under microwave irradiation without any metal catalyst, it was of primary importance to identify a suitable synthetic methodology which guaranteed the required quality, in order to rule out that the cyclization was taking place under the effect of transition metals (typically palladium and copper) present as contaminants. Among the main reported methodologies, the alkynylation of (hetero)aryl halides is well established and documented.[34] In fact, differently substituted alkynyl derivatives can be obtained in high yields under Sonogashira conditions. Moreover, we had to pay particular attention to the residual metal contamination of the products, since it was essential to prepare alkyne derivatives with the desired attribute of a metal content as low as possible.

Our attention was drawn by simplified Sonogashira protocols where, in particular, supported-metal catalysts were successfully applied. In the following Chapter 2, we examine the main literature findings which directed our choice of the most appropriate conditions and we present the experimental results we obtained.

In summary, the objectives of this Doctorate Thesis were:

1) To identify a green, convenient and efficient microwave-assisted methodology to prepare compounds of general formula **2**, based on the use of water as a solvent.

2) To verify if the abovementioned methodology was general and could be extended also to compounds of general formulas **4**, **6** and **7**.

3) To identify an efficient and general procedure capable to prepare the starting materials **1**, **3** and **5**, with metal contents as low as possible, necessary to carry out the cyclization investigations. Moreover, the effect of microwaves would be also tested.

Chapter 2

Preparation of the required starting materials

2.1 Analysis of the literature to identify a suitable method to prepare the starting materials for the microwave-assisted cyclization (1, 3 and 5)

As already stated in paragraph 1.5, our main objective was to investigate the cyclization of the suitably functionalized alkynes **1**, **3** and **5** operating under microwave irradiation, without the addition of metal catalysts (Figure 3).

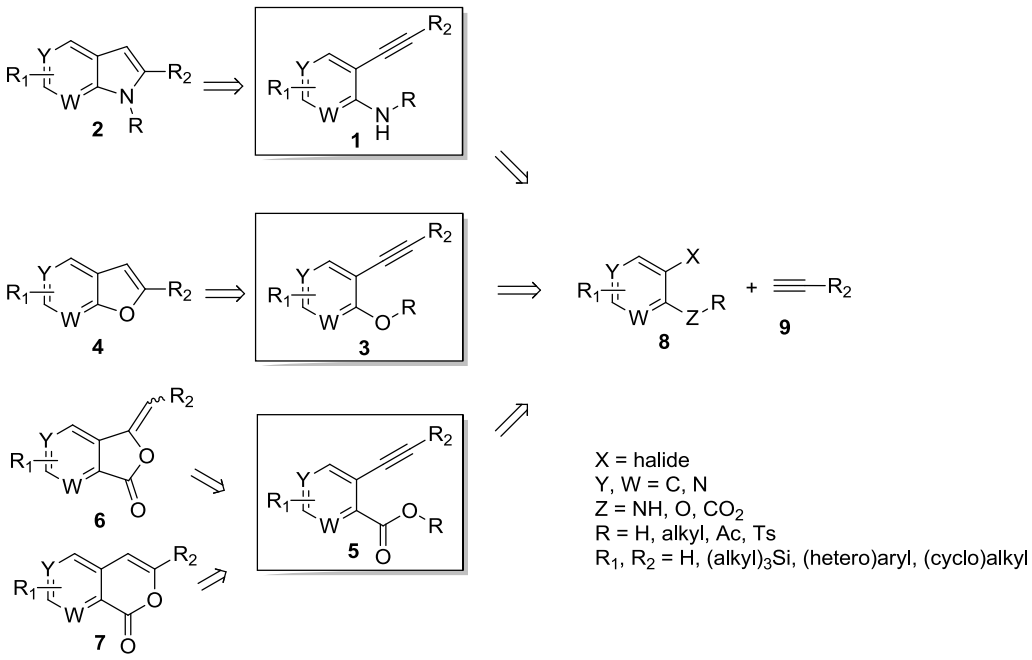
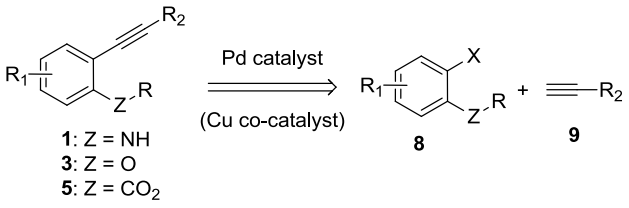


Figure 3

Therefore, the identification of a simple and efficient method to prepare the required substrates was critical. Our starting point in the method selection was the consideration that, according to the literature, palladium-catalyzed alkynylation of aryl halides represents a major synthetic methodology to prepare arylalkynes (Scheme 24).[34]



Scheme 24

However, since this was our election method, the metal contamination resulting from the application of traditional Sonogashira coupling conditions appeared us critical. In fact, the presence of metal contaminants could affect the results of the cyclization to **2**, **4**, **6**, **7**.

As a consequence, simplified Sonogashira protocols drew our attention. The most important simplification involves the omission of the copper co-catalyst, typically CuI,[34b,34c,58] which, besides being a potential contaminant, can cause drawbacks, such as the formation of homocoupling by-products of the terminal alkyne[59,60]. The described copper-free Sonogashira coupling procedures can be ideally divided in two main groups, according to the type of reagents used. The first group deals mostly with simple modifications of the Cassar-Heck alkynylation protocols.[61] Readily available Pd pre-catalysts are mainly applied, together with conventional ligands (*e.g.* PPh_3), bases and solvents. Some recent developments include microwave assistance, solventless and/or ligandless conditions, aqueous media, polymer supported ligands and/or catalysts. The second group makes use of complex and/or expensive catalytic systems, such as ligands which are costly and not easy to handle (*e.g.* $^tBu_3P$)[62] and/or special Pd catalysts (*e.g.* palladacycles)[63]. Despite the high efficiency and general applicability shown, this second approach appears less attractive due to poor commercial availability, high prices and difficult handling.

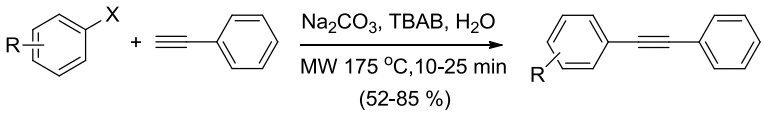
We eventually turned our attention towards the identification of a straightforward copper-free Sonogashira coupling methodology which makes use of cheap and readily available palladium species, ensuring their easy separation from the reaction mixture along with a low Pd leaching and, hopefully, a potential for recycle.[64] Hence, we focused our attention on heterogeneous catalysts, which are available on different supports such as polymers, charcoal, alumina, and silica. In fact, since when Heidereich[65] and Choudary[66] published in 2002, independently, the first modified Cassar-Heck protocols employing heterogeneous catalysts, their application to Sonogashira couplings have grown extremely rapidly. In particular, efficient and environmentally friendly processes were implemented, which comprised the easy recovering and recycling of the catalytic system and ensured a

very low heavy metal leaching. Our results and discussion on the selection and development of the synthetic methodology are described in paragraphs 2.1.2 and 2.2.2. However, before taking into consideration the use of supported catalysts, we could not disregard the few papers which exemplify the complete exclusion of transition metals in the coupling of alkynes with different aryl halides (paragraph 2.1.1).[67] These metal-free protocols were evaluated and tested and the results obtained, together with our considerations are reported in paragraph 2.2.1.

2.1.1 Described "metal-free" Sonogashira protocols

Two remarkable examples of microwave-assisted metal-free Sonogashira coupling appeared almost contemporary in 2003, published by Van der Eycken's group[67a] and by Leadbeater's group[67b].

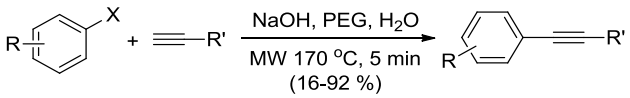
Van der Eycken *et al.* demonstrated that aryl iodides and bromides could be coupled in high yields with phenylacetylene in water as a solvent, in the presence of Na_2CO_3 as a base and TBAB. Microwaves were applied to heat the mixtures at 175 °C. Notably, the authors checked that Pd and Cu contents of the crude product mixtures were lower than 1 ppm by atomic absorption analysis (Scheme 25).[67a]



R	X	time	Yield (%)
H	I	25 min	—
4-MeO	I	15 min	78
H	Br	25 min	—
4-MeO	Br	20 min	70
4-NO_2	Br	15 min	52
4-Ac	Br	15 min	85
4-NH_2	Br	25 min	66
4-NMe_2	Br	25 min	59

Scheme 25

Leadbeater *et al.* described a similar protocol where water was used in a 50/50 mixture with PEG and NaOH was added as the base (Scheme 26).[67b]

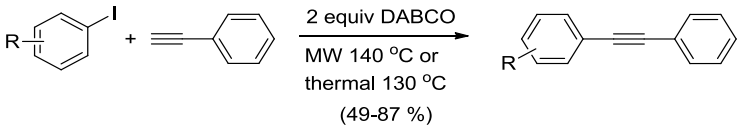


R	X	R′	Yield (%)
H	I	Ph	83
4-MeO	I	Ph	43
4-Ac	I	Ph	91
4-Me	I	Ph	92
4-Me	I	C_4H_9	16
4-Me	I	TMS	30
H	Br	Ph	41
4-Ac	Br	Ph	67

Scheme 26

Microwaves were applied to heat the mixtures to 170 °C. Moderate to good yields were obtained for a variety of aryl iodides and activated bromides. Also in this case, Pd and Cu contents of the crude reaction mixtures were demonstrated as being lower than 1 ppm.

As a matter of completeness, a very recent example of solvent- and metal-free Sonogashira coupling appeared in 2009 (Scheme 27).[67c] The authors discovered that DABCO can act as a catalyst in the cross-coupling between phenylacetylene and aryl iodides. The reactions were carried out at 130 °C with thermal heating. When electron-donating groups were present in the aryl halides, lower yields were observed. Notably, microwaves were also applied in a number of selected instances with good results. However, these interesting results appeared in the literature only in 2009 and, by that time, we had already found an efficient, clean and reliable method to prepare our metal-free alkynes. For this reason, this last methodology was not tested but it is reported to give a complete literature review on metal-free Sonogashira couplings.



R	Heating	T (°C)	time	Yield (%)
3-CF_3	thermal	130	48 h	86
3-F	thermal	130	48 h	73
3-F,5-CF_3	thermal	130	48 h	77
3-Me	thermal	130	48 h	61
2-OH	thermal	130	60 h	72
3-MeO	thermal	130	48 h	55
4-NH_2	thermal	130	48 h	49
3-CF_3	MW	140	1 h	80
3-F	MW	140	1.5 h	75
3-Me	MW	140	2 h	66
3-MeO	MW	140	2 h	49

Scheme 27

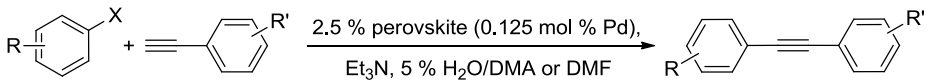
In conclusion, the published metal-free protocols looked considerably advantageous if they could be suitable to prepare substrates of general formulas **1**, **3** and **5**, since they offered the appealing possibility of easily and quickly obtaining products free from heavy metal contaminants. Therefore, with the aim of verifying the efficiency of the aforementioned methodologies, we run some experiments on model compounds following the first two protocols reported in Scheme 25 and Scheme 26. The results we obtained are detailed later on in paragraph 2.2.1.

2.1.2 Pd EnCat™ as a catalytic precursor in the copper-free Sonogashira coupling

As discussed previously in paragraph 2.1, the application of a copper-free Pd-catalysed alkynylation protocol looked particularly attractive for our purposes. Moreover, the use of heterogeneous catalytic systems could offer advantages in terms of low palladium contamination and even of recycling. What we needed was an efficient and easily available

heterogeneous catalyst, which was air and moisture-stable and effective in promoting Sonogashira-type reactions without the need of copper co-catalysis. An analysis of the recent literature allowed us to identify a selection of heterogeneous Pd catalysts which were described as giving efficient Sonogashira couplings with low Pd leaching. The examples which appeared us as the most interesting are given in the following schemes and tables.

In 2005 Ley's group published a study on the use of copper- and palladium-containing perovskites, commercially available with the brand name of LaPCat™ (Scheme 28).[68]



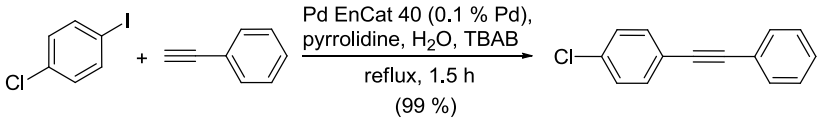
R	X	R′	Perovskite	Heating	T (°C)	time	Yield (%)
4-Cl	I	4-MeO	LaPdCu*	thermal	120	16 h	71
4-NO_2	I	4-MeO	LaPdCu*	thermal	120	16 h	96
4-Ac	I	4-MeO	LaPd*	thermal	120	16 h	96
4-MeO	I	4-MeO	LaPdCu*	thermal	120	16 h	47
4-NO_2	Br	4-MeO	LaPdCu*	thermal	120	16 h	71
4-Ac	I	4-NH_2	NdPdCu*	thermal	120	16 h	92
2-CO_2H	I	4-MeO	LaPdCu*	thermal	120	16 h	52
4-Cl	I	H	LaPdCu*	MW	175	20 min	75
4-Cl	I	H	LaPd*	MW	175	20 min	28

Scheme 28

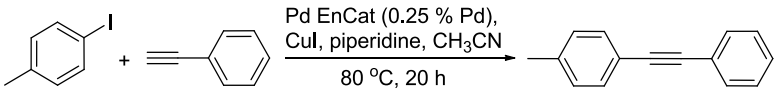
They reported that catalysts like LaPdCu*, LaPd* and NdPdCu* efficiently promoted Sonogashira couplings under both microwave and conventional heating. Notably, rather low Pd loadings (0.125 mol %) were applied.

Among the recently described supported palladium species, the commercially available Pd EnCat™ catalysts deserve a special attention for the features of giving low Pd leaching and of being easily removed and recycled.[69] These catalysts consist of Pd(II) acetate microencapsulated in a polyurea matrix, they are air and moisture stable and can be easily removed by filtration. They were successfully employed in several C-C bond formation reactions, notably Suzuki, Heck and Stille cross-couplings.[69,70] After an analysis of the

literature, we found that, as for Sonogashira-type alkynylations are concerned, no specific study on Pd EnCat catalysis was reported until 2007 (when this doctorate work was started) and, furthermore, only two isolated examples of efficient reactions were described (Scheme 29 and Scheme 30).[71]



Scheme 29

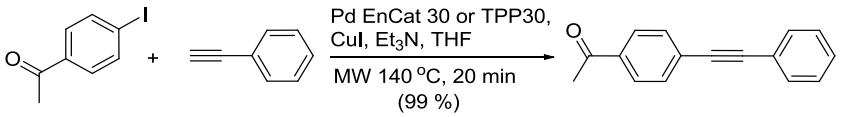


Pd EnCat	Yield (%)
Pd EnCat TPP30	85
Pd EnCat NP30	40

Scheme 30

Remarkably, as already observed for the LaPCat catalysts, the palladium loadings applied were rather low, being 0.1 % and 0.25 %, respectively. However, only in the example in Scheme 29 a copper-free protocol was employed, while in the other instance CuI was employed as co-catalyst (Scheme 30).

In 2008 Pitts, in his review on EnCat catalysts and microwave heating, described and compared two interesting instances of microwave-assisted Pd EnCat/CuI co-catalyzed Sonogashira reactions (Scheme 31).[69a] However, the aforementioned review reported neither experimental details nor bibliographic references; consequently we don't have any clues about the Pd loading applied.

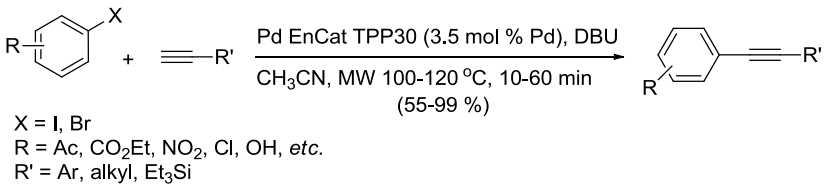


Scheme 31

Moreover, Pd EnCat™ appeared particularly attractive among the commercially available supported Pd catalysts also because it is available from an established and reliable supplier like Sigma Aldrich and because it is cheaper than LaPCat or Fibrecat (what is more, the latter was on the market only since the beginning of 2010). For these reasons, we decided to make an attempt with Pd EnCat catalysts in our copper-free alkynylation to obtain the required starting materials **1**, **3** and **5**. In addition, Pd EnCat looked well worth investigating, since no systematic study existed before 2007 on their use in copper- and solvent-free Sonogashira and we saw an opportunity for expanding that research area.

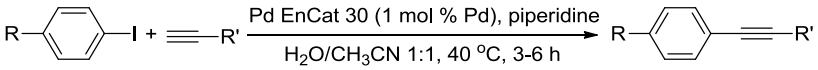
In the following section 2.2, we describe the results obtained in our laboratory to set up a suitable protocol for the copper-free alkynylation by using extremely low Pd EnCat loading (down to 0.01 mol % of Pd for the most reactive substrates). Furthermore, we demonstrated that both thermal and microwave heating can be applied successfully. This piece of work led to a paper publication in 2009.[72]

Notably, after our work on Pd EnCat was disclosed, a broad extension of our studies was published by Ley's group in 2009.[73] The authors included a larger range of acetylenes and of (hetero)aryl and alkenyl halides (Scheme 32). However, it must be said, the loading of palladium required to obtain satisfying yields was much higher than the one we applied in our procedures, notably 3.5 mol % instead of 0.01-0.1 mol %.



Scheme 32

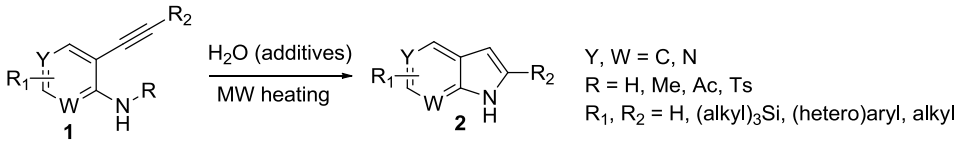
A further protocol of copper- and phosphine-free Sonogashira coupling catalyzed by Pd EnCat 30 appeared in late 2009 a bit after our paper on the same subject, thus confirming the considerable interest hold by the use of Pd EnCat in Sonogashira protocols (Scheme 33).[74]


Pd EnCat 30 (1 mol % Pd), piperidine
H2O/CH3CN 1:1, 40 °C, 3-6 h
R = H, MeO, NO2, Ac
R' = Ph, (cyclo)alkyl
(82-99 %)

Scheme 33

2.2 Preparation of arylalkynes 1, 3 and 5

As we stated in section 1.5, part of our plan was to study as a first instance the cyclization of 2-alkynylanilines **1 (**Y=W=C) to indoles **2**. In a second instance we would examine their aza analogues (Y=N and/or W=N).



As a consequence, 2-ethynylaniline, **1a**, and 2-phenyltehynylaniline, **1b**, were selected as the model substrates for our first microwave-assisted trials (Figure 4).

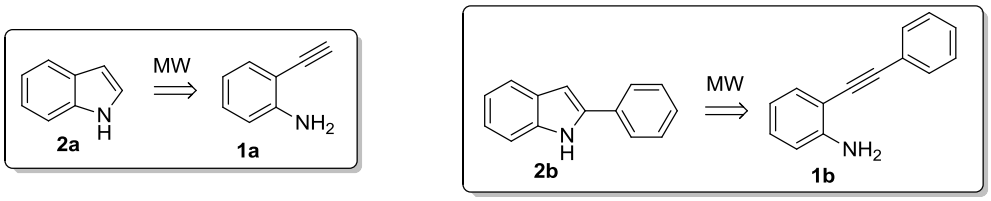
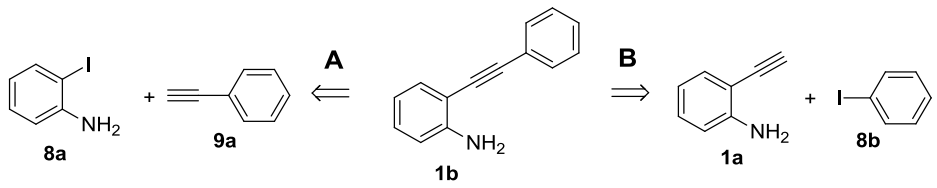


Figure 4

Notably, compound **1a** was commercially available and we deemed it simpler to proceed with the purchased compound, while we would set up an efficient method to prepare the diarylalkyne **1b** (Scheme 34).



Scheme 34

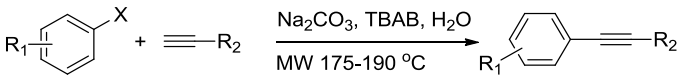
As for compound **1b**, two disconnection approaches were identified. In fact, the possibility of making use of commercially available **1a** offered a more useful disconnection approach (named **B** in Scheme 34), that we could use in case the one based on 2-iodoaniline did not work or was poorly efficient (named **A**).

However, before starting with the investigation of suitable conditions for the copper-free Sonogashira-coupling, we considered worth spending some efforts on the study of metal-free protocols. In a first instance, we tried the conditions previously described by Van deer Eycken and Leadbeater to verify if they were suitable to prepare substrates of general formula **1**.[67]

2.2.1 Microwave-assisted metal-free Sonogashira coupling results

A number of trials were conducted under microwave-assisted metal-free conditions with the objective to assess if the reported procedures[67] could be valuable as a synthetic methodology to prepare metal-free products. Following the conditions already discussed in the previous paragraph 2.1.1, we selected a series of model substrates from the list of the compounds prepared by the same authors. The following Table 1 and Table 2 contain the data we gathered.

Table 1. Sonogashira trial results obtained under Van deer Eycken's conditions.[a]



3a: R_1=2-OH, R_2=TMS
11: R_1, R_2= all other groups

Entry	R_1	X	R_2	Temperature	Time	Product	Results
1	2-OH	I	Me_3Si	175 °C	20 min	**3a**	recovered starting material
2	H	I	Ph	175 °C	20 min	**11a**	recovered starting material
3	4-MeO	I	Ph	175 °C	15 min	**11b**	2 % product
4	4-MeO	I	Ph	175 °C	30 min	**11b**	5 % product
5	4-MeO	I	Ph	190 °C	20 min	**11b**	12 % product
6	4-MeO	Br	Ph	175 °C	20 min	**11b**	recovered starting material
7	4-MeCO	I	Ph	175 °C	20 min	**11c**	degradation
8	4-MeCO	Br	Ph	175 °C	20 min	**11c**	degradation

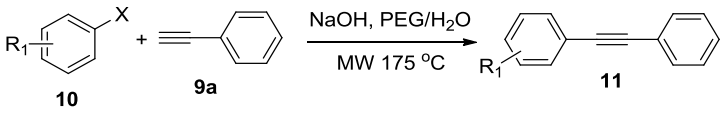
[a]Conditions: 1 mmol of halide **10**, 2 equiv of alkyne **9**, 1 equiv of TBAB, 4 equiv of Na_2CO_3 were mixed in 3 ml of water; the suspension was heated under microwaves to the temperature reported in the table.

However, after the first experiments, it was immediately clear that the aforementioned procedures were not able to give the desired products. In fact, in our hands, those conditions were not efficient, giving instead degradation of the reagents or unreacted starting materials. Notably, these results were obtained for the same substrates which the authors had already used successfully.

Only in the instance of *p*-iodoanisole, a 12 % of product **11b** could be observed when the iodide was reacted in the presence of TBAB and Na_2CO_3 at 190 °C.

On the other hand, when PEG/H_2O and NaOH were used, no product **11b** could be detected (compare entry 5 in Table 1 and entry 1 in Table 2).

Table 2. Sonogashira trial results obtained under Leadbeater's conditions.[a]



Entry	R_1	X	Time	Product	Results
1	4-MeO	I	20 min	**11b**	recovered starting material
2	4-MeO	Br	20 min	**11b**	recovered starting material
3	4-MeCO	Br	20 min	**11c**	degradation

[a]Conditions: 1 mmol of halide **10**, 2 equiv of **9a**, 2 equiv of NaOH were mixed in 2 ml of a mixture PEG/water 1:1; the solution was heated under microwaves to the temperature reported in the scheme.

The results described in Table 1 and Table 2 show that the methodology tested is clearly inadequate to prepare diarylalkynes **11** and **3**, since the yields could not be reproduced on the same substrates described by the authors.

However, these results were not completely unexpected to us. When we started our investigation on the metal-free Sonogashira coupling, we were well aware of previous similar findings on metal-free Suzuki coupling conditions reported by Leadbeater *et al*. in 2003. The authors discovered and optimized a metal-free procedure for the Suzuki coupling which made use of Na_2CO_3, water and TBAB, and gave from good to very good yields in the coupling products. Subsequently, a reassessment of the same methodology was

published in 2005 by the same authors who discovered that their procedure was not exactly "metal-free", but instead catalyzed by "homeopathic" amounts of palladium which were found in the Na_2CO_3 at ppb levels and proved responsible for the coupling occurrence.

Given these considerations and in the light of our experimental results, we concluded that the above-mentioned methodology was not of general scope, since it appeared not only dependent on the quality of the materials used, but also on the presence of the metal catalysts.

2.2.2 Development of an efficient Cu-free Sonogashira protocol catalyzed by Pd EnCat™

At the time we were examining "metal-free" Sonogashira protocols, we obtained much more interesting and useful results during the study on Sonogashira alkynylations using a heterogeneous immobilized catalyst such as Pd EnCat™.

Pd EnCat systems consist of Pd(II) acetate microencapsulated in a polyurea matrix; the commercial products contain 0.37-0.44 mmol of Pd per gram of catalyst and are available optionally with co-encapsulated phosphines such as PPh_3 or P(*o*-tolyl)$_3$, which simplifies the removal of not only Pd but also ligand.

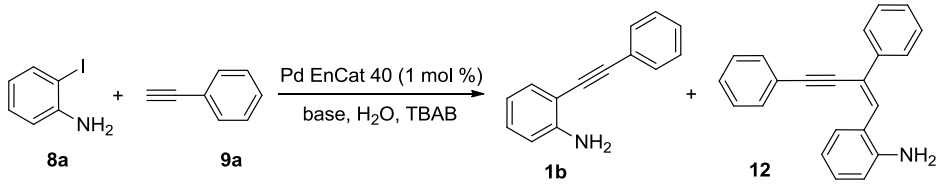
Table 3. Available Pd EnCat™ products.[69b]

Catalyst brand name	Matrix content (wt %)	wt % of Pd (mmol Pd/g)	mmol P/g	Ligand
Pd EnCat 40	40	3.9-4.6 (0.4)	n/a	n/a
Pd EnCat 30	30	3.9-4.6 (0.4)	n/a	n/a
Pd EnCat TPP30	30	3.9-4.6 (0.4)	0.26-0.35	PPh_3
Pd EnCat TOTP30	30	3.9-4.6 (0.4)	0.15-0.20	P(*o*-tolyl)$_3$

Pd EnCat 40 (a phosphine-free system containing 0.4 mmol of Pd/g) was selected in the Pd EnCat family for our cross-coupling trials, following the conditions reported by Nájera[71b] for the alkynylation of 4-chloroiodobenzene with phenylacetylene. As the model

substrates for optimizing our alkynylation conditions we chose phenylacetylene, **9a**, and 2-iodoaniline, **8a**, which represents a "difficult" aryl iodide being deactivated and ortho-substituted by a free amino group. In a first instance, a screening of conditions was run and the results are reported in Table 4.

Table 4. First trials with Pd EnCat 40 and **8a**.



8a 9a 1b 12

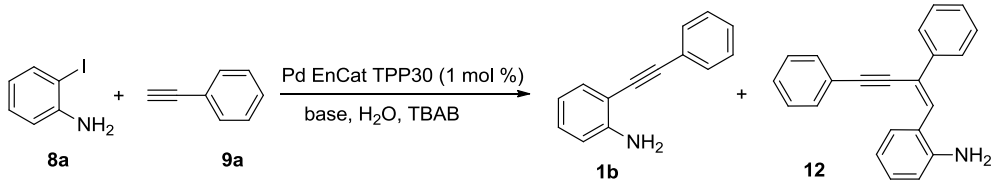
Entry	Solvent	Base	Temp	9a	Time	8a[a]	Ratio 1b:12[a]	Yield[b]
1	H_2O/ TBAB	pyrrolidine (2 equiv)	85°C	1.2 eq	1.5 h	—	85:15	64 %
2	H_2O/ CH_3CN[c]	pyrrolidine (2 equiv)	75°C	1.2 eq	2.5 h	—	92:8	72 %
3	H_2O/ TBAB	TEA (2 equiv)	100°C	1.5 eq	22 h	30	20:50	n.d.
4	H_2O/ TBAB	DIPEA (2 equiv)	85°C	3.5 eq	22 h	—	8:92	39 %[d]
5	H_2O/ TBAB	*t*-$BuNH_2$ (2 equiv)	85°C	1.2 eq	1.5 h	36	28:36	n.d.

[a]Values are expressed in % a/a HPLC; [b]Molar yields in **1b** after flash chromatography; [c]Without TBAB, H_2O/CH_3CN = 15/85. [d]Molar yield in **12** after flash chromatography.

As a first instance, the conditions we applied were using 1 mol % of Pd, water as the solvent, 2 equiv of pyrrolidine, 0.5 equiv of tetrabutylammonium bromide (TBAB) and 1.2 equiv of alkyne **9a**. After 1.5 h of heating at 85 °C, we found that the starting material was completely consumed. However, the higher molecular weight product **12** was formed along with the desired 2-(phenylethynyl)aniline, **1b**, which was isolated in 64% yield (Table 4, entry 1). The by-product **12** was isolated and characterized by means of NMR experiments that allowed establishing its regio- and stereochemistry (see the experimental part for more details).

A more favourable **1b**/**12** ratio and a better yield could be obtained in the absence of TBAB and working in a mixture of H_2O/CH_3CN as the solvent (Table 4, entry 2). More interestingly, we also observed that the relative amounts of **1b** and **12** were strongly affected by the nature of the base. In fact, when pyrrolidine was used, the major product was **1b**, while with a hindered tertiary base like diisopropylethylamine (DIPEA), **12** was primarily obtained (Table 4, entry 4). By using triethylamine (TEA) or a primary amine the reaction failed to reach completion, giving mixtures of products **1b** and **12** (Table 4, entries 3 and 5). Interestingly, when Pd EnCat TPP30 (which contains PPh_3 encapsulated in the same polymeric matrix) was the pre-catalyst, slightly better results were obtained in terms of selectivity, also when TEA was the base used (Table 5, entries 1 and 3).

Table 5. First trials with Pd EnCat TPP30 and **8a**.

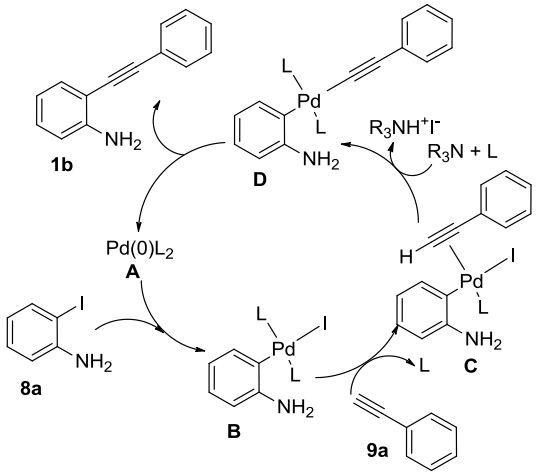


Entry	Solvent	Base	Temp	9a equiv	Time	8a[a]	1b[a]	12[a]	Yield of 1b[b]
1	H_2O/ CH_3CN	TEA (2 equiv)	60°C	1.5	3 h	2	85	13	52 %
2	H_2O/ TBAB	DIPEA (2 equiv)	85°C	1.2	2.5 h	35	33	32	—
3	H_2O/ TBAB	pyrrolidine (2 equiv)	85°C	1.5	5 h	—	99	1	78 %

[a]Ratio expressed in % a/a by HPLC; [b]Molar yields in **1b** after chromatography.

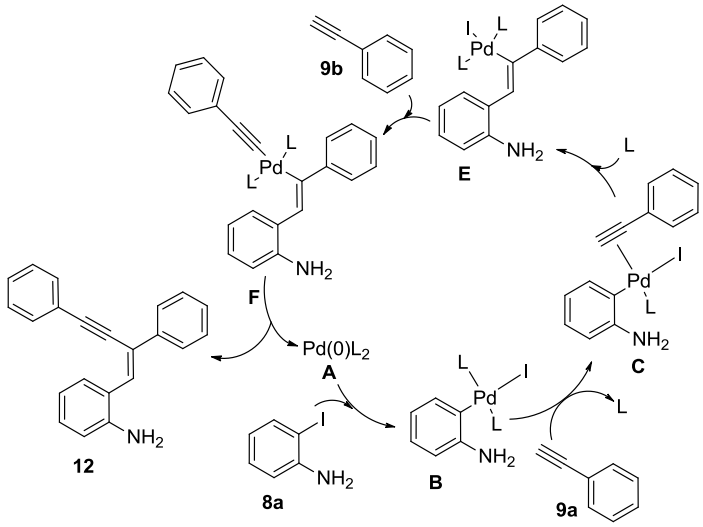
Having established that the relative amounts of **1b** and **12** were strongly affected by the nature of the base, we analysed the literature to understand more in details the role played by the base in the copper-free Sonogashira reaction in order to rationalize the behaviour we observed and to plan future improvements.[34,58a,75] According to literature findings, the mechanism of the copper-free Sonogashira is not well-known.[34] The generally accepted catalytic cycle for the Pd catalysis is depicted in Scheme 35 and is based on an usually fast

oxidative addition of R-X to the Pd(0)L_2 catalyst **A** generated from the Pd(II) precatalyst; in the second step, the complexation of the alkyne is supposed to proceed first by displacement of one ligand to give the intermediate complex **C**. The ligated alkyne would be deprotonated more easily by the amine since its proton is more acidic than in the free alkyne, thus forming the new complex **D**, which gives the coupling product **1b** after reductive elimination.



Scheme 35

In the absence of any amine or in the presence of a less basic one, a carbopalladation step takes place which leads from **C** to the complex **E** instead of **D** (Scheme 36).

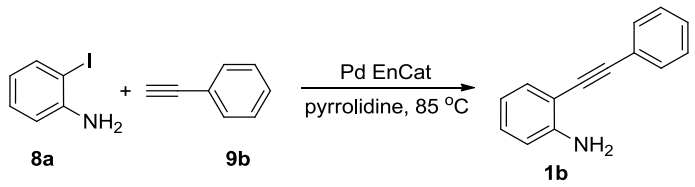


Scheme 36

Following this different path, the product **12** is obtained after reaction of **E** with another alkyne molecule to form **F**, followed by reductive elimination. A feature worth noting is that pyrrolidine is a better ligand for a Pd(II) complex like **B** or **C** than a more hindered base like DIPEA or TEA. In fact it is known that secondary amines can act as ligands to reversibly generate [(Ar)PdX(L)(amine)] complexes that might play a key role in the catalytic cycle in Scheme 35 (L= amine in compounds **B** and **C**).

Supported by our first experimental results and by the explanations found in the literature, we selected pyrrolidine as the base to carry out our optimization. What particularly looked promising was the idea of working under solvent-free conditions, without the need of TBAB. Then, with the objective of improving the yields and minimizing the amount of by-product **12**, we investigated the effect of the Pd loading. Almost all the trials were run at 85 °C, a temperature which roughly corresponded to the reflux temperature of the mixture. The results we obtained are reported in Table 6 and show that the solvent free conditions were more efficient and allowed for the isolation of **1b** in higher yields even with very low catalyst loadings: 0.2 and 0.1 mol % of palladium (Table 6, entries 1, 2 and 3). However, the yield drops considerably with 0.01 mol % of Pd (Table 6, entry 5).

Table 6. Condition optimization for the solvent free cross-coupling.



8a **9b** **1b**

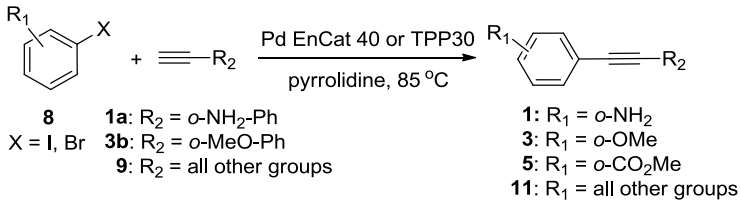
Entry	Catalyst	Pd loading (mol %)	time	Yield[a] (%)
1	Pd EnCat 40	1.0	30 min	> 99
2	Pd EnCat 40	0.2	3 h	83
3	Pd EnCat 40	0.1	5 h	77
4	Pd EnCat TPP30	0.1	1 h	73
5	Pd EnCat 40	0.01	24 h	40[b]

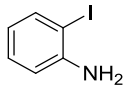
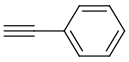
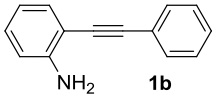
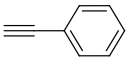
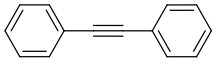
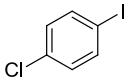
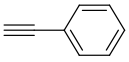
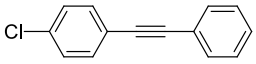
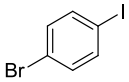
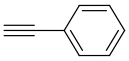
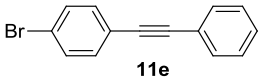
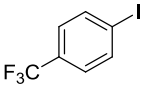
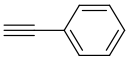
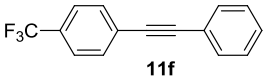
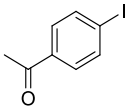
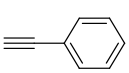
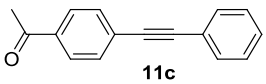
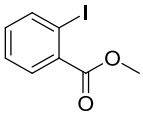
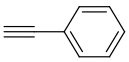
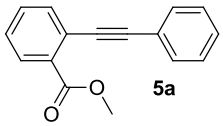
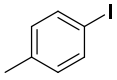
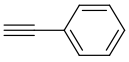
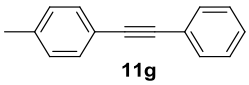
[a]Isolated yields. [b]50 % of starting **8a** was detected.

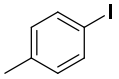
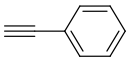
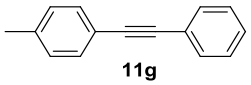
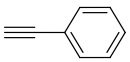
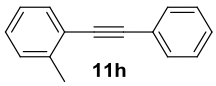
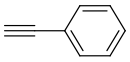
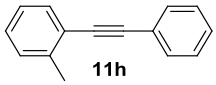
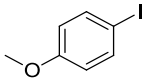
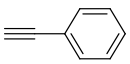
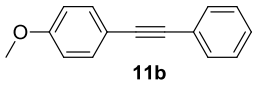
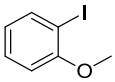
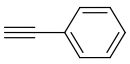
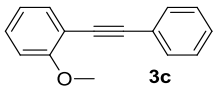
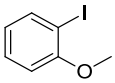
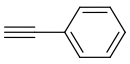
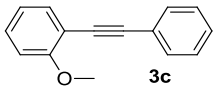
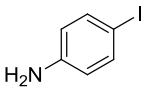
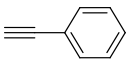
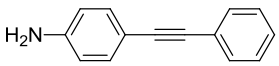
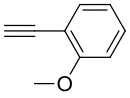
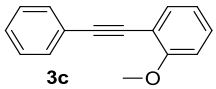
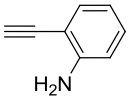
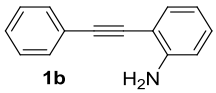
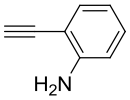
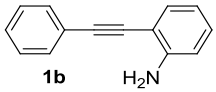
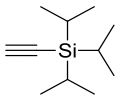
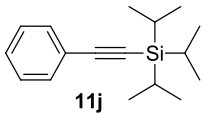
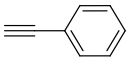
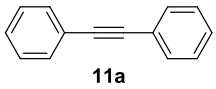
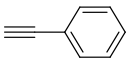
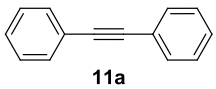
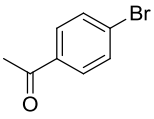
The results just presented show that Pd EnCat 40 and TPP30 represent efficient catalytic precursors for the alkynylation of **8a** even when low loading are used.

Our methodology looked so easy and straightforward that we decided to investigate it further and to test it on different aryl halides and alkynes. Therefore, a study was set up by selecting aryl iodides bearing electron withdrawing and donating groups and a few examples of aryl bromides. The outcomes are summarized in Table 7.

Table 7. Cu-free Sonogashira-type cross coupling for a selection of aryl halides and alkynes[a]



Entry	Aryl halide	Alkyne	Product	Pd loading (mol %)	Time	Yield[b] (%)
1			 **1b**	0.1	5 h	77
2			 **11a**	0.01	5 h	93
3			 **11d**	0.01	3.5 h	99
4			 **11e**	0.01	3 h	88
5			 **11f**	0.01	3.5 h	95
6			 **11c**	0.01	1 h	57
7			 **5a**	0.1[c]	1.5 h	60
8			 **11g**	0.01	24 h	63

9			 **11g**	0.1	3 h	74
10			 **11h**	0.1	5 h	73
11			 **11h**	0.1[c]	1.5 h	98
12			 **11b**	0.1	3 h	90
13			 **3c**	0.1	3 h	64
14			 **3c**	0.1[c]	1.5 h	99
15			 **11i**	0.1	3 h	54
16			 **3c**	0.01	7 h	61
17			 **1b**	0.01	2.5 h	84
18			 **1b**	0.1	0.5 h	99
19			 **11j**	0.1	4.5 h	99
20			 **11a**	0.1[c]	20 h	20
21			 **11a**	1[c]	1 h	31
22			**11c**	1[c]	0.5 h	69

[a]Reactions were run in open vessels, using 4 mmol of aryl halide, 1.5 equiv of alkyne, 2 equiv of pyrrolidine (0.67 ml) and the specified amount of Pd as Pd EnCat 40 (1 mg of Pd EnCat 40 for a Pd loading of 0.01 mol % and 10 mg for 0.1 mol % of Pd). The reaction mixtures were heated to 85 °C for the specified time. [b]Yields of products **1**, **3**, **5** or **11** after chromatographic purification. [c]Pd EnCat TPP30 was used (10 mg of Pd EnCat TPP30 for a Pd loading of 0.1 mol % and 100 mg for 1 mol % of Pd).

Very low catalyst loading (down to 0.01 mol % of Pd for the most reactive substrates) was applied and this ensured a low Pd contamination in the output. Where Pd EnCat 40 gave poorer yields and longer reaction times, more advantageous results were obtained by using the PPh_3-containing Pd EnCat TPP30 as a catalytic precursor.

In particular, Pd EnCat 40 gave good to excellent yields with 0.01 mol % of Pd when iodobenzene or aryl iodides bearing electron withdrawing groups were employed (Table 7, entries 2-6, 16 and 17), whereas electron-rich aryl iodides gave in general better results with 0.1 mol % of Pd (compare entry 2 with entry 4, Table 6, and entry 8 with entry 9, Table 7). Moreover, Pd EnCat 40 allowed excellent results even with *ortho*-substituted arylethynes and triisopropylsilylethyne (Table 7, entries 16-19).

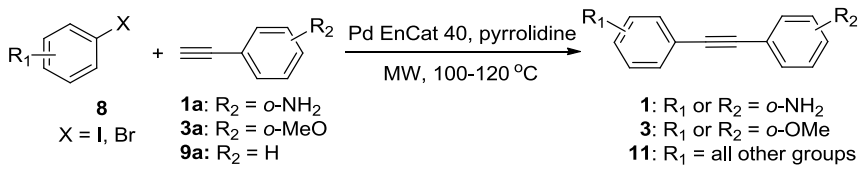
On the other hand, less reactive *ortho*-substituted iodides afforded higher yields when Pd EnCat TPP30 was used (Table 7, compare entries 10 and 13 with entries 11 and 14). With higher Pd loading, also the activated 4-bromo-acetophenone efficiently reacts in the presence of this catalyst, while bromobenzene gave poor results (Table 7, entries 20-22).

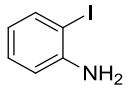
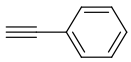
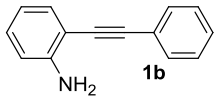
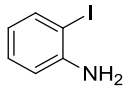
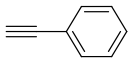
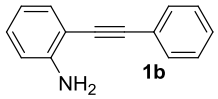
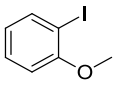
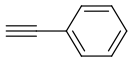
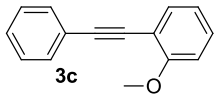
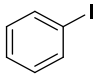
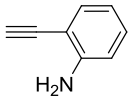
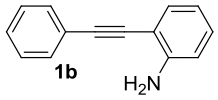
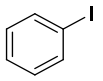
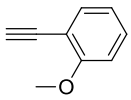
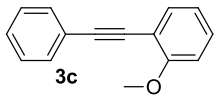
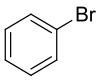
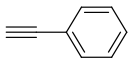
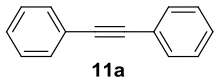
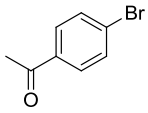
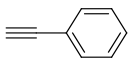
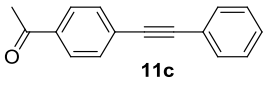
It is worth noting that all reactions were carried out without additional solvent, by simply mixing, under aerobic conditions, starting materials, catalytic precursor and pyrrolidine and by heating the resulting mixtures to 85 ºC for the specified times. No particular attention was paid to the anhydricity of reagents or equipments.

Finally, we studied the effects of microwave irradiation on our alkynylation conditions, for a selection of the more difficult aryl halides. Not surprisingly, Table 8 shows that, with respect to the thermal heating, microwave heating allowed a drastic reduction of reaction times, an enhancement of yields and a tenfold reduction of the catalyst loading.

A comparison reaction was run for the alkynylation of 2-iodoaniline by applying the same conditions under thermal heating (Table 8, compare entry 1 with entry 2). The results clearly showed that the use of microwaves gave significant advantages.

Table 8. Microwaves application in the Sonogashira coupling with Pd EnCat.[a]



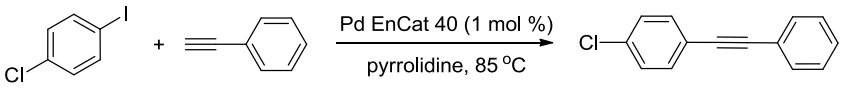
Entry	Aryl halide	Alkyne	Product	Pd loading (mol %)	Temp/ time	Yield[b] (%)
1				0.01	100°C /0.5 h	95
2				0.01	100°C /6.5 h	42[c]
3				0.01	120°C /0.3 h	59
4				0.01	100°C /0.5 h	99
5				0.01	100°C /0.5 h	76
6				0.1	100°C /1 h	40
7				0.1	100°C /0.5 h	74

[a]Reactions were run using 4 mmol of aryl iodide **8**, 1.5 equiv of alkyne **1a**, **3a**, **9a**, 2 equiv of pyrrolidine and the specified amount of Pd as Pd EnCat 40. [b]Isolated yields of compounds **1**, **3** and **11**. [c]Thermal heating was applied. The ratio 2-iodoaniline/product was 85/15 after 30 min at 100 °C, while it was 45/55 after 6.5 h where a complete consumption of phenylacetylene was detected.

2.2.3 Recycling experiments

Some preliminary data were gathered with 4-chloroiodobenzene as the model substrate in recycling procedures to test the behaviour of Pd EnCat 40. A loading of 1 mol % of Pd was applied in all the trials in order to have an amount of catalyst significant to weigh and to appreciate any occurring loss.

Table 9. Preliminary recycling experiments for Pd EnCat 40.



Run	Time	Temperature	Yield[a]
1	30 min	85°C	> 99 %
2	30 min	85°C	> 99 %
3	40 min	85°C	> 99 %

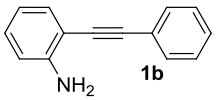
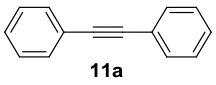
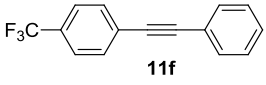
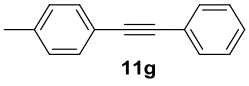
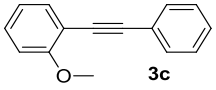
[a]Isolated yield after chromatographic purification.

As we can see from Table 9, the catalyst was recovered by filtration and recycled up to three times without significant loss of catalytic activity.

2.2.4 Metal contamination by atomic absorption

In order to verify the level of leaching of palladium in the products we prepared, we chose five of the arylalkynes we prepared for atomic absorption analyses. In Table 10 we report a summary of atomic absorption analysis results.

Table 10. Atomic absorption spectrophotometry data.

Compound	Entry	Catalyst (mol %)	Pd content (ppm)
 **1b**	1	Pd EnCat 40 (0.01)	<0.1
	2	Pd EnCat 40 (0.1)	6.0
	3	Pd EnCat 40 (1)	71.5
	4	Pd EnCat TPP30 (0.1)	1.0
 **11a**	5	Pd EnCat 40 (0.01)	<0.1
 **11f**	6	Pd EnCat 40 (0.01)	1.3
 **11g**	7	Pd EnCat 40 (0.1)	<0.2
 **3c**	8	Pd EnCat 40 (0.1)	<0.2
	9	Pd EnCat TPP30 (0.1)	2.5

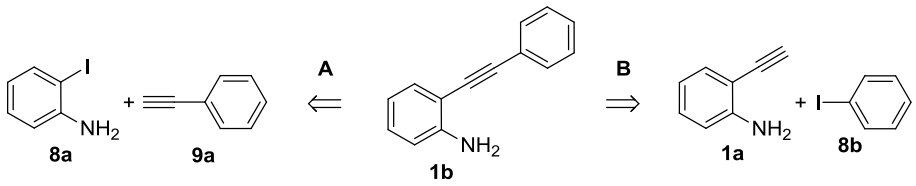
All the samples prepared with a loading of catalyst up to 0.1 mol % showed Pd contents lower than 6 ppm. In particular, the majority of results lay between 1 and less than 0.1 ppm, thus confirming the low level of leaching already reported for these catalysts.

When the loading of Pd EnCat 40 was 1 mol %, the leaching was slightly higher and we obtained a batch of **1b** contaminated by 71.5 ppm of palladium (Table 10, entry 3).

2.3 Selection and preparation of compounds 1

In Table 6, section 2.2.2, we showed that 2-phenylethynylaniline, **1b**, could be prepared efficiently by employing Pd EnCat 40 as a catalytic precursor and that the two selected synthetic approaches, as already discussed at the beginning of section 2.2 and exemplified in Scheme 34, are both practicable. In the following Table 11, we report a summary of the results obtained for the synthesis of **1b**. These data were already shown in the discussion contained in previous section 2.2.2 and are sorted out only to better exemplify our synthetic choices for preparing other compounds of general formula **1**.

Table 11. Summary of the results obtained for the synthesis of **1b**.

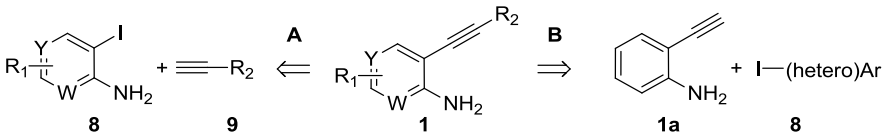


Disconnection	Pd (mol %)	Base (equiv)	Alkyne (equiv)	Temp (time)	Heating	Yields
A	Pd EnCat 40 (0.1)	pyrrolidine (2 equiv)	**9a** (1.5 equiv)	85 °C (5 h)	Thermal	77 %
A	Pd EnCat 40 (0.01)	pyrrolidine (2 equiv)	**9a** (1.5 equiv)	85 °C (6.5 h)	Thermal	42 %
B	Pd EnCat 40 (0.1)	pyrrolidine (2 equiv)	**1a** (1.5 equiv)	85 °C (2.5 h)	Thermal	99 %
B	Pd EnCat 40 (0.01)	pyrrolidine (2 equiv)	**1a** (1.5 equiv)	85 °C (2.5 h)	Thermal	84 %
A	Pd EnCat 40 (0.01)	pyrrolidine (2 equiv)	**9a** (1.5 equiv)	100 °C (30 min)	MW	95 %
B	Pd EnCat 40 (0.01)	pyrrolidine (2 equiv)	**1a** (1.5 equiv)	100 °C (30 min)	MW	99 %

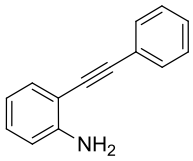
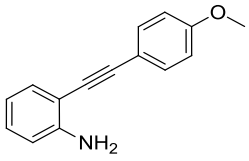
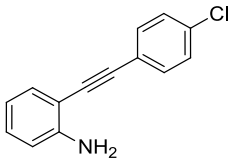
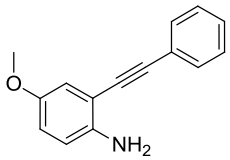
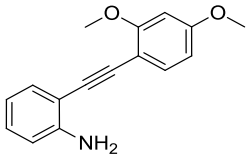
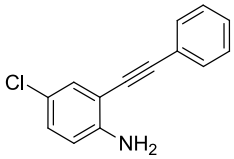
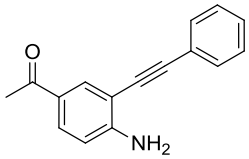
According to our results and as already pointed out, the application of microwave irradiation afforded **1b** in high yield even though with low Pd loading, thus offering the advantage of preparing compounds **1** with a minimal Pd contamination. In the following Table 12 we report the compounds that were prepared by the above described methodology

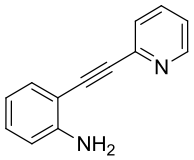
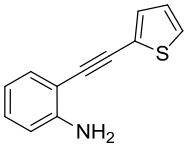
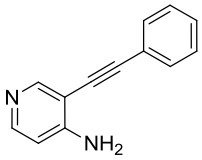
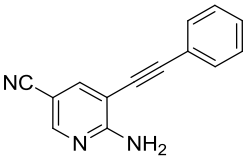
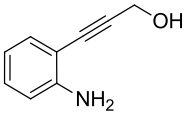
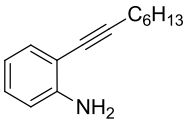
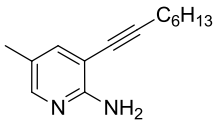
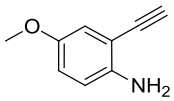
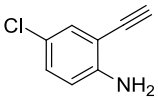
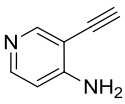
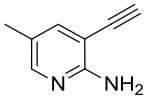
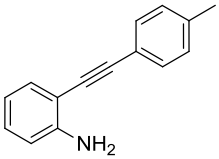
together with the corresponding conditions in terms of Pd loading, reaction temperature and time.

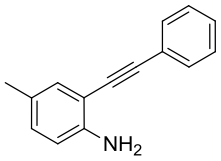
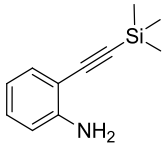
Table 12. Synthesis of compounds **1** *via* Cu-free Sonogashira coupling with Pd EnCat 40.[a]



8 9 1 1a 8

Entry	Disconnection	Product		Pd EnCat 40 (mol %)	Temp (time)	Heating	Yield[b]
1	**B**		**1b**	0.01	85 °C (2.5 h)	thermal	84 %
				0.01	100 °C (30 min)	MW	99 %
2	**B**		**1c**	0.01	85 °C (6 h)	thermal	90 %
				0.01	100 °C (30 min)	MW	98 %
3	**B**		**1d**	0.01	85 °C (3 h)	thermal	88 %
				0.01	100 °C (30 min)	MW	97 %
4	**A**		**1e**	0.1	85 °C (6 h)	thermal	65 %
				0.1	100 °C (20 min)	MW	75 %
5	**B**		**1f**	0.05	85 °C (8 h)	thermal	51 %
6	**A**		**1g**	0.01	100 °C (60 min)	MW	89 %
7	**A**		**1h**	0.01	100 °C (30 min)	MW	50 %

8	**B**		**1i**	0.01	85 °C (3.5 h)	thermal	85 %
9	**B**		**1j**	0.1	85 °C (9 h)	thermal	73 %
10	**A**		**1k**	0.1	85 °C (5 h)	thermal	92 %
11	**A**		**1l**	0.1	85 °C (1 h)	thermal	66 %
12	**A**		**1m**	0.2	85 °C (5 h)	thermal	39 %
13	**A**		**1n**	0.2	85 °C (22 h)	thermal	40 %
14	**A**		**1o**	0.2	85 °C (22 h)	thermal	59 %
15	**A**		**1p**[c]	0.1	100 °C (20 min)	MW	49 %
16	**A**		**1q**[c]	0.1	100 °C (30 min)	MW	79 %
17	**A**		**1r**[c]	0.1	100 °C (40 min)	MW	82 %
18	**A**		**1s**[c]	0.1	100 °C (20 min)	MW	67 %
19	**B**		**1t**	0.05	85 °C (2.5 h)	thermal	85 %

20	**A**		**1u**	0.1	85 °C (18 h)	thermal	65 %
21	**A**		**1v**	0.05	100 °C (1h)	MW	51 %

[a]Reactions were run using 4 mmol of iodide **8**, 1.5 equiv of alkyne **9** or **1a**, 2 equiv of pyrrolidine and the specified amount of Pd as Pd EnCat 40. [b]Isolated yields of compounds **1** after chromatography. [c]The coupling was run between the corresponding iodo-derivative and trimethylsilylacetylene, followed by de-silylation with NaOH in methanol.

As depicted in Table 12, the method we set up with Pd EnCat 40 and pyrrolidine confirmed its applicability and its aptitude to represent a general synthetic methodology to prepare diarylalkynes with a wide variety of functional groups. In some instances, a comparison between thermal heating and microwave heating was run, usually with increased yields in favour of microwaves. In particular, when volatile alkynes were involved in the cross coupling (*e.g.* trimethylsilylacetylene) we found microwave heating especially useful since the use of a closed vessel equipment allowed to reach temperature higher than the reagent boiling points (Table 12, entries 15-18).

Moreover, sample compounds were analyzed by atomic absorption analysis and the data obtained for Pd confirmed the low contents expected. As a further confirm, also copper was analyzed to find that it was below detection limits.

Table 13. Atomic absorption analysis data.

Sample	Compound	Catalyst (mol %)	Pd content (ppm)	Cu content (ppm)
1	2-(Phenylethynyl)aniline, **1b**	Pd EnCat 40 (0.01)	< 0.1	< 0.1
2	2-{[4-(Methyloxy)phenyl]ethynyl}aniline, **1c**	Pd EnCat 40 (0.01)	< 0.1	< 0.1
3	2-[(4-Chlorophenyl)ethynyl]aniline, **1d**	Pd EnCat 40 (0.01)	< 0.1	< 0.1

2.4 Conclusions

In summary, the methodology we developed for the copper- and solvent-free Sonogashira-type coupling mediated by Pd EnCat^{TM} catalysts (*i.e.* Pd EnCat 40 and Pd EnCat TTP30) demonstrated its broad scope and furnished satisfying results for a vast number of differently substituted aryl halides and alkynes. Our efficient and very simple procedure allowed for the alkynylation of aryl iodides bearing both electron-withdrawing and electron-donating substituents and of activated aryl bromides. What particularly deserves attention is that the pre-catalysts maintained its activity even at low loadings (down to 0.01 mol % of Pd for the most reactive substrates). Moreover, its efficiency could be enhanced by microwave irradiation

Finally, these conditions proved not sensitive to moisture and air and furnished alkynyl derivatives free from significant heavy metal contaminations. In addition, the preliminary data gathered in recycling experiments show that Pd EnCat 40 possessed a good potential for reusing. This piece of work led to a paper publication in 2009.[72]

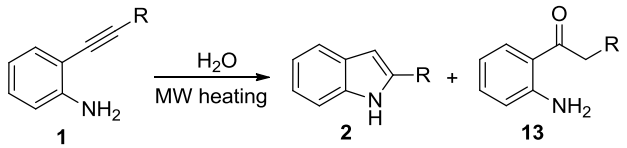
Chapter 3

Microwave-assisted cycloisomerization of 2-alkynylanilines and pyridinamines in water without adding catalysts, acids or bases

3.1 First trials of microwave-assisted cyclization in water

As discussed earlier during the objective statements, our key idea was that a microwave-assisted cycloisomerization of 2-alkynylanilines and pyridinamines taking place *via* an intramolecular hydroamination might be a feasible way to prepare substituted (aza)indoles. In particular, we wanted to explore the use of water as a solvent and to apply microwave irradiation to reach the water "near critical"[23] region. To the best of our knowledge, this methodology is unprecedented and would represent the first example of microwave-assisted cyclization of 2-alkynylanilines achieved without any added metal catalyst. The main results of our first attempts are summarized in Table 14.

Table 14. Microwave-assisted cycloisomerization first attempts.[a]



Entry	R	1	Temperature	Time	2	HPLC conv. (% a/a)	Yields (%)[b]	
							13	2
1	H	**1a**	150 °C	10 min	**2a**	1	—	1
2	H	**1a**	190 °C	10 min	**2a**	8	—	7
3	H	**1a**	200 °C	10 min	**2a**	42	—	23
4	H	**1a**	200 °C	30 min	**2a**	45	25	17
5	H	**1a**	200 °C	60 min	**2a**	57	50	6
6	H	**1a**	220 °C	30 min	**2a**	87	5	25
7	Ph	**1b**	200 °C	30 min	**2b**	15	—	14
8	Ph	**1b**	200 °C	60 min	**2b**	19	—	17
9	Ph	**1b**	200 °C	120 min	**2b**	35	—	33

[a]Reaction conditions: 2-alkynylaniline **1** (0.1 mmol), water (2 ml). [b]Yields in solution determined by HPLC, using a calibration curve.

As model substrates we chose one terminal alkyne, the commercially available 2-ethynylaniline, **1a**,[76] to give 1*H*-indole, **2a**, and the diarylalkyne, 2-(phenylethynyl)aniline, **1b**, to obtain 2-phenylindole, **2b**. In order to avoid potential metal contaminants, we used

ACS UltraTrace water, where most common transition and non transition metals are present at a 10^{-5} ppm level. In addition, we always employed new glassware.

In a first instance, we worked with 2-ethynylaniline, **1a**, to identify the temperature required for the cyclization. Although this substrate showed some instability when heated above 150 °C, a certain amount of indole, **2a**, could be obtained at 200 °C in 10 min (Table 14, entry 3), while at lower temperatures no significant conversion was observed (Table 14, entries 1 and 2).

However, prolonged heating at 200-220 °C for more than 10 minutes proved detrimental, since degradation of both product and starting material occurred, as we can notice by comparing the conversion measured by HPLC with the yield observed. What is more, 2-aminoacetophenone, **13a**, resulting from the hydration of the starting alkyne, was formed along with the desired indole, **2a** (Table 14, entries 4-6).

The second model compound, **1b**, showed a good stability in the applied conditions, without significant hydration but proved rather less reactive than **1a** within shorter reaction times (entry 7, Table 14). However, a not negligible amount of **2b** was formed when the reaction mixture was heated to 200 °C for times longer than 30 minutes (Table 14, entries 8 and 9).

This full assessment of the cyclization feasibility in water required not only significant improvements in the formation of indole derivatives, but also a systematic study to highlight the importance of the role presumably played by water as the reaction medium. For this reason a solvent screening was put in place as described in the following paragraph 3.1.1.

3.1.1 Solvent screening

A list of common solvents was selected among those typically employed in microwave-assisted synthesis.

To our surprise, we found that the cycloisomerization of **1b** afforded only 0–3 % of 2-phenylindole, **2b**, in media different from water (Table 15, entries 1-10). On the other hand, the addition of water to a selection of solvents gave somewhat better results (Table 15, entries 11-13).

Table 15. Solvent screening for the microwave-assisted cycloisomerization of 2-phenylethynylaniline, **1b**.[a]

Entry	Solvent	Water (% v/v)	Temperature	Time	Yield[b] of 2b
1	EtOH	—	200 °C	30 min	2
2	*n*-BuOH	—	200 °C	30 min	3
3	DMF	—	200 °C	30 min	1
4	CH_3CN	—	200 °C	30 min	1
5	THF	—	200 °C	30 min	1
6	NMP	—	200 °C	30 min	2
7	1,2-dichlorobenzene	—	200 °C	30 min	2
8	toluene	—	200 °C	30 min	—
9	DMSO	—	200 °C	30 min	—[c]
10	$[BMIm]BF_4$	—	200 °C	30 min	—
11	EtOH	25 %	200 °C	30 min	6
12	NMP	25 %	200 °C	30 min	3
13	DMF	25 %	200 °C	30 min	10[c]
14	$[BMIm]BF_4$	25 %	200 °C	30 min	—[c]

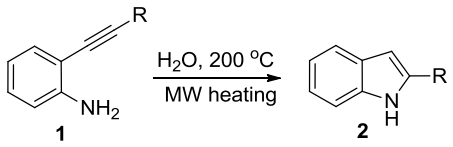
[a]Reaction conditions: 0.1 mmol of **1b**, solvent (2 ml). [b]Yields in solution determined by HPLC, using a calibration curve. [c]Significant degradation of starting material observed.

3.1.2 Microwave-assisted cycloisomerization in water: method development

Since the presence of water appears so important for the cycloisomerization, we moved forwards with a condition optimization plan in aqueous media which included, in a first instance, an extension of microwave irradiation times in order to see if a yield enhancement was possible. However, prolonging heating at 200 °C for 2 hours or more was often accompanied in our equipment by leakage from the reaction caps with loss of water and compounds and some degradation of the substrates.

For this reason we thought that the application of short cycles of microwave heating could provide an overall long irradiation but in conditions less stressful for the equipment, since reaction vials are cooled and de-pressurized between one cycle of heating and the other. The effect of MW short cycles was investigated for four different substrates, as shown in Table 16. All the arylalkynes **1** were prepared according to our procedure (see paragraph 2.3).[72]

Table 16. Condition optimization for the cycloisomerization of 2-aminophenylalkynes.[a]



1 2

Entry	R	1	MW cycles		mmol of 1/ml	total time (h)	2	Yield[b] (%)
			cycle number	cycle time				
1	H	**1a**	1	10 min	0.05	0.16	**2a**	23
2	H	**1a**	3	5 min	0.05	0.25	**2a**	16[c]
3	Ph	**1b**	1	120 min	0.05	2	**2b**	33
4	Ph	**1b**	3	30 min	0.05	1.5	**2b**	63
5	Ph	**1b**	9	10 min	0.05	1.5	**2b**	65
6	Ph	**1b**	18	5 min	0.05	1.5	**2b**	69
7	Ph	**1b**	18	5 min	0.10	1.5	**2b**	59
8	Ph	**1b**	18	5 min	0.15	1.5	**2b**	44
9	Ph	**1b**	18	5 min	0.25	1.5	**2b**	27
10	4-MeO-Ph	**1c**	3	30 min	0.05	1.5	**2c**	56
11	4-MeO-Ph	**1c**	9	10 min	0.05	1.5	**2c**	58
12	4-MeO-Ph	**1c**	18	5 min	0.05	1.5	**2c**	77
13	4-MeO-Ph	**1c**	18	5 min	0.10	1.5	**2c**	78
14	4-MeO-Ph	**1c**	18	5 min	0.15	1.5	**2c**	31
15	4-Cl-Ph	**1d**	3	30 min	0.05	1.5	**2d**	36
16	4-Cl-Ph	**1d**	9	10 min	0.05	1.5	**2d**	49
17	4-Cl-Ph	**1d**	18	5 min	0.05	1.5	**2d**	65
18	4-Cl-Ph	**1d**	18	5 min	0.10	1.5	**2d**	40
19	4-Cl-Ph	**1d**	18	5 min	0.15	1.5	**2d**	26

[a]Reactions conditions: the specified amount of 2-aminophenylalkyne **1** was suspended in water (2 ml) and heated to 200 °C under microwave irradiation for the allotted time. [b]Yields in solution determined by HPLC, using a calibration curve. [c]Degradation observed; 2-aminoacetophenone, **13a**, was the main product.

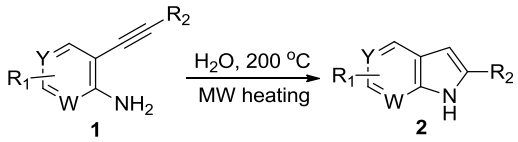
What we immediately observed when shorter cycles where applied was that not only leakages and degradation were minimized, but also yields were significantly improved (see Table 16, compare entries 3-6, entries 10-12 and entries 15-17), except for 2-ethynylaniline, **1a**, where the yield remained low (Table 16, entries 1 and 2). Having these interesting results in hands, we tried to increase the concentration of substrates from 0.05 up to 0.15 mmol/ml. However, when reactions were run with a concentration of 0.1 mmol/ml, slightly lower yields were observed for **2b** and **2d** (Table 16, entries 7 and 18), mainly as a result of the presence of not reacted starting materials. A further increase in the concentrations to 0.15 mmol/ml caused a more drastic decrease in the yield for all the substrates (Table 16, entries 8, 14 and 19). In addition, in the instance of substrate **1b**, we tried to further increase the concentration reaching 0.25 mmol/ml and the dropping trend was confirmed by a yield of 27 % (Table 16, entry 9).

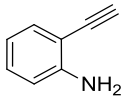
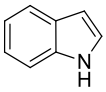
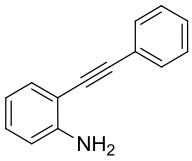
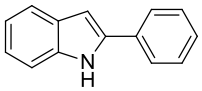
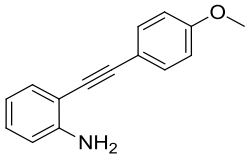
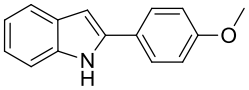
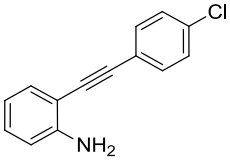
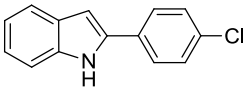
Notably, we could have further extended the number of cycles to increase the conversion at higher concentrations. However, a microwave irradiation of 1.5 h is considerably long already. Moreover, our objective was to find efficient conditions for the cycloisomerization also in terms of irradiation times. Having said that, we selected 0.1 mmol/ml as the preferred concentration to run efficiently the cyclization in water and we continued our studies as described in the following Chapter 4, in the search for more efficient procedures.

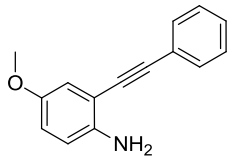
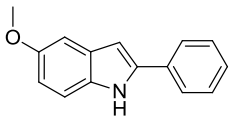
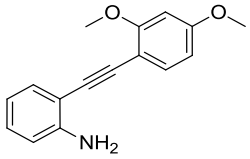
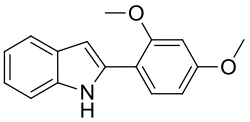
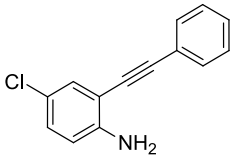
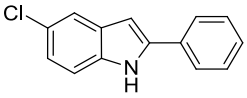
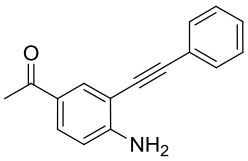
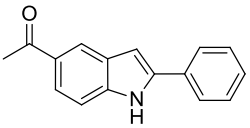
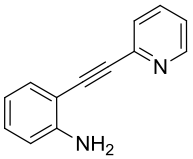
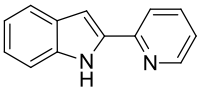
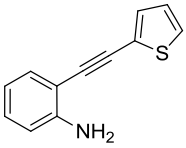
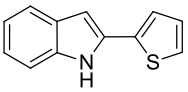
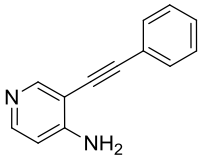
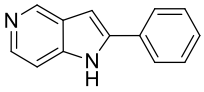
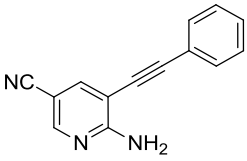
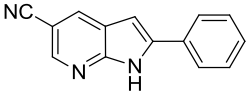
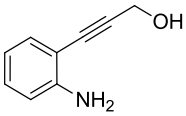
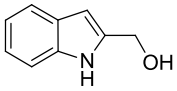
3.2 Case study on indoles and azaindoles synthesis

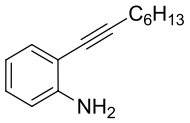
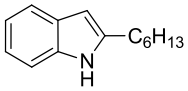
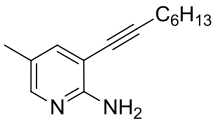
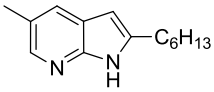
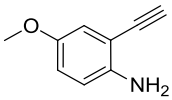
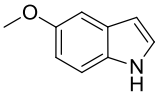
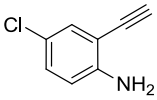
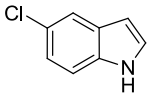
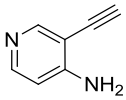
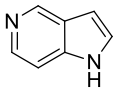
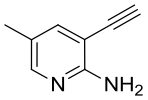
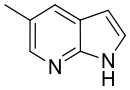
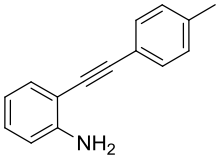
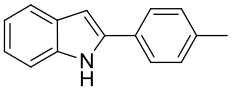
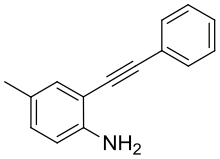
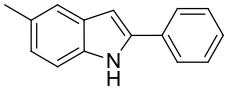
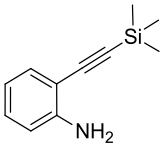
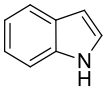
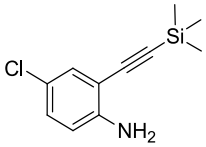
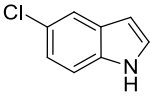
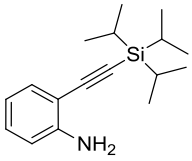
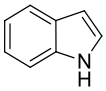
With the aim of extending the scope of our cyclization conditions, we explored the reactivity of different substrates. We prepared a series of differently substituted 2-aminophenylacetylenes and 2-aminopyrydinylacetylenes (following the procedure described in paragraph 2.3) and the most efficient conditions found so far were applied to achieve the cyclization. The 0.1 mmol/ml concentration was selected, since we showed during the process optimization that higher concentrations gave lower yields. Concentrations lower than 0.1 mmol/ml might probably perform better, but with a lower synthetic significance and applicability. In Table 17 we summarized our results.

Table 17. Preparation of indoles and azaindoles *via* cycloisomerization reactions of 2-amino(hetero)arylalkynes.[a]



Entry	Alkyne	1	Indole	2	Conditions (cycles N/min)	Yield[b] (%)
1		**1a**		**2a**	1/10	23[c]
2		**1b**		**2b**	18/5	46
3		**1c**		**2c**	18/5	79
4		**1d**		**2d**	18/5	34

5		**1e**		**2e**	10/5	59
6		**1f**		**2f**	18/5	50
7		**1g**		**2g**	18/5	49
8		**1h**		**2h**	18/5	20
9		**1i**		**2i**	18/5	97
10		**1j**		**2j**	18/5	85
11		**1k**		**2k**	18/5	97
12		**1l**		**2l**	18/5	27[d]
13		**1m**		**2m**	10/5	29[c]

14		**1n**		**2n**	18/5	9[e]
15		**1o**		**2o**	18/5	<1
16		**1p**		**2p**	6/5	69
17		**1q**		**2q**	6/5	67
18		**1r**		**2r**	6/5	62
19		**1s**		**2s**	4/5	74
20		**1t**		**2t**	18/5	33
21		**1u**		**2u**	18/5	46
22		**1v**		**2a**	6/5	20
23		**1x**		**2q**	6/5	5
24		**1y**		**2a**	18/5	< 1

[a]Reactions were run in sealed tubes with 0.4 mmol of 2-aminoarylalkyne suspended in 4 ml of water and the suspension heated to 200 °C by microwave irradiation applied in cycles as specified in the Table. [b]Isolated yields after chromatography. [c]Significant degradation observed. [d]Alkyne hydration was the main reaction. [e]The main product was 1-(2-aminophenyl)-1-octanone which was isolated in 67 % mol yield.

Moderate to good isolated yields were obtained for 2-(arylethynyl)anilines (Table 17, entries 2-7), except for **1h** (20 %, Table 17, entry 8), with the best cyclization yields achieved with substrates bearing electron-donating substituents. Low yields in **2a** were obtained starting from both **1a** and from the corresponding trimethylsilyl derivative **1v** (Table 17, entries 1 and 22), since in both cases degradation prevailed. Also the (alkylethynyl)anilines **1m** and **1n** gave **2m** and **2n** in very low yields (Table 17, entries 13 and 14).

A series of heteroarylalkynes were also prepared and tested under the same conditions. What we found was that these substrates were giving in general very high yields and better results than compounds not bearing a heteroatom. While for 2-(arylethynyl)anilines electron-rich substrates cyclized more easily than electron-poor ones, substrates containing both electron-rich and electron-poor heteroaromatic rings gave high yields (Table 17, entries 9-11).

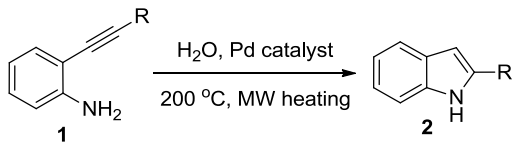
At this regard, we speculated that the higher solubility of heteroaryl compounds in water could be mainly responsible for the increased reactivity observed, not underestimating also the increased polarity of the reaction mixture and the consequent increased interaction with microwaves. The only exception to the observed general trend was represented by compound **1o** which was basically not reactive in water alone and gave the corresponding azaindole **2o** only in traces.

A small number of terminal alkynes were also synthesized and tested to find that very good yields could be obtained (Table 17, entries 16-19) and that such substrates were not as unstable as **1a** when heated in water at 200 °C. As for trialkylsilylalkynes, we found that the presence of a R_3Si group inhibited the cyclization which took place only when the R_3Si group cleavage occurred in significantly high conversions. In fact, when deprotection was more difficult, as for *i*-Pr_3Si group, cyclization to indole hardly happened.

3.3 Effect of Pd salts on the cycloisomerization

Before going further with our studies, we felt necessary to verify that our cycloisomerization reactions were not taking place because of the presence of the Pd salts which could potentially contaminate our starting arylalkynes. In other words, by means of studying the effect of the presence of palladium at different concentrations, we wanted to show that this effect was negligible at our concentrations, which were surely lower than 0.1 ppm according to atomic absorption analyses. These results are reported in Table 18.

Table 18. Cyclization of **1** in water in the presence of Pd sources.[a]



Entry	R	1	Palladium		Time (min)	Ratio 2/1	Yield[b] (%)
			Catalyst	Loading (mol %)			
1	Ph	**1b**	none	none	30 min	15/85	14
2	Ph	**1b**	$PdCl_2$	0.1	30 min	99/1	56
3	Ph	**1b**	$Pd(OAc)_2$	0.1	30 min	17/83	15
4	Ph	**1b**	$Pd(OAc)_2$	0.1	90 min	70/30	51
5	Ph	**1b**	$PdCl_2$	0.01	30 min	18/82	16
6	Ph	**1b**	$Pd(OAc)_2$	0.01	30 min	20/80	19
7	Ph	**1b**	n.d.	0.013[c]	30 min	15/85	12
8	H	**1a**	none	none	10 min	99/1	23
9	H	**1a**	$PdCl_2$	0.1	10 min	99/1	9
10	H	**1a**	$Pd(OAc)_2$	0.1	10 min	99/1	29

[a]Reaction conditions: **1** (0.3 mmol), water (2 ml) and the specified amount of Pd catalyst were heated to 200 °C by microwave irradiation for the allotted time. [b]Yields in solution determined by HPLC, using a calibration curve. [c] Palladium present as contaminant in the starting material (see Table 10, entry 3, page 74).

A first screening of catalyst loadings showed that the presence of Pd salts holds indeed an important effect at certain concentrations. When the reaction was conducted with a 0.1 mol % of palladium, cyclization of **1b** to **2b** was visibly accelerated even if considerable degradation of starting material occurred (Table 18, entries 2-4). If a lower amount of

palladium was applied, down to 0.01 mol %, cyclization yields were not significantly higher than in the absence of added catalyst (compare Table 14, entry 7 and Table 18, entries 5 and 6). Also, a low yield was observed when a Pd contaminated starting alkyne was used, without any added Pd species (Table 18, entry 7). A strong effect was observed in the case of terminal alkyne **1a** in the presence of 0.1 mol % of palladium. In fact, hydration to acetophenone and decomposition were accentuated (Table 18, entries 9 and 10).

As described in paragraph 2.3, our starting arylalkynes were prepared with a methodology which used 0.2-0.01 mol % as Pd loading. Moreover, we demonstrated that the Pd leaching after the Sonogashira coupling was really limited since we produced substrates containing less than 0.1 ppm of that metal, which corresponded to a loading lower than $2x10^{-5}$ mol %. This value was significantly lower than the percentage giving significant catalytic activity in the cycloisomerization reported in Table 18. As a consequence, we can reasonably exclude at that level of concentration an effective participation of palladium in the ring closure.

3.4 Conclusions

In summary, we demonstrated that 1*H*-indole, **2a**, 2-substituted indoles and azaindoles of general formula **2** can be obtained by a simple and straightforward methodology which involves the microwave-promoted cycloisomerization of the corresponding 2-alkynylanilines and pyridinamines in water. The first ambitious objective we fixed at the beginning of this work was thus almost reached, since neither acid/basic additives, nor metal catalysts were added to promote the reactions.

The results presented in Chapter 3 were the subject of a paper publication appeared in 2009.[77]

However, there was still place for further developments, since we encountered two significant limits in this first part of the work: *i*) yields were only moderate for certain substrates, that is our method was not completely general; *ii*) above certain substrate concentrations, yields decreased thus diminishing the interest and applicability of our procedure. In the following Chapter 4, we will illustrate the work done to overcome these limits and to further develop our methodology.

Chapter 4

Microwave-assisted cycloisomerization in water of 2-alkynylanilines and alkynylpyridinamines promoted by catalytic amounts of neutral or basic salts

4.1 The effect of inorganic salts in the microwave-assisted cycloisomerization in water of 2-alkynylanilines and alkynylpyridinamines

In the previous Chapter 3 we presented the first example of microwave-assisted cyclization of 2-alkynylanilines and alkynylpyridinamines in water achieved without any added metal catalyst. We demonstrated that 1*H*-indole, 2-substituted indoles and azaindoles can be obtained by a straightforward methodology which involves a microwave-promoted cycloisomerization in water, taking place *via* intramolecular hydroamination from the corresponding 2-alkynylanilines. The cyclization proceeded without any additive, either acid or basic, and without any metal catalyst.

However, even though moderate to good yields were achieved for a variety of substrates, the methodology presented clear limitations especially in terms of applicability. In fact, if high yields were obtained for compounds bearing electron-donating substituents, the introduction of an alkyl substituent on the triple bond or of certain substituent on the phenyl groups (*e.g.* CH_3CO, Cl, or CH_3) caused a significant decrease in yield.

Nonetheless, the main and more penalizing limitation emerged when we tried to increase the substrate concentration above 0.1 mmol/ml. In fact, yield dropped in the cases we investigated, and, after significant efforts, it appeared clear that a further improvement of these conditions was not straightforward. Therefore, a considerable amount of work was performed to develop a more efficient method, which still made use of water and applied simple conditions, but which also worked better for a wider range of both substrates and concentrations.

In the search for more efficient cyclization conditions, with the aim of developing a more general method suitable for higher substrate loadings and for diversified starting materials, we tried to find species that, if added to water, could help the cyclization, enhance the interaction of the substrates with microwaves and/or possibly increase the solubility in water of the less reactive substrates.

Our first intent was to explore the effect of the addition of small amounts of inorganic salts (neutral, acid or basic). Our idea arose from the well known principle[20a23a] that the dielectric loss of water (and as a consequence its loss tangent) can be significantly increased by the addition of inorganic salts, even in small amounts, since microwave absorbance is improved by ionic conduction.

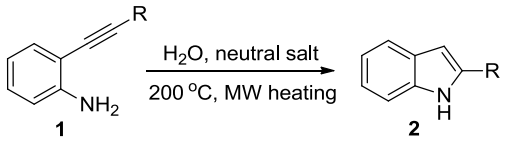
Moreover, we speculated that relatively low salt concentrations (0.03 M–0.001 M) could be sufficient to play an influence on the reactivity of the near-critical water medium.

4.1.1 Salt screening on model compounds 1a and 1b

To identify a possible effect played by inorganic salts on the cycloisomerization in water, we screened neutral, basic and acid salts as additives. We worked on two model substrates, the terminal alkyne **1a**, and the diarylalkyne **1b**. Both substrates **1a** and **1b** were prepared according to our aforementioned procedure.[72]

The results obtained from the neutral salt screening are summarized in Table 19.

Table 19. Microwave-assisted cycloisomerization: screening of neutral salts[a]



1 2

Entry	R	1	Salt	Equiv of salt	Time (min)	2	Yield of 2[b] (%)
1	H	**1a**	—	—	15	**2a**	15[c]
2	H	**1a**	KCl	0.1	15	**2a**	35[c]
3	H	**1a**	KBr	0.1	15	**2a**	25[c]
4	H	**1a**	KI	0.1	15	**2a**	23[c]
5	H	**1a**	(*n*-Bu)$_4$NBr	0.1	15	**2a**	27[c]
6	H	**1a**	KCl	0.1	5	**2a**	15[c]
7	H	**1a**	KCl	0.1	30	**2a**	25[c]
8	Ph	**1b**	—	—	30	**2b**	14
9	Ph	**1b**	LiCl	0.1	30	**2b**	30
10	Ph	**1b**	NaCl	0.1	30	**2b**	41

11	Ph	**1b**	KCl	0.1	30	**2b**	60
12	Ph	**1b**	LiBr	0.1	30	**2b**	40
13	Ph	**1b**	NaBr	0.1	30	**2b**	38
14	Ph	**1b**	KBr	0.1	30	**2b**	37
15	Ph	**1b**	LiI	0.1	30	**2b**	38
16	Ph	**1b**	NaI	0.1	30	**2b**	30
17	Ph	**1b**	KI	0.1	30	**2b**	33
18	Ph	**1b**	(*n*-Bu)$_4$NCl	0.1	30	**2b**	15
19	Ph	**1b**	(*n*-Bu)$_4$NBr	0.1	30	**2b**	16
20	Ph	**1b**	(*n*-Bu)$_4$NI	0.1	30	**2b**	21

[a]Reaction conditions: 2-aminophenylalkyne **1** (0.1 mmol) was suspended in water (2 ml) and heated to 200 °C in the presence of the corresponding salt under microwave irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve. [c]2-Aminoacetophenone was the main product, along with considerable degradation.

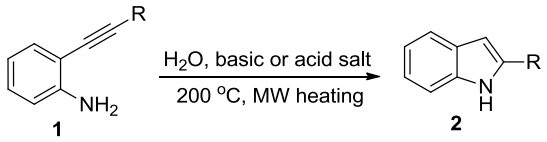
Although substrate **1a** showed a considerable instability under our set of conditions, an encouraging yield of 35 % in 1*H*-indole, **2a**, could be obtained after 15 minutes at 200 °C by adding 0.1 equiv of KCl (Table 19, entry 2). However, all the other salts screened under the same conditions gave rise to degradation and/or hydration to 2-aminoacetophenone (Table 19, entries 3-7).

On the other hand, the second model compound, **1b**, proved stable under the applied conditions without significant hydration, but appeared rather less reactive than **1a**. For this reason the salt screening was run at 200 °C with 30 minutes of microwave irradiation, where significant amounts of indole **2b** were formed. The screening indicated that, also for **2b**, most of the salts are able to improve the yields with respect to water alone. In particular, the best result was obtained in the presence of KCl, where after 30 minutes a 60 % yield in **2b** was observed (Table 19, entry 11).

In a second instance, we examined the use of basic and acid inorganic additives, still working with the two model substrates **1a** and **1b**. The results of the study are reported in Table 20.

Not surprisingly, all the basic salts tested allowed a significant improvement in the cyclization yields with respect to water alone after 30 min at 200 °C.

Table 20. Microwave-assisted cycloisomerization: screening of basic and acid salts[a]



Entry	R	1	Salt	Equiv of salt	Time (min)	2	Yield of 2[b] (%)
1	H	**1a**	NaOH	0.1	30	**2a**	66
2	H	**1a**	$NaHCO_3$	0.1	15	**2a**	45
3	H	**1a**	$NaHCO_3$	0.1	30	**2a**	60
4	H	**1a**	NH_4Cl	0.1	15	**2a**	<1[c]
5	Ph	**1b**	LiOH	0.1	30	**2b**	65
6	Ph	**1b**	NaOH	0.1	30	**2b**	53
7	Ph	**1b**	KOH	0.1	30	**2b**	40
8	Ph	**1b**	$NaHCO_3$	0.1	30	**2b**	70
9	Ph	**1b**	Na_2CO_3	0.1	30	**2b**	48
10	Ph	**1b**	$KHCO_3$	0.1	30	**2b**	58
11	Ph	**1b**	K_2CO_3	0.1	30	**2b**	66
12	Ph	**1b**	Na_2HPO_4	0.1	30	**2b**	46
13	Ph	**1b**	KF	0.1	30	**2b**	55
14	Ph	**1b**	$(n\text{-Bu})_4NF$	0.1	30	**2b**	45
15	Ph	**1b**	AcONa	0.1	30	**2b**	30
16	Ph	**1b**	NH_4Cl	0.1	30	**2b**	10[d]

[a]Reaction conditions: 2-aminophenylalkyne **1** (0.1 mmol) was suspended in water (2 ml) and heated to 200 °C in the presence of the corresponding additive under microwave irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve. [c]2-Aminoacetophenone was the main isolated product. [d]1-(2-Aminophenyl)-2-phenylethanone was the main isolated product.

Nonetheless, very good results were obtained with $NaHCO_3$ for both **1a** and **1b** with 60 % and 70 % yield, respectively (see Table 20, entries 3 and 8). On the other hand, when an acid salt like ammonium chloride was used, hydration of the triple bond to the corresponding arylketone was the main reaction observed. In fact, 2-aminoacetophenone, **13a**, was the main product isolated in 75 % yield from **1a**, while 1-(2-aminophenyl)-2-phenylethanone, **13b**, was the main product isolated in 85 % yield from **1b** (Table 20, entries 4 and 16).

4.1.2 Salt-promoted cycloisomerization optimization: the selection of KCl and $NaHCO_3$ as preferred additives

Having demonstrated that the addition of a salt (neutral or basic) in catalytic amount facilitates the cycloisomerization, we worked with the objective to render our reaction even more attractive not only for the novelty of the methodology but also for its applicability. In paragraph 3.1.2, we showed that an increase in the concentration of the substrates caused a drastic decrease in the yield of the cycloisomerization in water alone. The use of aqueous salt solutions as the cyclization media could represent a possibility to overcome this limitation. In particular, in consideration of the results obtained during the salt screening, potassium chloride and sodium bicarbonate were selected for further studying since they gave higher cyclization yields, as illustrated in Table 19 and Table 20.

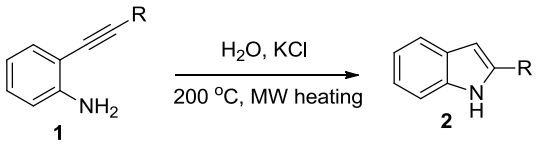
To extend the study, two reaction sets were planned with KCl and $NaHCO_3$, each analyzing a selected group of parameters: salt and substrate concentrations, MW irradiation time, number and duration of irradiation cycles.

The addition of a salt demonstrated beneficial for the yield. However, since the beginning of our investigation, we immediately observed that it was accompanied by a significant increase in the pressure which developed inside the reaction vials during the heating process. In particular, when 1 equiv of salt was added, we observed substantial leakages from the reaction caps with loss of water and compounds when the temperature was approaching 200 °C. In some instances the target temperature was not even reached due to overpressure taking place when the temperature arrived at 190 °C (the maximum pressure tolerated by our equipment was 20 bars) and lower conversions were obtained consequently. Following these preliminary observations, we thought it more advantageous working with substoichiometric amounts of inorganic salts which maintained their efficacy in promoting the cyclization but allowed higher temperatures inside the vials since pressure remained below the allowed safety limits.

Moreover, as we previously described for reactions run in water without additives, the application of short cycles of microwave heating helped in managing the overpressure problem. In fact, reaction vials were cooled and de-pressurized between one cycle of heating and the other, offering the same irradiation time in conditions less stressful for the equipment, even at the higher substrate concentrations that we applied. This practice, together with a careful tune of the additive concentration, was able to guarantee that the internal pressure remained below 20 bars while the operating temperature reached 200 °C.

The catalytic amount of salt was varied between 0.1 and 0.5 equiv and a group of model substrates was identified to collect these results, as shown in the following Table 21 and Table 22.

Table 21. Condition optimization for the cycloisomerization of 2-aminophenylalkynes in water with KCl[a]



1 2

Entry	R	1	MW cycles		mmol of 1/ml	Total time (h)	Equiv of KCl	2	Yield[b] (%)
			Cycle number	Cycle time					
1	H	**1a**	1	20 min	0.1	0.33	0.1	**2a**	30
2	H	**1a**	1	20 min	0.25	0.33	0.1	**2a**	28
3	H	**1a**	4	5 min	0.25	0.33	0.1	**2a**	50
4	H	**1a**	4	5 min	0.25	0.33	0.2	**2a**	60
5	H	**1a**	6	5 min	1.0	0.5	0.2	**2a**	51
6	Ph	**1b**	1	30 min	0.05	0.5	0.1	**2b**	56
7	Ph	**1b**	1	30 min	0.05	0.5	0.2	**2b**	77
8	Ph	**1b**	1	30 min	0.05	0.5	0.05	**2b**	14
9	Ph	**1b**	1	30 min	0.05	0.5	0.3	**2b**	66
10	Ph	**1b**	1	30 min	0.05	0.5	0.4	**2b**	55
11	Ph	**1b**	1	30 min	0.05	0.5	0.5	**2b**	54
12	Ph	**1b**	3	30 min	0.10	1.5	0.1	**2b**	68
13	Ph	**1b**	6	10 min	0.10	1.0	0.1	**2b**	69
14	Ph	**1b**	12	5 min	0.10	1.0	0.1	**2b**	73
15	Ph	**1b**	18	5 min	0.25	1.5	0.1	**2b**	75

16	Ph	**1b**	18	5 min	0.25	1.5	0.2	**2b**	59
17	Ph	**1b**	18	5 min	0.50	1.5	0.1	**2b**	45
18	4-MeO-Ph	**1c**	3	30 min	0.10	1.5	0.1	**2c**	79
19	4-MeO-Ph	**1c**	12	5 min	0.10	1.0	0.1	**2c**	68
20	4-MeO-Ph	**1c**	18	5 min	0.10	1.5	0.1	**2c**	71
21	4-MeO-Ph	**1c**	18	5 min	0.20	1.5	0.1	**2c**	73
22	4-MeO-Ph	**1c**	18	5 min	0.25	1.5	0.1	**2c**	72
23	4-Cl-Ph	**1d**	3	30 min	0.10	1.5	0.1	**2d**	45
24	4-Cl-Ph	**1d**	12	5 min	0.10	1.0	0.1	**2d**	49
25	4-Cl-Ph	**1d**	18	5 min	0.10	1.5	0.1	**2d**	67
26	4-Cl-Ph	**1d**	18	5 min	0.20	1.5	0.1	**2d**	58
27	4-Cl-Ph	**1d**	18	5 min	0.25	1.5	0.1	**2d**	55

[a]Reaction conditions: the specified amount of 2-aminophenylalkyne **1** was suspended in water (2 ml) and the corresponding amount of salt was added. The mixture was heated to 200 °C under MW irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve.

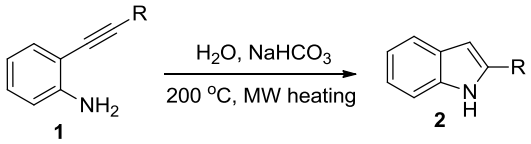
The cyclization yield of 2-ethynylaniline, **1a**, was 30 % in the presence of 0.1 equiv of KCl, but it could be raised up to 60 % when 0.2 equiv of KCl and MW irradiation in cycles of 5 minutes were applied (Table 21, entries 1-4). A certain effect played by concentration increase was observed, however, with 1 mmol/ml also, where a moderately good yield of 51 % was obtained for **2a** (Table 21, entry 5).

As for the cyclization of 2-(phenylethynyl)aniline, **1b**, we analyzed KCl concentrations in the range between 0.05 and 0.5 equiv with 0.05 mmol/ml of **1b**. We found that 0.05 equiv of KCl did not have a significant effect on the reaction since the yield was the same already observed in water alone (compare Table 21, entry 8 with Table 14, entry 7). When KCl concentration grew from 0.1 to 0.5 equiv, we observed a general yield enhancement with a maximum corresponding to 0.2 equiv of KCl (Table 21, entries 6-11). However, a slightly different behaviour was recorded at a concentration of **1b** of 0.25 mmol/ml, where 0.1 equiv of KCl worked better than 0.2 equiv (Table 21, compare entries 15 and 16). Considering that the higher was the concentration of KCl the higher was the internal pressure developed (close to safety cut off), we selected 0.1 equiv of salt for further studies.

The highest yield of **2b** (75 %) was obtained with 0.1 equiv of KCl after 1.5 h of MW irradiation in 5 minute cycles (Table 21, entry 15). As already noticed in other studies, the yield decreased with a raise in concentration of **1b** above 0.25 mmol/ml (Table 21, entry 17). However, a 45 % yield obtained with 0.5 mmol/ml remained a remarkable value. Similar trends were observed for the other two model substrates **1c** and **1d**. The two substrates cyclized with good yields in the presence of 0.1 equiv of KCl at concentrations up to 0.25 mmol/ml (Table 21, entries 18-22 and 23-27).

Satisfying results could be achieved for indoles **2a-d** with $NaHCO_3$ as well, as described in Table 22.

Table 22. Condition optimization for the cycloisomerization of 2-aminophenylalkynes in water with $NaHCO_3$[a]



1 2

Entry	R	1	MW cycles		mmol of 1/ml	Total time (h)	Equiv of $NaHCO_3$	2	Yield[b] (%)
			Cycle number	Cycle time					
1	H	**1a**	1	30 min	1.0	0.5	0.2	**2a**	60
2	H	**1a**	6	5 min	1.0	0.5	0.2	**2a**	61
3	Ph	**1b**	1	30 min	0.05	0.5	0.1	**2b**	68
4	Ph	**1b**	1	30 min	0.05	0.5	0.2	**2b**	60
5	Ph	**1b**	18	5 min	0.25	1.5	0.1	**2b**	70
6	Ph	**1b**	18	5 min	0.50	1.5	0.1	**2b**	46
7	4-MeO-Ph	**1c**	1	30 min	0.05	0.5	0.1	**2c**	69
8	4-MeO-Ph	**1c**	1	30 min	0.05	0.5	0.2	**2c**	76
9	4-MeO-Ph	**1c**	18	5 min	0.20	1.5	0.1	**2c**	66
10	4-MeO-Ph	**1c**	18	5 min	0.25	1.5	0.1	**2c**	61
11	4-Cl-Ph	**1d**	1	30 min	0.05	0.5	0.1	**2d**	48
12	4-Cl-Ph	**1d**	1	30 min	0.05	0.5	0.2	**2d**	50
13	4-Cl-Ph	**1d**	18	5 min	0.20	1.5	0.1	**2d**	66
14	4-Cl-Ph	**1d**	18	5 min	0.25	1.5	0.1	**2d**	62

[a]Reaction conditions: the specified amount of 2-aminophenylalkyne **1** was suspended in water (2 ml) and the corresponding amount of salt was added. The mixture was heated to 200 °C under MW irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve.

The cyclization of 2-ethynylaniline, **1a**, proceeded efficiently with $NaHCO_3$, which allowed a rise in the cyclization yield up to 61 %, minimizing the decomposition of **1a** (Table 22, entries 1 and 2). Moreover, we verified that an increase in loading of **1a** up to 1 mmol/ml did not affect the yield significantly.

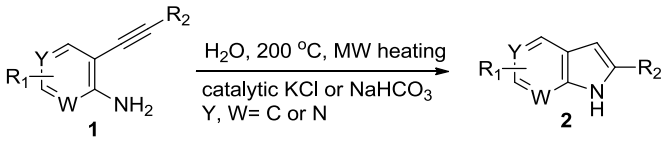
As for the cyclization of 2-(arylethynyl)anilines **1b-d**, very good yields were obtained with 0.1 equiv of $NaHCO_3$ after 1.5 h of MW irradiation in 5 minute cycles (Table 22, entries 5, 9 and 13). However, as already observed for substrate **1b** in the presence of KCl, a raise in the concentration above 0.25 mmol/ml caused a decrease in yield (Table 22, entry 6).

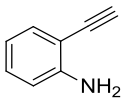
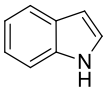
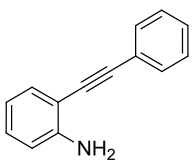
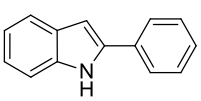
In conclusion, after a careful optimization which involved salt concentration, reaction time, number and time of microwave cycles, we were able to obtain good yields for indoles **2a-d**. The screening and optimization studies done for the model substrates **1a-d** demonstrated that the addition of catalytic amounts of a salt like KCl or $NaHCO_3$ is able to accelerate the cyclization considerably and, in addition, to work with substrate concentrations up to 1 mmol/ml which represent a significant improvement respect to the methodology in water alone. Also, the microwave irradiation in short cycles confirmed its positive effect on the reaction.

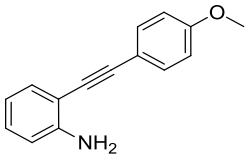
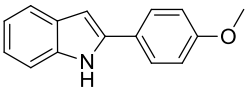
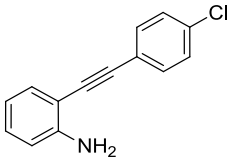
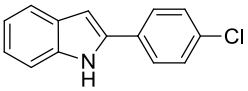
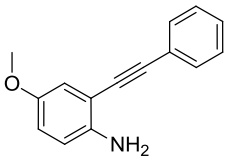
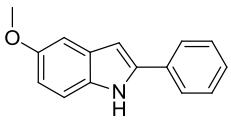
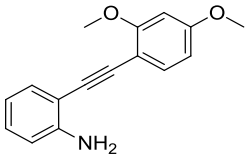
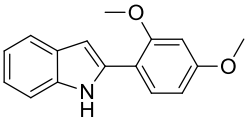
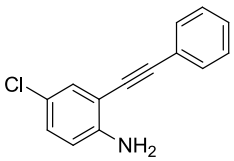
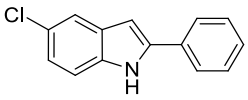
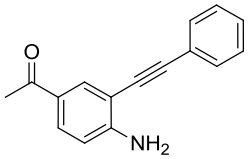
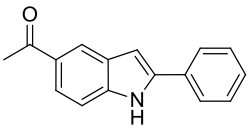
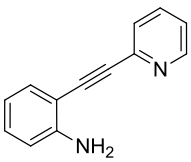
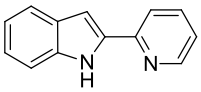
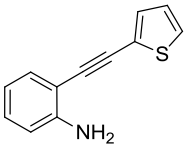
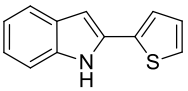
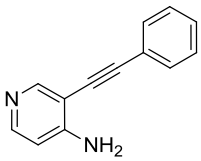
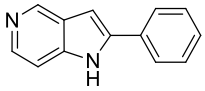
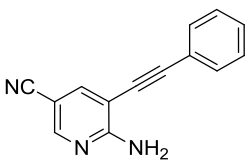
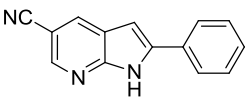
4.2 Case study: cycloisomerization to indoles and aza-indoles with KCl or $NaHCO_3$

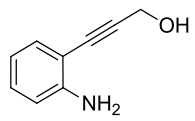
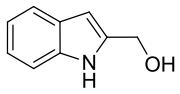
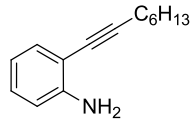
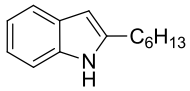
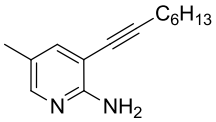
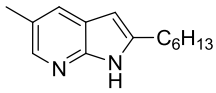
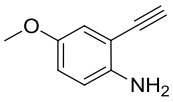
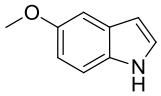
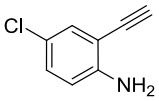
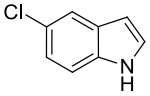
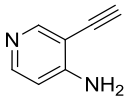
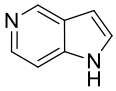
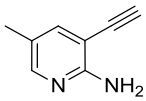
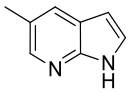
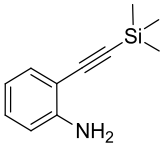
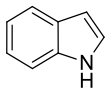
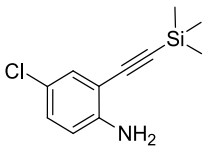
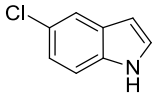
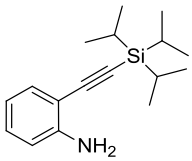
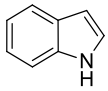
Considering the results obtained during the studies described in the previous paragraph 4.1.2, and with the aim of extending the scope of the cyclization conditions optimized on model compounds, we tested the reactivity of different substrates. For this reason, a series of differently substituted 2-aminoarylacetylenes and 2-aminopyridinylacetylenes was prepared by using our copper-free alkynylation procedure which ensured low Pd-contents.[72] Afterwards, we applied the most efficient conditions found during process optimization, which make use of catalytic amounts of KCl or $NaHCO_3$. After a screening, we chose a substrate concentration of 0.25 mmol/ml, which represents, as already shown, a good compromise between efficiency and applicability. In Table 23, we summarized the results obtained for a series of (hetero)arylalkynylanilines and (arylalkynyl)pyridines. In order to have a straightforward comparison between the use of KCl and $NaHCO_3$, we reported both yields for each compound, specifying the conditions applied (salt concentration, reaction time and cycle number).

Table 23. Preparation of 2-substituted indoles and azaindoles *via* cycloisomerization reaction of 2-amino(hetero)arylalkynes[a]



Entry	Alkyne	1	Indole	2	Conditions (cycles N/min)	Yield[b] (%)
1		**1a**		**2a**	20 mol % KCl (4/5)	60
					20 mol % $NaHCO_3$ (4/5)	61
2		**1b**		**2b**	10 mol % KCl (18/5)	70
					10 mol % $NaHCO_3$ (18/5)	75

3		**1c**		**2c**	10 mol % KCl (18/5)	72
					10 mol % $NaHCO_3$ (18/5)	61
4		**1d**		**2d**	10 mol % KCl (18/5)	55
					10 mol % $NaHCO_3$ (18/5)	62
5		**1e**		**2e**	10 mol % KCl (18/5)	83
					10 mol % $NaHCO_3$ (18/5)	87
6		**1f**		**2f**	10 mol % KCl (18/5)	60
					10 mol % $NaHCO_3$ (18/5)	48
7		**1g**		**2g**	10 mol % KCl (18/5)	68
					10 mol % $NaHCO_3$ (18/5)	67
8		**1h**		**2h**	10 mol % KCl (18/5)	77
					10 mol % $NaHCO_3$ (18/5)	88
9		**1i**		**2i**	10 mol % KCl (9/5)	85
					10 mol % $NaHCO_3$ (18/5)	96
10		**1j**		**2j**	10 mol % KCl (12/5)	87
					10 mol % $NaHCO_3$ (12/5)	95
11		**1k**		**2k**	10 mol % KCl (12/5)	98
					10 mol % $NaHCO_3$ (18/5)	99
12		**1l**		**2l**	10 mol % KCl (18/5)	45[c]
					10 mol % $NaHCO_3$ (18/5)	—[d]

13		**1m**		**2m**	10 mol % KCl (18/5)	10
					10 mol % $NaHCO_3$ (18/5)	23
14		**1n**		**2n**	20 mol % KCl (18/5)	31
					20 mol % $NaHCO_3$ (18/5)	60
15		**1o**		**2o**	20 mol % KCl (18/5)	5
					20 mol % $NaHCO_3$ (18/5)	52
16		**1p**		**2p**	10 mol % KCl (4/5)	87
					10 mol % $NaHCO_3$ (4/5)	89
17		**1q**		**2q**	10 mol % KCl (4/5)	72
					10 mol % $NaHCO_3$ (4/5)	78
18		**1r**		**2r**	10 mol % KCl (4/5)	79
					10 mol % $NaHCO_3$ (4/5)	80
19		**1s**		**2s**	10 mol % KCl (6/5)	98
					10 mol % $NaHCO_3$ (4/5)	60
20		**1v**		**2a**	20 mol % KCl (4/5)	57
					20 mol % $NaHCO_3$ (4/5)	55
21		**1x**		**2q**	10 mol % KCl (6/5)	9
					10 mol % $NaHCO_3$ (6/5)	2
22		**1y**		**2a**	10 mol % KCl (6/5)	—
					10 mol % $NaHCO_3$ (6/5)	8

[a]Reactions were run in sealed tubes where 0.5 mmol of 2-amino(hetero)arylalkyne **1** were suspended in 2 ml of water and the suspension heated to 200 °C by microwave irradiation in the presence of the corresponding salt. [b]Isolated yields after chromatography. [c]2-Phenyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid was obtained as a by-product in 35 % yield after chromatography. [d]Complete hydrolysis to 6-amino-5-(phenylethynyl)-3-pyridinecarboxylic acid was observed, without cyclization product.

As we can see from the previous table, good to very good isolated yields ranging from 60 to 99 % could be observed for the majority of both electron-rich and electron-poor substrates. The concentration of substrates applied in the study was 0.25 mmol/ml, so more than doubled respect to that used for water alone.

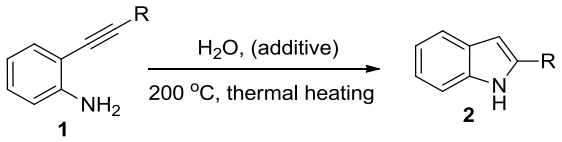
Worthy of note is the behaviour of the heteroarylalkynes examined, since, as already observed when water alone was used, they seemed to cyclize in most instances more easily than the considered arylalkynes, giving elevated yields by using both KCl and $NaHCO_3$. Moreover, differently from **1a**, substituted 2-ethynylanilines **1p** and **1q** and 2-ethynylaminopyridines **1r** and **1s** proved less unstable under the applied conditions and gave the corresponding indoles **2p** and **2q** and azaindoles **2r** and **2s** in very high yields and without significant degradation or hydration (Table 23, entries 16-19). In the case of alkynes containing trialkylsilyl groups, the cyclization took place only when the R_3Si group cleavage to the free terminal alkyne occurred in significantly high conversions. In fact, when *in situ* deprotection was more difficult as for compounds **1x** and **1y** (Table 23, entries 21 and 22), cyclization to indole hardly happened.

On the other hand, only low or moderate yields were obtained for octynylpyridinamine **1o**, which gave 5 % yield with 0.2 equiv of KCl and 52 % with 0.2 equiv of $NaHCO_3$ (Table 23, entry 15). As for the propynol **1m**, neither KCl nor $NaHCO_3$ gave acceptable results, but mainly degradation products were observed (Table 23, entry 13).

4.3 Thermal heating experiments

In order to explore the role of microwave heating to obtain significant yields in short reaction times, we carried out a comparison study between thermal heating and microwave irradiation by running some cycloisomerization trials of 2-ethynylaniline, **1a**, and 2-(phenylethynyl)aniline, **1b**, in an oil bath, using pressure resistant glass sealed tubes. In the trials, 0.1 mmol of substrate were suspended in 2 ml of UltraTrace water and the required amount of additive was introduced. The reactions were heated to 200 °C and monitored for 7 h, sampling at different reaction times. The results are summarized in Table 24.

Table 24. Thermal heating experiments[a]



Entry	R	1	Additive	Time	Yield of 2[b] (%)
1	H	**1a**	none	7 h	2
2	H	**1a**	KCl (0.1 equiv)	7 h	2
3	H	**1a**	$NaHCO_3$ (0.1 equiv)	7 h	1
4	Ph	**1b**	none	7 h	n.d.
5	Ph	**1b**	KCl (0.1 equiv)	30 min	1
6	Ph	**1b**	KCl (0.1 equiv)	7 h	21
7	Ph	**1b**	$NaHCO_3$ (0.1 equiv)	30 min	n.d.
8	Ph	**1b**	$NaHCO_3$ (0.1 equiv)	7 h	1

[a]Reaction conditions: 2-aminophenylalkyne **1** (0.1 mmol) was suspended in water (2 ml) with the corresponding amount of additive, and heated to 200 °C in an oil bath for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve.

In the instance of 2-ethynylaniline, **1a**, the cycloisomerization did not proceed under thermal heating and, in fact, both in pure water and when KCl or $NaHCO_3$ were added, negligible amounts of indole were obtained (Table 24, entries 1-3).

In the instance of 2-phenylindole, **2b**, only traces of product could be observed in most cases from **1b** under thermal heating conditions. Not reacted starting material was the only

recovered product in pure water, even after 7 h of heating at 200 °C (Table 24, entry 1). Notably, when 0.1 equiv of KCl were added, a 21 % yield was observed after 7 h at 200 °C (Table 24, entry 6). Also $NaHCO_3$ did not prove more efficient than pure water (Table 24, entries 7 and 8).

4.4 Conclusions

In summary, we demonstrated that differently substituted indoles and azaindoles can be obtained by a simple and straightforward methodology which involves the microwave-promoted cycloisomerization of 2-alkynylanilines and alkynylpyridinamines in water. The cyclization is efficiently expedited by the use of catalytic amounts of inorganic salts such as KCl and $NaHCO_3$. In fact, the addition of such additives allowed enhancing the capability of water to interact with microwaves through ionic conduction and visibly accelerated the cycloisomerization of the substrates examined. Moreover, higher yields could be obtained respect to the use of water alone for a variety of both electron-rich and electron-poor substrates, even bearing labile functional groups.

The experimental results described in Chapter 4 were the subject of a publication appeared in 2010.[78]

Chapter 5

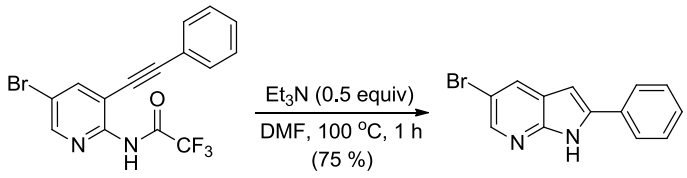
Microwave-assisted synthesis of indole and azaindole derivatives in water *via* cycloisomerization of 2-alkynylanilines and alkynylpyridinamines promoted by organic bases

5.1 Organic base-promoted cycloisomerization

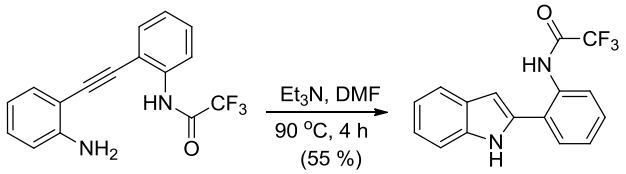
The data in Table 19 and Table 20 in paragraph 4.1.1 show a definite effect of neutral and basic inorganic salts in improving significantly the cyclization yield. However, in the instance of **1a** the results obtained were only moderately satisfactory, since the highest yields we could obtain were 66 % and 60 % in the presence of NaOH and $NaHCO_3$, respectively (Table 20, entries 1 and 3). On the other hand, the aforesaid experimental results demonstrate that basic additives play a positive effect in many cases, even greater than neutral ones. Therefore, we decided to enlarge our investigation including also organic base additives. Moreover, a few literature findings supported our observation, as illustrated in the following section 5.1.1.

5.1.1 Literature findings on metal-free organic base-promoted cyclization

The literature describes that strong bases, such as NaOH, *t*-BuOK or KH, promote the cyclization of 2-alkynylanilines to indoles.[33e,35] However, we could also find a few remarkable examples reporting the preparation of indoles by using Et_3N in the cyclization of 2-alkynyl(trifluoroanilides) (Scheme 37 and Scheme 38).[33d,36d]

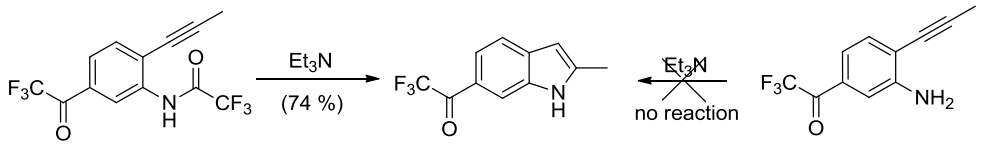


Scheme 37



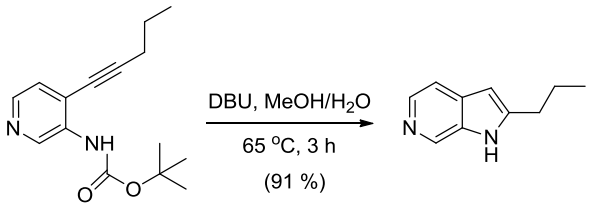
Scheme 38

Notably, in one example, when the cyclization was conducted with the free amino group, no product formation could be detected (Scheme 39).[79]



Scheme 39

Moreover, also DBU was described in the cyclization of a *t*-butyl [(alkynyl)pyridinyl] carbamate in MeOH/H_2O 3:1 mixture (an example is given in Scheme 40). The authors claimed that the corresponding free aniline did not cyclize under the same conditions.

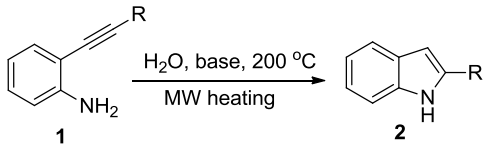


Scheme 40

5.1.2 Screening of organic bases and method optimization

An organic base screening was run working on a selection of model substrates to investigate their effect under our conditions. Catalytic to stoichiometric amounts of organic bases were tested, assuming they could be compatible with various functionalities of the starting 2-alkynylanilines. The collected results are shown in Table 25.

Table 25. Microwave-assisted cycloisomerization: screening of organic bases[a]



Entry	R	1	Base	Base equiv	Time (min)	2	Yield (%)[b]
1	H	**1a**	Et_3N	1	15	**2a**	28
2	H	**1a**	DBU	1	15	**2a**	41
3	H	**1a**	DABCO	1	15	**2a**	65

4	H	**1a**	piperidine	1	15	**2a**	84
5	H	**1a**	piperidine	2	15	**2a**	85
6	H	**1a**	pyrrolidine	1	15	**2a**	79
7	H	**1a**	pyrrolidine	0.5	15	**2a**	49
8	H	**1a**	pyrrolidine	2	15	**2a**	90
9	Ph	**1b**	Et_3N	1	30	**2b**	8
10	Ph	**1b**	$(i\text{-Pr})_2EtN$	1	30	**2b**	9
11	Ph	**1b**	$t\text{-BuNH}_2$	1	30	**2b**	12
12	Ph	**1b**	DABCO	1	30	**2b**	38
13	Ph	**1b**	DBU	1	30	**2b**	46
14	Ph	**1b**	pyridine	1	30	**2b**	10
15	Ph	**1b**	pyrrolidine	1	30	**2b**	54[c]
16	Ph	**1b**	pyrrolidine	1	60	**2b**	53
17	Ph	**1b**	pyrrolidine	2	30	**2b**	36
18	Ph	**1b**	piperidine	1	30	**2b**	26
19	Ph	**1b**	piperidine	2	30	**2b**	50
20	Ph	**1b**	morpholine	2	30	**2b**	12
21	4-MeO-Ph	**1c**	pyrrolidine	1	30	**2c**	70
22	4-MeO-Ph	**1c**	pyrrolidine	2	30	**2c**	74
23	4-Cl-Ph	**1d**	pyrrolidine	1	30	**2d**	56
24	4-Cl-Ph	**1d**	pyrrolidine	2	30	**2d**	65

[a]Reaction conditions: 2-aminoarylalkyne **1** (0.1 mmol) and the specified base were added to water (2 ml) and the mixture heated to 200 °C under microwave irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve. [c]A similar yield of 52 % was obtained when 6 cycles of 5 minutes of MW irradiation was applied.

Notably, most of the organic bases tested did show a significant effect on cyclization for all the model compounds, with really good results obtained especially when pyrrolidine was used (Table 25, entries 6, 8, 15, 22 and 24). The beneficial effect was particularly evident for substrate **1a**, where a yield of 90 % was obtained after 15 min at 200 °C in the presence of 2 equiv of pyrrolidine (Table 25, entry 8). Also good results were obtained when piperidine was used (Table 25, entries 4 and 5).

In addition, pyrrolidine gave remarkable results in the case of 2-(arylethynyl)anilines with a 54 % yield for **1b** and a 74 % for **1c** after 30 min at 200 °C (Table 25, entries 15 and

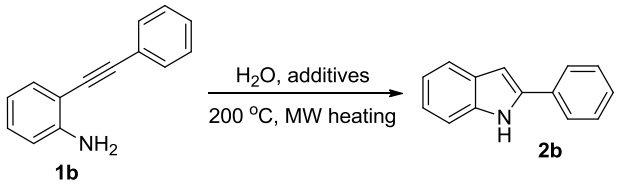
22). Good yields were obtained also for **1d**, which cyclized with a 65 % yield after 30 minutes (Table 25, entry 24).

The base screening and the optimization studies done for the model substrates **1a-d** showed that the yields previously described for the cyclization in water alone can be considerably improved if an organic base, pyrrolidine in particular, was added. An extension of the study to a broader number of substrates was run as described onward.

5.1.3 The effect of organic and inorganic additive combination

In view of the considerable effect played by a salt such as KCl and by an organic base such as pyrrolidine, further studies were run by combining both additives together in the same reaction vial. The study was conducted by working on one single model substrate, **1b**.

Table 26. Cyclization with KCl and pyrrolidine.[a]



Entry	Irradiation time (cycles N/min)	KCl (equiv)	Pyrrolidine (equiv)	Conc. of 1b (mmol/ml)	Yield[b] (%)
1	1/30	0.1	—	0.05	57
2	1/30	0.1	0.5	0.05	65
3	1/30	0.1	1.0	0.05	62
4	1/30	0.2	—	0.05	77
5	1/30	0.2	0.5	0.05	52
6	1/30	0.2	1.0	0.05	75
7	18/5	0.1	—	0.20	74
8	18/5	0.1	0.5	0.20	70
9	18/5	0.2	—	0.25	60
10	18/5	0.2	0.5	0.25	50

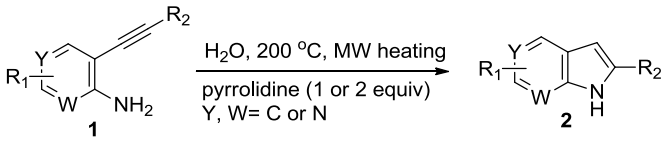
[a]Reaction conditions: 2-phenylethynylaniline and the specified amount of pyrrolidine were added to water (2 ml) and the mixture heated to 200 °C under microwave irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve.

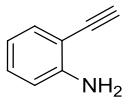
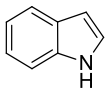
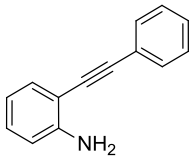
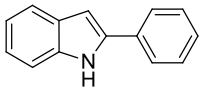
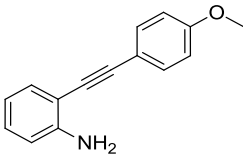
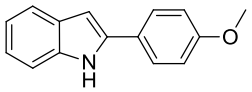
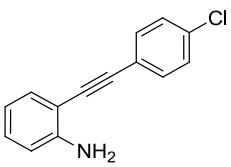
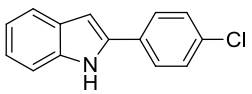
As we can see from the data collected for the model substrate, the joint addition of the two additives (KCl and pyrrolidine) did not represent a significant improvement *versus* the use of single additives. On the other hand, somewhat lower yields were obtained under some conditions.

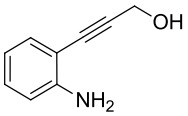
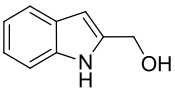
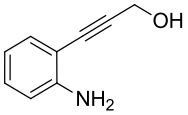
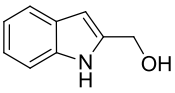
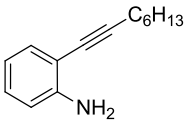
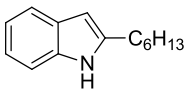
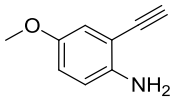
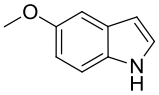
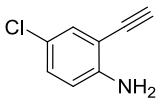
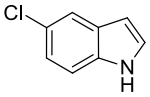
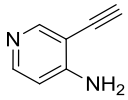
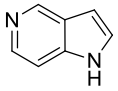
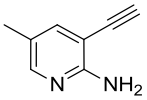
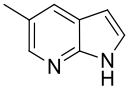
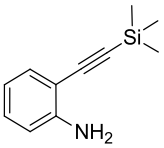
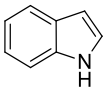
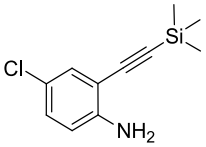
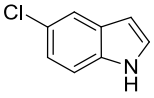
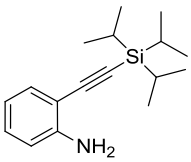
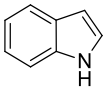
5.2 Case study on indoles and azaindoles

With the aim of extending the scope of organic base-assisted cyclization conditions, we explored the reactivity of different substrates. As already done for the other studies we run, we used our procedure, which ensures low Pd contents,[72] to prepare a series of differently substituted 2-aminoarylacetylenes and 2-aminopyridinylacetylenes. After a screening, we chose for our studies a substrate concentration of 0.25 mmol/ml, which represents, as already shown, a good compromise between efficiency and applicability. In Table 27 we summarized the results obtained for a series of (hetero)arylalkynylanilines and arylalkynylpyridines.

Table 27. Preparation of 2-substituted indoles and azaindoles *via* cycloisomerization reaction of 2-amino(hetero)arylalkynes promoted by pyrrolidine[a]



Entry	Alkyne	1	Indole	2	Equiv of pyrrolidine	cycles N/min	Yield[b] (%)
1		**1a**		**2a**	2	1/15	90
2		**1b**		**2b**	2	18/5	85
3		**1c**		**2c**	2	18/5	79
4		**1d**		**2d**	2	18/5	77

5		**1m**		**2m**	1	18/5	53
6		**1m**		**2m**	2	18/5	25
7		**1n**		**2n**	2	18/5	25
8		**1p**		**2p**	2	1/15	90
9		**1q**		**2q**	2	1/15	86
10		**1r**		**2r**	2	1/15	82
11		**1s**		**2s**	2	1/15	72
12		**1v**		**2a**	2	1/15	79
13		**1x**		**2q**	2	1/30	3
14		**1y**		**2a**	2	1/30	29

[a]Reactions were run in sealed tubes where 0.5 mmol of 2-amino(hetero)arylalkyne **1** were suspended in 2 ml of water and the suspension heated to 200 °C by microwave irradiation in the presence of 1 or 2 equiv of pyrrolidine. [b]Isolated yields.

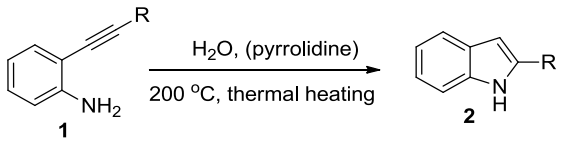
The use of pyrrolidine was tested for some model substrates such as **1a-d** (Table 27, entries 1-4), and for those substrates with which neither KCl nor $NaHCO_3$ gave satisfying results during our previous studies. For example, propynol **1m** gave only 10 and 23 % yield with 10 mol % of KCl or $NaHCO_3$, respectively, while cyclized rather effectively in the presence of 1 equiv of pyrrolidine with a 53 % yield (Table 27, entry 5). On the other hand, a low yield of 25 % was obtained for compound **1n** (Table 27, entry 6).

As we already observed in paragraphs 3.2 and 4.2, differently from **1a**, substituted 2-ethynylanilines **1p** and **1q** and 2-ethynylaminopyridines **1r** and **1s** were more stable under the applied conditions and gave the corresponding indoles **2p** and **2q** and azaindoles **2r** and **2s** in very high yields and without significant degradation or hydration. However, even if also the addition of catalytic amounts of KCl and $NaHCO_3$ gave very good results, we thought interesting to test those substrates with pyrrolidine as well, which proved, in fact, efficient (Table 27, entries 8-11). Lower yields were observed only in the instance of silyl derivatives **1x** and **1y**, that did not tend to undergo *in situ* deprotection and, as a consequence, cyclization to indole hardly happened.

5.3 Thermal heating experiments

In order to explore the role of microwave heating to obtain significant yields in short reaction times, we carried out a comparison study between thermal heating and microwave irradiation. Thermal heating was applied during some cycloisomerization trials on 2-ethynylaniline, **1a**, and 2-(phenylethynyl)aniline, **1b**, using pressure resistant glass sealed tubes. In the trials, 0.1 mmol of substrate were suspended in 2 ml of UltraTrace water and the required amount of pyrrolidine was introduced. The reactions were heated to 200 °C in an oil bath and monitored for 4-7 h, sampling at different reaction times. The results are summarized in Table 28.

Table 28. Thermal heating experiments.[a]



Entry	Aryl alkyne	Additive	Time	Yield of 2[b] (%)
1	**1a**	none	7 h	2
2	**1a**	pyrrolidine (2 equiv)	30 min	11
3	**1a**	pyrrolidine (2 equiv)	4 h	95
4	**1b**	none	7 h	n.d.
5	**1b**	pyrrolidine (2 equiv)	7 h	n.d.

[a]Reaction conditions: 2-aminophenylalkyne **1** (0.1 mmol) was suspended in water (2 ml) with the corresponding amount of additive, and heated to 200 °C in an oil bath for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve.

In the instance of 2-ethynylaniline, **1a**, the cycloisomerization proceeds efficiently also under thermal heating conditions in the presence of pyrrolidine, and, even if considerably slower than under microwave irradiation, it gives a 95 % yield in **2a** after 4 h at 200 °C (Table 28, entry 3).

In the instance of 2-phenylindole, **2b**, under thermal heating conditions only not reacted starting material was recovered, even after 7 h at 200 °C and also when pyrrolidine was added (Table 28, entries 4 and 5).

5.4 Conclusions

In summary, we demonstrated that differently substituted indoles and azaindoles can be obtained by a simple and straightforward methodology which involves the microwave-promoted cycloisomerization of 2-alkynylanilines and alkynylpyridinamines in water. The cyclization is efficiently expedited by the addition of organic bases, in particular pyrrolidine. We obtained from good to very good yields for a variety of both electron-rich and electron-poor substrates, even bearing labile functional groups. These results can be considered complementary to the previously described catalytic methodology which made use of inorganic salts like KCl and $NaHCO_3$.

Chapter 6

Further developments: cyclization of *N*-protected anilines and 2-methoxyphenyl derivatives

6.1 Broadening the scope of MW-assisted cyclization

The core of this Doctorate Thesis was represented by the development of an efficient method to prepare indoles and azaindoles under microwave irradiation and our work followed the course described in the previous chapters 3, 4 and 5. Notably, we disclosed results that were unprecedented in the literature. In particular, the MW irradiation in cycles was a measure which proved extremely effective in improving yields and reaction rates.

As a natural extension of our studies, we were interested in verifying the behaviour of *N*-protected anilines and pyridinamines in the cycloisomerization to (aza)indoles, since these substrates are described as being more reactive in such reactions, as already discussed in paragraphs 1.4.2.1 and 5.1.1. Moreover, a further expansion would be represented by the inclusion of oxygen- or sulfur-bearing substrates, and, in particular, (2-methoxyaryl)alkynes and/or (2-carboxylaryl)alkynes.

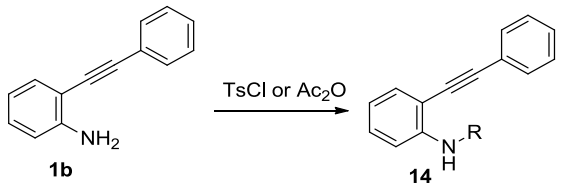
Unfortunately, our work program could not be extended enough to include in-depth experimental data sets acquisition within the deadlines established for this Doctorate Thesis. As a consequence, only preliminary and partial results could be collected, as it is shown in the following paragraphs 6.1.1 and 6.1.2. In particular, interesting preliminary results could be gained in the cycloisomerization to prepare indoles starting from *N*-tosylamides.

6.1.1 MW-assisted cyclization in water with *N*-protected 2-phenylethynylanilines

N-Protected 2-phenylethynylanilines are common precursors to indole derivatives. They are frequently applied in place of the corresponding free anilines, which are typically poorly reactive under the same conditions (see paragraph 1.4.2.1 for the literature analysis). In general, tosyl, mesyl, acetyl, trifluoroacetyl and *t*-butylcarboxylate groups are commonly used to protect the nitrogen functionality. During the cyclization process they can be released or retained in the indole products, depending on their lability and on the conditions applied.

Our few explorative trials were carried out with different amides prepared from 2-(phenylethynyl)aniline, **1b**. Our intent was to run a three-step process consisting of aniline protection, cyclization and likely deprotection of the corresponding *N*-protected indole. For this purpose, we selected the sulfonamide and acetamide derivatives **14**. The first compound **14a** was prepared from **1b** by treatment with *p*-toluensulfonyl chloride in the presence of pyridine (Table 29, entry 1). The second derivative **14b** was prepared by treatment of **1b** with an excess of acetic anhydride at room temperature (Table 29, entry 2).

Table 29. Preparation of *N*-protected anilines.



1b **14**

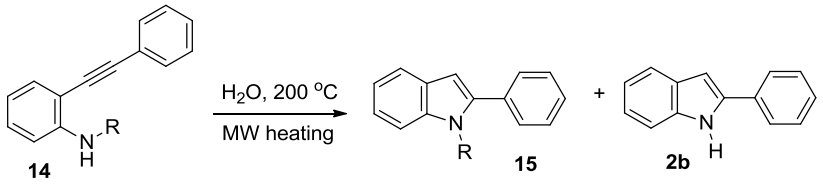
Entry	R	14	Conditions	Yield[a]
1	Ts	**14a**	Py, TsCl, CH_2Cl_2, r.t.	82 %
2	Ac	**14b**	Ac_2O, r.t.	69 %

[a]Isolated yields after chromatography.

In the first instance, the cyclization of compounds **14** was examined in water alone without any additive. In these first trials the sulfonamide **14a** did react to give the

corresponding *N*-Ts-indole, while the acetamide **14b** proved not reactive, giving only a partial deprotection of the starting acetamide (Table 30, entries 1-3).

Table 30. Exploring the cyclization of *N*-protected anilines in water.[a]



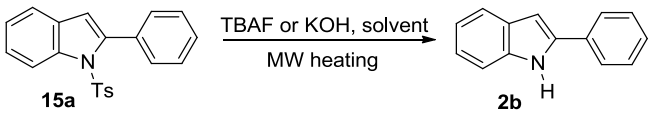
Entry	Time	R	15	Yield of 15[b]	Yield of 2b[b]	14 (mg)
1	30 min	Ts	**15a**	72 %	—	**14a** (50)
2	2 cycles of 30 min	Ts	**15a**	78 %	—	**14a** (200)
3	30 min	Ac	**15b**	—	—	**14b** (51)

[a]Reaction conditions: **14** was suspended in water (2 ml) and heated to 200 °C by microwave irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve.

At a first glance, the sulfonamide **14a** seemed more reactive than the corresponding free aniline **1b**; the reaction was also less sensitive to the concentration of starting materials, since higher loadings were applied with respect to trials run with **1b**.

To achieve deprotection, the resulting *N*-Ts-indole **15a** was treated according to literature conditions, which describe the use of 1 equiv of $(n\text{-Bu})_4NF$ (TBAF) in THF to remove the tosyl group or, in another procedure, KOH in a H_2O/THF mixture.[80] We tried to expedite the thermal-heated deprotection reaction by applying microwave irradiation. Our results are reported in the following Table 31.

Table 31. Screening of conditions for indole *N*-detosylation.



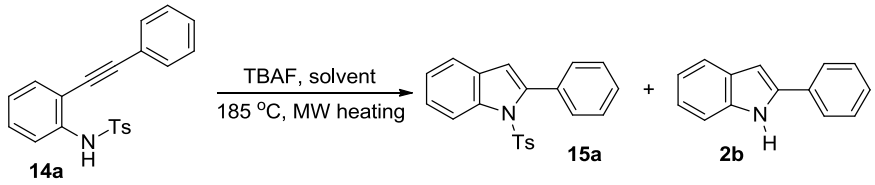
Entry	Conditions	Temp (time)	Yield in 2b[a]
1	H_2O, TBAF (1 equiv)	185 °C[b] (30 min)	< 1 %
2	THF, TBAF (1 equiv)	100 °C (30 min)	99 %
3	H_2O, KOH (1 equiv)	200 °C (15 min)	99 %

[a]Yield in solution determined by HPLC with a calibration curve. [b]Maximum achievable temperature due to overpressure.

As we said at the beginning of paragraph 6.1, we did not have enough time during the course of this Doctoral Thesis to plan and execute an exhaustive study on the cyclization of *N*-protected anilines. Therefore, we run spot reactions in order to understand in which direction to progress for a potential future work development. Particularly attractive was the possibility of using basic conditions, which already proved efficient in the case of free anilines, as discussed in paragraphs 4.1.1, 4.1.2 and 5.1.2.

Among all the possible organic and inorganic bases which could promote the cycloisomerization, we identified potassium hydroxide and TBAF. In fact, they are both used in literature procedures[80] to deprotect *N*-tosyl(aza)indoles in solvent like water and/or THF. Our objective was to set up an efficient procedure where a one-pot cyclization-deprotection process took place. Whilst TBAF was efficient in promoting the deprotection of *N*-tosyl indole **15a** (at least in THF, Table 31, entry 2), it was less efficient in the cycloisomerization step (Table 32). The operating temperature applied was 185 °C, the maximum temperature achievable by the system due to overpressure.

Table 32. Exploring the cyclization of **14a** with TBAF.



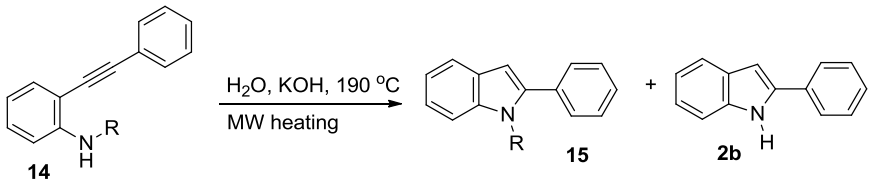
Entry	Solvent	TBAF equiv	Time	Yield of 15a	Yield of 2b[a]	14a (mg/ml)
1	THF	1	30 min	—	42 %	25
2	H_2O/THF 3:1	1	30 min	—	40 %	25
3	H_2O/toluene 3:1	1	30 min	—	26 %	25

[a]Yields in solution determined by HPLC with a calibration curve.

On the other hand, the addition of KOH proved more effective since it enhanced the yield of the cyclization and allowed the *in situ* efficient deprotection of the *N*-protected indole. Therefore, a rapid screen of reaction time and KOH equiv was run, as it is reported

in Table 33. Also in this case, we had a limit for the operating temperature applied, since the maximum temperature achievable by the system was 190 °C due to overpressure.

Table 33. Exploring the cyclization of *N*-protected anilines in water with KOH.



Entry	Time	KOH equiv	R	15	Yield of 15[a]	Yield of 2b[a]	14 (mg/ml)
1	10 min	2	Ts	**15a**	34 %	66 %	25
2	20 min	1	Ts	**15a**	45 %	55 %	25
3	30 min	2	Ts	**15a**	—	90 %	24
4	30 min	1	Ac	**15b**	10 %	61 %	25
5	30 min	2	Ac	**15b**	—	80 %	24

[a]Yields in solution determined by HPLC with a calibration curve.

In conclusion, the preliminary results just presented above demonstrate that *N*-protected ethynylanilines possess a good potential for the cycloisomerization in water both with and without the addition of additives. In particular, KOH showed good yields in the one-pot cycloisomerization-deprotection process starting from *N*-tosyl and *N*-acetyl 2-(phenylethynyl)aniline.

Unfortunately, we could not run an extensive screening of conditions, additives and substrates and we were only able to illustrate the good potential of the process, opening up for future studies.

6.1.2 Synthesis of benzofurans *via* MW-assisted cyclization in water

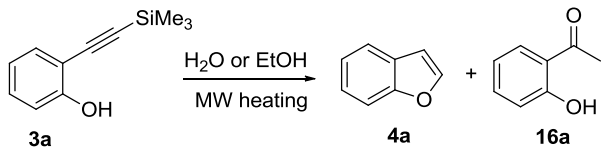
Benzofurans are important components of many biologically active molecules and active pharmaceutical ingredients. Hence, the identification of efficient and green methodologies for their synthesis and functionalization is of significant importance. The cycloisomerization methodology in water developed for the preparation of indoles and aza-analogues that we described in the previous chapters 3, 4 and 5 could represent a further methodology of considerable interest. However, it must be said, a number of methodologies already exist which make use of microwave irradiation and do not employ transition metal catalysts (see paragraph 1.4.2.2 for literature examples). Nonetheless, we considered that if our metal-free methodology in water was efficient, it could represent a valuable alternative to existing methods. Moreover, a few trials on substrates like 2-alkynylphenols and (2-alkynyl)phenylethers were worth doing also to test the generality of our conditions. Unfortunately, we can present only preliminary results since it was not possible to conduct a general study within the duration allowed to this Doctorate Thesis.

However, during our incomplete investigation we had enough time to assess the behaviour of three substrates under different conditions and the collected results are reported in the following schemes and tables.

We started our investigation with the preparation of benzofuran, **4a**. The results obtained are reported in Table 34. A study was carried out on the microwave-assisted cyclization in water of 2-[(trimethylsilyl)ethynyl]phenol, **3a**, which, upon treatment with water under microwaves at 200 °C efficiently cyclized to benzofuran with the concurrent cleavage of trimethylsilyl group. In particular, good results were obtained in water alone, where, after 20 min at 200 °C, a yield of 68 % in benzofuran was observed (Table 34, entry 3). The only by-product formed was the corresponding ketone **16a**, resulting by alkyne hydration. Notably, the addition of a salt like NaCl allowed only a slight yield enhancement (Table 34, entry 5). In order to have a comparison with literature conditions described for

2-methoxyphenylalkynes,[53d-f] we conducted a cyclization trial in EtOH with 1 equiv of *p*-toluenesulfonic acid (Table 34, entry 6) and only a 2 % of benzofuran was observed, while the main product was the ketone **16a**.

Table 34. Synthesis of benzofuran, *via* cycloisomerization of 2-trimethylsilylethynylphenol.[a]



3a **4a** **16a**

Entry	Temperature	Time	Additive	4a/16a NMR ratio	Yield of 4a[b]
1	170 °C	10 min	—	75/25	51 %
2	200 °C	10 min	—	70/30	63 %
3	200 °C	20 min	—	70/30	68 %
4	220 °C	20 min	—	60/40	58 %
5	200 °C	20 min	NaCl (1 equiv)	75/25	73 %
6[c]	150 °C	20 min	*p*-TsOH (1 equiv)	4/96	2 %

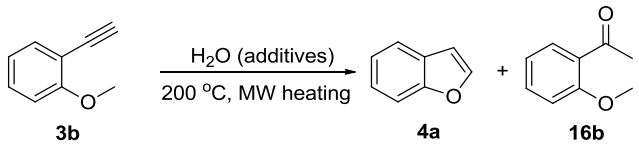
[a]Reaction conditions: 2-ethynylphenol **3a** (0.25 mmol) was suspended in water (2 ml) and heated to the specified temperature in the presence of the corresponding additive by microwave irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve. [c]This trial was run under literature conditions with EtOH in place of water.[53d-f]

Bearing in mind the methodologies described by Alami and coll. to prepare benzofurans,[53d-f] 1-alkynyl-2-methoxybenzenes also represent interesting starting materials to collect some data on the cycloisomerization in water. As model compounds, two substrates were tested, 1-ethynyl-2-methoxybenzene, **3b** (a commercially available compound) and 1-methoxy-2-(phenylethynyl)benzene, **3c**. The collected data are reported in Table 35 and Table 36, respectively.

Notably, the cycloisomerization of 1-ethynyl-2-methoxybenzene, **3b**, did not occur in water alone or in the presence of additives. In fact, in trials 1 and 2 in Table 35 the only recovered compound was the starting alkyne.

On the other hand, in the presence of NaCl or HCl 0.1 N the main product formed was the ketone **16b (**Table 35, entries 3 and 4).

Table 35. Synthesis of benzofuran *via* cycloisomerization of 2-methoxyethynylbenzene.[a]



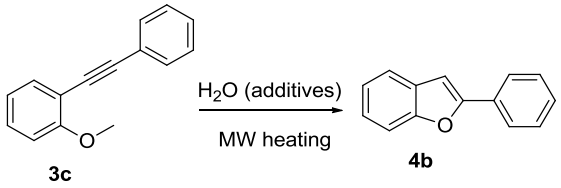
3b 4a 16b

Entry	Time	Additive	Yield of 4a[b]	Yield of 16b[b]
1	20 min	—	—	—
2	60 min	—	—	—
3	30 min	NaCl (1 equiv)	—	35 %
4	30 min	HCl 0.1 N	—	85 %

[a]Reaction conditions: 2-ethynylphenol **3b** (0.25 mmol) was suspended in water (2 ml) and heated to 200 °C in the presence of the corresponding additive by microwave irradiation for the time reported in the table. [b]Yields in solution determined by HPLC, using a calibration curve.

Also the second model compound **3c** did not cyclize efficiently. In particular, in water alone or in the presence of KCl as an additive, no trace of 2-phenylbenzofuran, **4b**, could be detected (Table 36, entries 1 and 2). Very low yields were observed when the cyclization was conducted under acid conditions (Table 36, entries 3 and 4). However, the operating temperature could be only in the range between 185 and 190 °C due to overpressure.

Table 36. Synthesis of 2-phenylbenzofuran *via* cycloisomerization.



3c 4b

Entry	Temperature	Time	Additive	Yield of 4b[b]
1	200 °C	30 min	-	—
2	190 °C[c]	30 min	KCl (3 equiv)	—
3	185 °C[c]	30 min	NH_4Cl (3 equiv)	5 %
4	190 °C[c]	30 min	HCl 0.1 N	10 %

[a]Reaction conditions: 1-methoxy-2-(phenylethynyl)benzene, **3c**, (0.1 mmol) was suspended in water (2 ml) and heated to the specified temperature in the presence of the corresponding additive under 30 min of microwave irradiation. [b]Yields in solution determined by HPLC, using a calibration curve. [c]Maximum temperature achievable due to overpressure.

In conclusion, the data collected during these spot trials showed that the examined methodology could offer potential application in the preparation of benzofurans. However, they are preliminary data, obtained for a limited number of substrates and further investigation should be run to assess the general applicability of the procedure.

Moreover, due to time constraints, we were not able to explore the synthesis of phtalides and isocoumarins *via* intramolecular cyclization of enynecarboxylic acid/ester systems, another process which would deserve a dedicated study.

Chapter 7

Experimental Section

7.1 General experimental

All materials were obtained from commercial suppliers and used without further purification. 2-Alkynylanilines and pyridines **1b**-**y** were prepared from commercially available starting materials, according to the procedure for the copper-free Sonogashira coupling described below. 2-Ethynylaniline, **1a**, Pd EnCat™ 40 and TPP 30 used in the copper-free Sonogashira coupling were purchased from Aldrich; all the calculations for the required amount of catalyst were based on a Pd loading of 0.4 mmol/g (as given in the Aldrich catalogue). KCl and $NaHCO_3$ were purchased from Aldrich with a purity of 99.99 % trace metal basis. All reactions were carried out in air without particular care for anhydrous or inert environment. For the microwave-assisted reactions a CEM Explorer with infrared temperature control system was applied as a focused microwave unit; the reactions were conducted in 10 ml reaction tubes sealed with septa caps. The pressure was measured by the system by an Intellivent® pressure control module. The purification of the crude products was conducted with a Biotage Flash+® Purification System with pre-packed silica cartridges. The yields in solution were determined using an Agilent 1100 HPLC system. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer and on a Varian Inova 600 spectrometer. For mass spectra a Agilent 1100 Series LC/MSD with APCI source was used, while for the high resolution mass an Acquity UPLC™-LCT Premiere System was used. ATR IR spectrum for compound **12** was acquired with a Nicolet Magna 760 spectrometer. Atomic absorption spectrophotometry (AAS) analyses for compounds **1b**-**d** were carried out with a Perkin–Elmer 4100 ZL spectrophotometer, equipped with an electrothermally heated graphite furnace and a longitudinal Zeeman effect background corrector. The limit of detection (lod) calculated for palladium and copper was 2 ppb.

7.2 Preparation of alkynes

Experimental procedures and characterisations of compounds are given.

7.2.1 Typical procedure for the copper-free Sonogashira cross-coupling of (hetero)aryl halides with acetylenes to prepare (hetero)arylethynylanilines and aminopyridines 1b-l and 1t-u

The (hetero)aryl halide (4 mmol), the alkyne (1.5 equiv, 6 mmol), pyrrolidine (2 equiv, 8 mmol) and 1-10 mg of Pd EnCat 40 catalyst (0.01-0.1 mol % of Pd) were mixed and the resulting mixture was stirred at 85-100 °C for the required time until consumption of starting (hetero)aryl halide. Ethyl acetate (2 × 20 ml) and a saturated NH_4Cl aqueous solution (20 ml) were added and the collected organic layers washed with water (20 ml), separated and dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude products were purified by chromatography on silica gel using cyclohexane / ethyl acetate as eluent.

7.2.1.1 2-(Phenylethynyl)aniline (1b)

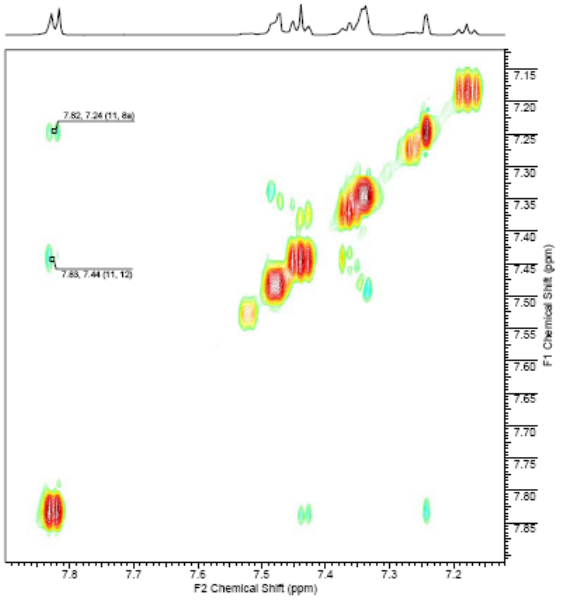
White solid (650 mg, 84 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.51 (m, 2H), 7.43-7.31 (m, 4H), 7.16 (ddd, J = 8.29, 7.32, 1.56 Hz, 1H), 6.77-6.70 (m, 2H), 4.29 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 132.2, 131.5, 129.7, 128.4, 128.2, 123.3, 118.0, 114.4, 108.0, 94.7, 85.8. Spectral properties were in accordance with the literature.[81]

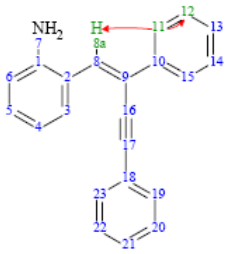
7.2.1.2 2-[(1Z)-2,4-diphenyl-1-buten-3-yn-1-yl]aniline (12)

Pale yellow solid; m. p. 131-132°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 7.4 Hz, 2H), 7.49-7.46 (m, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 6.6 Hz, 1H), 7.35-7.33 (m, 3H), 7.24 (s, 1H), 7.18 (td, J = 7.7, 1.6 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 3.87 (br. s, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.72, 139.08, 131.58, 130.18, 129.48, 129.42, 128.51, 128.33, 127.96, 126.43, 123.36, 123.03, 122.98, 118.42, 115.95, 96.01, 88.26. IR ν 3442.2, 3359.2, 3053.6, 3026.3, 2920.4, 2849.4,

2193.1, 1616.9, 1595.0, 1487.5, 1453.1, 1438.9, 1275.2, 747.1, 694.5 cm^{-1}; HRMS: $[M+H]^+$ measured mass: 296.1444; calculated mass 296.1439 for $C_{22}H_{18}N$.

Acquisition Time (sec)	(0.2796, 0.0699)	*Comment*	richiesta cd/17613 vrta/7826/54/1 spettro s5434			*Date*	25 Jul 2007 11:39:20
Date Stamp	Jul 25 2007	*File Name*	\\Versfux050.corpnet2.com\specdata\i600\s4994-s5563_310807\s5434roesy.fid\fid				
Frequency (MHz)	(599.71, 599.71)	*Nucleus*	(1H, 1H)	*Number of Transients*	2	*Original Points Count*	(1024, 256)
Owner	SP15157	*Points Count*	(2048, 512)	*Pulse Sequence*	Troesy .da	*Solvent*	CDCl3
Sweep Width (Hz)	(3663.00, 3663.00)						





No.	F2 Atom	F1 Atom	F2 (ppm)	F1 (ppm)
1	11	8a	7.82	7.24
2	11	12	7.83	7.44

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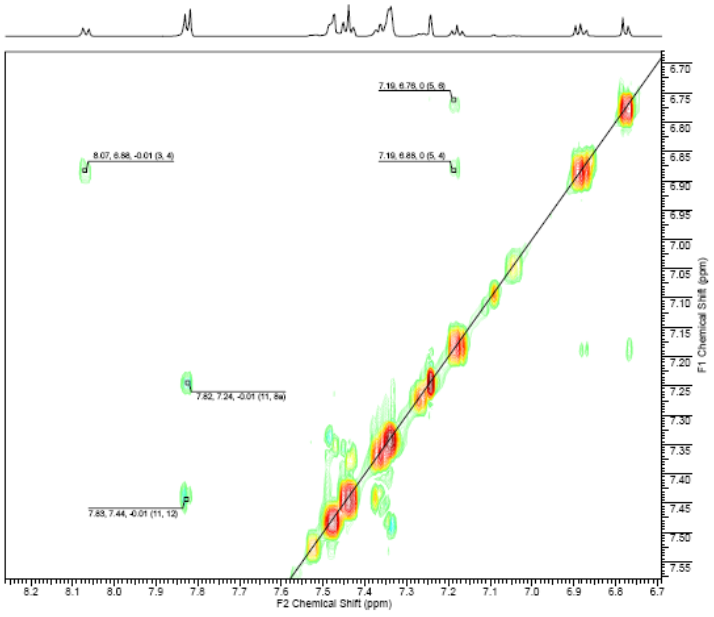
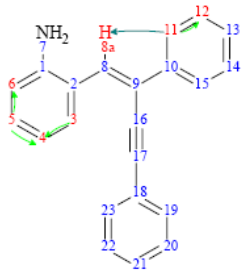
Sweep Width (Hz)	(3663.00, 3663.00)						





No.	F2 Atom	F1 Atom	F2 (ppm)	F1 (ppm)
1	3	4	8.07	6.88
2	5	4	7.19	6.88
3	5	6	7.19	6.76
4	11	8a	7.82	7.24
5	11	12	7.83	7.44

7.2.1.3 2-{[4-(Methyloxy)phenyl]ethynyl}aniline (1c)

White solid (804 mg, 90 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 9.0 Hz, 2H), 7.36 (dd, J = 8.2, 1.6 Hz, 1H), 7.17-7.11 (m, 1H), 6.89 (d, J = 9.0, 2H), 6.75-6.70 (m, 2H), 4.27 (br. s, 2H), 3.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 147.6, 132.9, 132.0, 129.4, 118.0, 115.4, 114.3, 114.0, 108.3, 94.6, 84.4, 55.3. Spectral properties were in accordance with the literature.[82]

7.2.1.4 2-[(4-Chlorophenyl)ethynyl]aniline (1d)

White solid (802 mg, 88 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.6 Hz, 2H), 7.38-7.31 (m, 3H), 7.19-7.13 (m, 1H), 6.76-6.71 (m, 2H), 4.27 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 134.2, 132.6, 132.2, 129.9, 128.7, 121.8, 118.0, 114.4, 107.5, 93.5, 86.9. Spectral properties were in accordance with the literature.[38a]

7.2.1.5 4-(Methyloxy)-2-(phenylethynyl)aniline (1e)

Pale yellow solid (581 mg, 65 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2H), 7.40-7.32 (m, 3H), 6.94 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 8.8, 2.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 4.02 (br. s, 2H), 3.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 142.0, 131.5, 128.4, 128.3, 123.2, 117.4, 115.9, 115.8, 108.6, 94.6, 85.9, 55.8. Anal. calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87. Found: C, 80.86; H, 5.93. $[M+H]^+$ = 224. Spectral properties were in accordance with the literature.[83]

7.2.1.6 2-{[2,4-bis(Methyloxy)phenyl]ethynyl}aniline (1f)

Pale yellow solid (517 mg, 51 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.2 Hz, 1H), 7.35 (dd, J = 7.6, 1.4 Hz, 1H), 7.15-7.08 (m, 1H), 6.76-6.67 (m, 2H), 6.53-6.47 (m, 2H), 4.47 (br. s, 2H), 3.90 (s, 3H), 3.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 160.9, 147.8, 133.2, 131.1, 129.1, 117.6, 114.0, 108.6, 105.3, 104.8, 98.4, 91.3, 89.1, 55.8, 55.5. Anal. calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.97; H, 6.12. $[M+H]^+$ = 254.

7.2.1.7 4-Chloro-2-(phenylethynyl)aniline (1g)

Yellow solid (811 mg, 89 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.40-7.34 (m, 4H), 7.09 (dd, J = 8.7, 2.5 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 4.28 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 131.5, 131.3, 129.6, 128.5, 128.4, 122.8, 122.3, 115.4, 109.3, 95.6, 84.6. Anal. calcd for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43. Found: C, 73.47; H, 4.62. $[M+H]^+$ = 228.

7.2.1.8 1-[4-Amino-3-(phenylethynyl)phenyl]ethanone (1h)

Pale yellow solid (470 mg, 50 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 1.9 Hz, 1H), 7.81 (dd, J = 8.6, 1.9 Hz, 1H), 7.58-7.51 (m, 2H), 7.41-7.35 (m, 3H), 6.73 (d, J = 8.6 Hz, 1H), 4.76 (br. s, 2H), 2.54 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 151.6, 133.8, 131.5, 130.4, 128.6, 128.5, 127.5, 122.7, 113.3, 106.7, 95.2, 84.6, 26.09. Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.85; H, 5.71. $[M+H]^+$ = 236.

7.2.1.9 2-(2-Pyridinylethynyl)aniline (1i)

Yellow solid (661 mg, 85 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 5.3 Hz, 1H), 7.68 (dd, J = 7.9, 1.8 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.23 (dd, J = 7.5, 4.8 Hz, 1H), 7.19-7.14 (m, 1H), 6.72 (d, J = 7.9 Hz, 2H), 4.41 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 148.5, 143.5, 136.1, 132.6, 130.4, 126.9, 122.5, 117.8, 114.3, 106.6, 94.0, 86.1. Spectral properties were in accordance with the literature.[46b]

7.2.1.10 2-(2-Thienylethynyl)aniline (1j)

Yellow oil (574 mg, 73 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 1H), 7.30-7.28 (m, 2H), 7.19-7.13 (m, 1H), 7.04-7.01 (m,1H), 6.76-6.69 (m,2H), 4.26 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 132.0, 131.7, 129.9, 127.2, 127.1, 123.2, 117.9, 114.3, 107.5, 89.5, 87.6. Spectral properties were in accordance with the literature.[84]

7.2.1.11 3-(Phenylethynyl)-4-pyridinamine (1k)

Yellow solid (715 mg, 92 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.16 (d, J = 5.7 Hz, 1H), 7.57-7.50 (m, 2H), 7.42-7.32 (m, 3H), 6.58 (d, J = 5.7 Hz, 1H), 4.80 (br. s,

2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 152.6, 149.1, 131.5, 128.6, 128.4, 122.6, 108.2, 104.9, 97.1, 82.5. Spectral properties were in accordance with the literature.[85]

7.2.1.12 6-Amino-5-(phenylethynyl)-3-pyridinecarbonitrile (1l)

Off-white solid (579 mg, 66 %); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.69-7.65 (m, 3H), 7.45-7.41 (m, 2H), 7.40-7.20 (br. s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.8, 155.7, 152.6, 142.2, 131.7, 129.0, 128.5, 121.9, 118.0, 101.4, 95.3, 83.2. Anal. calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14. Found: C, 76.81; H, 4.53. $[M+H]^+$ = 220.

7.2.1.13 2-[(4-Methylphenyl)ethynyl]aniline (1t)

Pale yellow solid (704 mg, 85 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.2 Hz, 2H), 7.39-7.35 (m, 1H), 7.20-7.11 (m, 3H), 6.76-6.70 (m, 2H), 4.28 (br. s, 2H), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.68, 138.33, 132.06, 131.34, 129.52, 129.12, 120.21, 117.96, 114.27, 108.18, 94.83, 85.14, 21.49. Spectral properties were in accordance with the literature.[49a]

7.2.1.14 4-Methyl-2-(phenylethynyl)aniline (1u)

White solid (539, 65 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.51 (m, 2H), 7.40-7.31 (m, 3H), 7.22-7.19 (m, 1H), 7.00-6.95 (m, 1H), 6.67 (d, J = 8.2 Hz, 1H), 4.15 (br. s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.42, 132.21, 131.42, 130.57, 128.34, 128.10, 127.21, 123.39, 114.52, 107.95, 94.40, 86.08, 20.26. Spectral properties were in accordance with the literature.[46b]

7.2.2 Typical procedure for the copper-free Sonogashira cross-coupling of aryl halides with alkylacetylenes to prepare 2-(ethynyl)anilines and pyridines 1m-o

The (hetero)aryl halide (4 mmol), alkynylethyne (1.5 equiv, 6 mmol), pyrrolidine (2 equiv, 8 mmol) and 20 mg of Pd EnCat 40 catalyst (0.2 mol % of Pd) were mixed and the

reaction mixture was heated to 85 °C until consumption of starting aryl halide. Ethyl acetate (2 × 20 ml) and a saturated NH_4Cl aqueous solution (20 ml) were added and the collected organic layers washed with water (20 ml), separated and dried over Na_2SO_4. The resulting crudes were purified by chromatography on silica gel using cyclohexane / ethyl acetate as eluent.

7.2.2.1 3-(2-Aminophenyl)-2-propyn-1-ol (1m)

Pale yellow solid (230 mg, 39 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 1H), 7.16-7.12 (m, 1H), 6.71-6.67 (m, 2H), 4.55 (s, 2H), 4.34-4.14 (br. s, 2H), 1.99-1.58 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 132.3, 129.9, 117.9, 114.4, 107.2, 92.6, 82.4, 51.7. Spectral properties were in accordance with the literature.[35d]

7.2.2.2 2-(Octyn-1-yl)aniline (1n)

Yellow oil (322 mg, 40 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (dd, J = 7.7, 1.5 Hz, 1H), 7.11-7.05 (m, 1H), 6.71-6.64 (m, 2H), 4.17 (br. s, 2H), 2.47 (t, J = 7.0 Hz, 2H), 1.68-1.59 (m, 2H), 1.53-1.43 (m, 2H), 1.37-1.31 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 132.0, 128.7, 117.8, 114.1, 109.0, 95.8, 76.9, 31.3, 28.9, 28.6, 22.6, 19.6, 14.0. Spectral properties were in accordance with the literature.[46b]

7.2.2.3 5-Methyl-3-(octyn-1-yl)-2-pyridinamine (1o)

Pale yellow solid (510 mg, 59 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 2.2 Hz, 1H), 4.78 (br. s, 2H), 2.45 (t, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.65-1.58 (m, 2H), 1.49-1.42 (m, 2H), 1.36-1.29 (m, 4H), 0.93-0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 146.9, 140.4, 122.4, 103.8, 96.6, 75.9, 31.3, 28.7, 28.6, 22.5, 19.6, 17.2, 14.0. Anal. calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32. Found: C, 77.91; H, 9.74. $[M+H]^+$ = 217.

7.2.3 Typical procedure for the copper-free Sonogashira cross-coupling of (hetero)aryl halides with ethynyl(trimethyl)silane to prepare 2-(ethynyl)anilines and pyridines 1p-s

The (hetero)aryl halide (4 mmol), ethynyl(trimethyl)silane (1.5 equiv, 6 mmol), pyrrolidine (2 equiv, 8 mmol) and 10 mg of Pd EnCat 40 catalyst (0.1 mol % of Pd) were mixed in a 10 ml glass microwave vial equipped with a magnetic stirrer. The vessel was placed in the microwave apparatus and irradiated at an initial power of 200 W to ramp the temperature from room temperature to 100 °C where it was held with stirring by modulating the microwave power for 20-40 minutes. Ethyl acetate (2 × 20 ml) and a saturated NH_4Cl aqueous solution (20 ml) were added and the collected organic layers washed with water (20 ml), separated and dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude products were dissolved in 20 ml of MeOH and 20 ml of 2 N NaOH were added. The mixture was stirred overnight at room temperature then evaporated to dryness. The resulting crude was purified by chromatography on silica gel using cyclohexane / ethyl acetate as eluent.

7.2.3.1 2-Ethynyl-4-(methyloxy)aniline (1p)

Yellow oil (289 mg, 49 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, J = 2.6 Hz, 1H), 6.79 (dd, J = 8.8, 3.0 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 3.98 (br. s, 2H), 3.79 (s, 3H), 3.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 142.7, 117.8, 116.3, 115.9, 107.2, 82.4, 80.6, 55.8. Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16. Found: C, 73.73; H, 5.97. $[M+H]^+$ = 148.

7.2.3.2 4-Chloro-2-ethynylaniline (1q)

Pale yellow solid (479 mg, 79 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 2.2 Hz, 1H), 7.10 (dd, J = 8.5, 2.4 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 4.25 (br. s, 2H), 3.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 131.8, 130.2, 122.0, 115.4, 107.9, 83.4, 79.3. Spectral properties were in accordance with the literature.[86]

7.2.3.3 3-Ethynyl-4-pyridinamine (1r)

Yellow oil (388 mg, 82 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.15 (d, J = 5.7 Hz, 1H), 6.55 (d, J = 5.7 Hz, 1H), 4.76 (br. s, 2H), 3.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 153.1, 149.5, 149.4, 109.3, 108.2, 85.1. Anal. calcd for $C_7H_6N_2$: C, 71.17; H, 5.12. Found: C, 70.93; H, 5.37. $[M+H]^+$ = 119.

7.2.3.4 3-Ethynyl-5-methyl-2-pyridinamine (1s)

Yellow solid (355 mg, 67 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 4.90 (br. s, 2H), 3.39 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 148.4, 141.2, 122.3, 101.4, 83.2, 79.5, 17.2 Spectral properties were in accordance with the literature.[46b]

7.2.4 Typical procedure for the copper-free Sonogashira cross-coupling of (hetero)aryl halides with acetylenes to prepare diarylacetylenes 11

The aryl halide (4 mmol), the alkyne (1.5 equiv, 6 mmol), pyrrolidine (2 equiv, 8 mmol) and the Pd EnCat catalyst (the required amount is indicated in Table 3) were mixed and the resulting mixture was stirred at 85°C for the indicate time. Ethyl acetate (2 × 20 ml) and a saturated NH_4Cl aqueous solution (20 ml) were added and the organic layer washed with water (20 ml), separated and dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude products were purified by chromatography on silica gel using cyclohexane / ethyl acetate as eluent.

7.2.4.1 Diphenylacetylene (11a)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.51 (m, 4H), 7.41-7.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.63, 128.36, 128.27, 123.30, 89.39. Spectral properties were in accordance with the literature.[87]

7.2.4.2 1-Chloro-4-(phenylethynyl)benzene (11d)

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2H), 7.50-7.44 (m, 2H), 7.39-7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.27, 132.82, 131.62, 128.71, 128.50, 128.41, 122.94, 122.17, 121.18, 90.33, 88.25. Spectral properties were in accordance with the literature.[88]

7.2.4.3 1-Bromo-4-(phenylethynyl)benzene (11e)

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.47 (m, 4H), 7.44-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.00, 131.60, 131.58, 128.49, 128.38, 122.89, 122.45, 122.24, 90.48, 88.28. Spectral properties were in accordance with the literature.[87]

7.2.4.4 1-(Phenylethynyl)-4-(trifluoromethyl)benzene (11f)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.60 (m, 4H), 7.59-7.53 (m, 2H), 7.43-7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.82, 131.76, 128.84, 128.46, 125.35, 125.31, 125.27, 125.23, 122.57, 91.76, 87.97. Spectral properties were in accordance with the literature.[87]

7.2.4.5 1-[4-(Phenylethynyl)phenyl]ethanone (11c)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.92 (m, 2H), 7.65-7.60 (m, 2H), 7.59-7.54 (m, 2H), 7.41-7.36 (m, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.32, 137.92, 136.21, 131.76, 131.72, 128.83, 128.46, 128.29, 122.67, 92.73, 88.63, 26.65. Spectral properties were in accordance with the literature.[87]

7.2.4.6 Methyl 2-(phenylethynyl)benzoate (5a)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, J = 7.61, 1.17 Hz, 1H), 7.66 (dd, J = 7.81, 0.78 Hz, 1H), 7.63-7.56 (m, 2H), 7.51 (td, J = 7.61, 1.37 Hz, 1H), 7.42-7.34 (m, 4H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.72, 133.96, 131.85, 131.71, 131.66, 130.45, 128.49, 128.33, 127.86, 123.68, 123.30, 94.30, 88.18, 52.17. Spectral properties were in accordance with the literature.[89]

7.2.4.7 1-Methyl-4-(phenylethynyl)benzene (11g)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.50 (m, 2H), 7.47-7.41 (m. 2H), 7.40-7.29 (m, 3H), 7.17 (d, J = 7.81 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.40, 131.56, 131.51, 129.12, 128.32, 128.08, 123.50, 120.21, 89.57, 88.72, 21.54. Spectral properties were in accordance with the literature.[81]

7.2.4.8 1-Methyl-2-(phenylethynyl)benzene (11h)

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.54 (m, 2H), 7.54-7.50 (m, 1H), 7.41-7.32 (m, 3H), 7.29-7.23 (m, 2H), 7.23-7.16 (m, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.21, 131.85, 131.53, 129.48, 128.38, 128.32, 128.19, 125.60, 123.58, 123.04, 93.36, 88.36, 20.78. Spectral properties were in accordance with the literature.[34f]

7.2.4.9 1-(Methyloxy)-4-(phenylethynyl)benzene (11b)

Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.51 (m, 2H), 7.51-7.47 (m, 2H), 7.37-7.32 (m, 3H), 6.92-6.87 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.60, 133.04, 131.43, 128.28, 127.91, 123.58, 115.37, 113.98, 89.35, 88.05, 55.29. Spectral properties were in accordance with the literature.[87]

7.2.4.10 1-(Methyloxy)-2-(phenylethynyl)benzene (3c)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.55 (m, 2H), 7.52 (dd, J = 7.61, 1.76 Hz, 1H), 7.40-7.28 (m, 4H), 6.99-6.89 (m, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.92, 133.56, 131.65, 129.73, 128.22, 128.07, 123.56, 120.47, 112.46, 110.69, 93.41, 85.70, 55.83. Spectral properties were in accordance with the literature.[81]

7.2.4.11 4-(Phenylethynyl)aniline (11i)

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H), 7.39-7.27 (m, 5H), 6.68-6.61 (m, 2H), 3.82 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.60, 132.93, 131.32, 128.23, 127.62, 123.88, 114.71, 112.60, 90.07, 87.29. Spectral properties were in accordance with the literature.[34f]

7.2.4.12 Tris(1-methylethyl)(phenylethynyl)silane (11j)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.45 (m, 2H), 7.33-7.28 (m, 3H), 1.15 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.04, 128.28, 128.18, 123.55, 107.12, 90.46, 18.69, 11.34. Spectral properties were in accordance with the literature.[90]

7.2.5 Preparation of *N*-protected anilines

Experimental details and characterizations of compounds **14** are given.

7.2.5.1 4-Methyl-*N*-(2-phenylethynyl-phenyl)-benzenesulfonamide (14a)

According to a literature procedure,[43b] compound **14a** was prepared from 2-phenylethynylaniline, **1b**, (5 mmol, 966 mg) by adding 2 equiv of pyridine in CH_2Cl_2 (20 ml) at room temperature. *p*-Toluenesulfonic chloride (1.5 equiv) was added in 5 minutes to the resulting solution. After completion, H_2O (10 ml) was added to the reaction mixture and the organic phase was separated and washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by column chromatography with AcOEt/cyclohexane to give **14a** (82 %). White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.61 (m, 3H), 7.48-7.15 (m, 10H), 7.09-7.03 (m, 1H), 2.33 (s, 3H). Spectral properties were in accordance with the literature.[37b]

7.2.5.2 *N*-(2-Phenylethynyl-phenyl)-acetamide (14b)

Compound **14b** was prepared by treating 5 mmol (966 mg) of 2-phenylethynylaniline, **1b**, with 10 equiv of acetic anhydride at room temperature. Afer completion, the mixture was diluted with CH_2Cl_2 (20 ml) and water (20 ml) was carefull added. The organic phase was separated and washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by column chromatography with AcOEt/cyclohexane to give **14b** (69 %). White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34-8.32 (m, 1H), 7.90 (s, 1H), 7.46-7.40 (m, 3H), 7.32-7.24 (m, 4H), 7.02-6.97 (m, 1H), 2.17 (s, 3H). Spectral properties were in accordance with the literature.[91]

7.3 Preparation of indoles

Experimental procedures and characterisations are given for compounds **2a**-**u** and **15a**.

7.3.1 Typical procedure for the microwave-assisted cycloisomerization in water

The 2-alkynylaniline (0.4 mmol) and 4 ml of water were mixed in a 10 ml glass microwave vial equipped with a magnetic stirrer. The vessel was placed in the microwave apparatus and irradiated at an initial power of 300 W to ramp the temperature from r.t. to 200 °C where it was held with stirring by modulating the microwave power for the reaction time specified in Table 17. The mixture was then cooled down to room temperature and extracted twice with ethyl acetate (2 × 20 ml). The organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude products were purified by chromatography on silica gel using cyclohexane / ethyl acetate as eluent. The yields obtained are reported in Table 17.

7.3.2 Typical procedure for the microwave-assisted cycloisomerization in water with additives

The required 2-alkynylaniline or alkynylpyridine (0.5 mmol) and 2 ml of water were mixed in a 10 ml glass microwave vial equipped with a magnetic stirrer. The corresponding amount of salt or base was added as indicated in Table 23 and Table 27. The vessel was placed in the microwave apparatus and irradiated at an initial power of 200 W to ramp the temperature from r.t. to 200 °C, where it was held with stirring by modulating the microwave power for the specified reaction time. The mixture was then cooled down to room temperature and extracted twice with ethyl acetate (2 × 20 ml). The organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude

product was purified by chromatography on silica gel using dichloromethane or methanol / ethyl acetate as eluent. The yields obtained are reported in Table 23 and Table 27.

7.3.3 Compound characterizations

7.3.3.1 1*H*-Indole (2a)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (br. s, 1H), 7.73 (dd, J = 7.8, 1.0 Hz, 1H), 7.45 (dd, J = 8.1, 1.0 Hz, 1H), 7.31-7.24 (m, 2H), 7.23-7.17 (m, 1H), 6.65-6.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 127.8, 124.1, 121.9, 120.7, 119.8, 111.0, 102.6. Spectral properties were in accordance with the literature.[92]

7.3.3.2 2-Phenyl-1*H*-indole (2b)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (br. s, 1H), 7.71-7.64 (m, 3H), 7.50-7.40 (m, 3H), 7.38-7.32 (m, 1H), 7.25-7.20 (m, 1H), 7.18-7.13 (m, 1H), 6.87-6.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.8, 132.4, 129.2, 129.0, 127.7, 125.1, 122.3, 120.6, 120.3, 110.9, 100.0. Spectral properties were in accordance with the literature.[93]

7.3.3.3 2-[4-(Methyloxy)phenyl]-1*H*-indole (2c)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.37 (dd, J = 8.0, 1.0 Hz, 1H), 7.09-6.94 (m, 4H), 6.76 (dd, J = 2.1, 0.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.7, 137.7, 136.9, 128.8, 126.3, 124.9, 121.0, 119.6, 119.2, 114.3, 111.0, 97.3, 55.2. Spectral properties were in accordance with the literature.[93]

7.3.3.4 2-(4-Chlorophenyl)-1*H*-indole (2d)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (br. s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.45-7.39 (m, 3H), 7.26-7.20 (m, 1H), 7.18-7.12 (m, 1H), 6.83 (dd, J = 2.0, 0.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 136.6, 133.4, 130.8, 129.2, 129.1, 126.3, 122.7, 120.7, 120.4, 110.9, 100.5. Spectral properties were in accordance with the literature.[93]

7.3.3.5 5-(Methyloxy)-2-phenyl-1*H*-indole (2e)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (br. s, 1H), 7.68-7.63 (m, 2H), 7.48-7.42 (m, 2H), 7.36-7.28 (m, 2H), 7.11 (d, J = 2.3 Hz, 1H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H), 6.79-6.76 (m, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 138.6, 132.4, 132.0, 129.7, 129.0, 127.6, 125.0, 112.6, 111.6, 102.2, 99.8, 55.8. Spectral properties were in accordance with the literature.[93]

7.3.3.6 2-[2,4-bis(Methyloxy)phenyl]-1*H*-indole (2f)

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (br. s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.19-7.07 (m, 2H), 6.79 (dd, J = 2.1, 0.8 Hz, 1H), 6.65-6.58 (m, 2H), 4.01 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 156.9, 136.1, 135.9, 129.2, 128.2, 121.3, 119.9, 119.7, 113.8, 110.7, 105.8, 99.3, 98.5, 55.8, 55.5. Spectral properties were in accordance with the literature.[94]

7.3.3.7 5-Chloro-2-phenyl-1*H*-indole (2g)

Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (br. s, 1H), 7.70-7.63 (m, 2H), 7.62-7.58 (m, 1H), 7.51-7.43 (m, 2H), 7.40-7.29 (m, 2H), 7.15 (dd, J = 8.6, 1.9 Hz, 1H), 6.80-6.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 135.1, 131.8, 130.3, 129.1, 128.1, 125.8, 125.2, 122.6, 120.0, 111.8, 99.5. Spectral properties were in accordance with the literature.[95]

7.3.3.8 1-(2-Phenyl-1*H*-indol-5-yl)ethanone (2h)

Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (br. s, 1H), 8.33-8.30 (m, 1H), 7.89 (dd, J = 8.6, 1.6 Hz, 1H), 7.73-7.67 (m, 2H), 7.51-7.34 (m, 4H), 6.93 (dd, J = 2.1, 0.8 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 139.5, 139.5, 131.7, 130.3, 129.1, 128.8, 128.2, 125.2, 122.8, 122.6, 110.8, 101.1, 26.6. Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.93; H, 5.67. $[M+H]^+$ = 236.

7.3.3.9 2-(2-Pyridinyl)-1*H*-indole (2i)

Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (br. s, 1H), 8.60 (d, J = 4.8 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.73 (dd, J = 7.9, 1.8 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.24 (t, 7.5 Hz, 1H), 7.21-7.16 (m, 1H), 7.15-7.11 (m, 1H), 7.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 149.1, 136.7, 136.6, 129.1, 123.1, 122.0, 121.1, 120.1, 119.9, 111.4, 111.3, 100.6. Spectral properties were in accordance with the literature.[46b]

7.3.3.10 2-(2-Thienyl)-1*H*-indole (2j)

Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (br. s, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 6.1 Hz, 1H), 7.27-7.25 (m, 1H), 7.21 (m, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.11-7.08 (m, 1H), 6.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 135.6, 132.3, 129.1, 127.9, 124.6, 122.9, 122.5, 120.5, 120.4, 110.7, 100.4. Spectral properties were in accordance with the literature.[96]

7.3.3.11 2-Phenyl-1H-pyrrolo[3,2-c]pyridine (2k)

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (br. s, 1H), 8.81 (s, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.90 (d, J = 7.5 Hz, 2H), 7.49 (t, J = 7.7 Hz, 2H), 7.40-7.33 (m, 2H), 7.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.9, 140.4, 140.3, 138.9, 131.4, 129.0, 128.1, 125.7, 125.4, 106.6, 97.5. Spectral properties were in accordance with the literature.[97]

7.3.3.12 2-Phenyl-1*H*-pyrrolo[2,3-b]pyridine-5-carbonitrile (2l)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.8 (br. s, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.01-7.93 (m, 2H), 7.52-7.47 (m, 2H), 7.43-7.39 (m, 1H), 7.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 145.4, 139.6, 132.1, 131.2, 130.6, 129.0, 128.9, 125.7, 120.3, 97.9. Anal. calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14. Found: C, 76.67; H, 4.18. $[M+H]^+$ = 220. *2-Phenyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid.* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.4 (br. s, 1H), 8.75 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 1.8 Hz, 1H), 8.01-7.94 (m, 2H), 7.52-7.47 (m, 2H), 7.43-7.39 (m, 1H), 7.04 (s, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 167.6, 150.8, 143.1, 128.9, 128.3, 127.4, 125.4, 122.5, 119.9, 97.9. $[M+H]^+$ = 239.

7.3.3.13 1*H*-indol-2-ylmethanol (2m)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br. s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 8.12 Hz, 1H), 7.22-7.18 (m, 1H), 7.14-7.11 (m, 1H), 6.49 (d, J = 1.1 Hz, 1H), 4.79 (s, 2H), 2.16-2.02 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 136.3, 128.0, 122.1, 120.6, 119.9, 110.9, 100.5, 58.6. Spectral properties were in accordance with the literature.[98]

7.3.3.14 2-Hexyl-1*H*-indole (2n)

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (br. s, 1H), 7.55-7.51 (m, 1H), 7.33-7.28 (m, 1H), 7.14-7.04 (m, 2H), 6.26-6.23 (m, 1H), 2.76 (t, J = 7.6 Hz, 2H), 1.78-1.68 (m, 2H), 1.46-1.29 (m, 6H), 0.95-0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 136.0, 128.9, 120.9, 119.7, 119.5, 110.2, 99.4, 31.6, 29.2, 29.0, 28.3, 22.6, 14.1. Spectral properties were in accordance with the literature.[98]

7.3.3.15 2-Hexyl-5-methyl-1*H*-pyrrolo[2,3-b]pyridine (2o)

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, J = 2.0 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.89 (s, 1H), 7.34 (d, J = 8.3 Hz, 1H), 3.08-2.93 (m, 2H), 2.53 (s, 3H), 1.88 (quin, J = 7.0 Hz, 2H), 1.51-1.14 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 155.1, 136.2, 135.2, 130.8, 122.4, 120.5, 39.2, 31.7, 29.2, 22.5, 18.5, 14.0. Spectral properties were in accordance with the literature.[99]

7.3.3.16 5-Methyloxy-1*H*-indole (2p)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br. s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.19 (t, J = 2.6 Hz, 1H), 7.14 (d, J = 2.2 Hz, 1H), 6.89 (dd, J = 8.8, 2.2 Hz, 1H), 6.53-6.48 (m, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 130.9, 128.2, 124.8, 112.3, 111.7, 102.4, 102.3, 55.8. Spectral properties were in accordance with the literature.[99]

7.3.3.17 5-Chloro-1*H*-indole (2q)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (br. s, 1H), 7.65-7.60 (m, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.26-7.22 (m, 1H), 7.17 (dd, J = 8.6, 2.0 Hz, 1H), 6.54-6.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 129.2, 128.9, 125.5, 122.3, 120.1, 111.9, 102.4. Spectral properties were in accordance with the literature.[100]

7.3.3.18 1*H*-pyrrolo[3,2-c]pyridine (2r)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.28 (d, J = 5.7 Hz, 1H), 7.36 (d, J = 5.7 Hz, 1H), 7.32 (d, J = 3.1 Hz, 1H), 6.67 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 139.9, 139.5, 126.0, 125.0, 106.9, 101.8. Spectral properties were in accordance with the literature.[101]

7.3.3.19 5-Methyl-1*H*-pyrrolo[2,3-b]pyridine (2s)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.86-10.64 (m, 1H), 8.20 (d, J = 1.8 Hz, 1H), 7.77 (s, 1H), 7.34 (d, J = 3.5 Hz, 1H), 6.44 (d, J = 3.3 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 143.5, 128.9, 125.2, 124.7, 120.2, 100.0, 18.5. Anal. calcd for $C_8H_8N_2$: C, 72.70; H, 6.10. Found: C, 72.27; H, 5.98. $[M+H]^+$ = 133.

7.3.3.20 2-(4-Methylphenyl)-1*H*-indole (2t)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br. s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.41 (dd, J = 8.0, 1.0 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.23-7.11 (m, 2H), 6.81 (dd, J = 2.1, 0.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.03, 137.63, 136.66, 129.69, 129.55, 129.31, 125.04, 122.10, 120.50, 120.18, 110.77, 99.38, 21.22. Spectral properties were in accordance with the literature.[93]

7.3.3.21 5-Methyl-2-phenyl-1*H*-indole (2u)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (br. s, 1H), 7.69-7.64 (m, 2H), 7.48-7.42 (m, 3H), 7.36-7.28 (m, 2H), 7.06-7.02 (m, 1H), 6.78-6.76 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.92, 135.13, 132.50, 129.53, 129.47, 128.97, 127.56,

125.04, 123.97, 120.28, 110.51, 99.54, 21.46. Spectral properties were in accordance with the literature.[46b]

7.3.3.22 1-(Toluene-4-sulfonyl)-2-phenyl-indole (15a)

White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32-8.30 (m, 1H), 7.52-7.28 (m, 10H), 7.04-7.01 (m, 2H), 6.53 (s, 1H), 3.27 (s, 3H). Spectral properties were in accordance with the literature.[37b]

Chapter 8

References

1. For general books on microwave-assisted synthesis see: (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; (b) Loupy, A. *Microwaves in Organic Synthesis* (2nd Edition); Editor: Loupy, André; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006; (c) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (d) Kappe, C. O.; Dallinger, D.; Murphee, S. S. *Practical Microwave Synthesis for Organic Chemists*; Wiley-VCH: Weinheim, 2009.

2. For general reviews on microwave-assisted synthesis: (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225; (b) Kappe, C. O. *Angew. Chem. Int. Ed*. **2004**, *43*, 6250; (c) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem*. **2004**, *6*, 128-141; (d) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66-77; (e) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903-918; (f) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev*. **2005**, *34*, 164-178; (g) Kappe, C. O.; Dallinger, D. *Nature Rev. Drug Discov*. **2006**, *5*, 51-64; (h) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res*. **2008**, *41*, 629-639; (i) Kappe, C. O. *Chem. Soc. Rev*. **2008**, *37*, 1127-1139; (j) Kappe, C. O.; Dallinger, D. *Mol. Divers*. **2009**, *13*, 71-193; (k) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325-3355.

3. (a) Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Proc. Res. Dev.* **2005**, *9*, 516-518; (b) Razzaq, T.; Kappe, C. O. *Chem. Sus. Chem.* **2008**, *1*, 123-132.

4. Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev*. **1991**, *20*, 1-47.

5. For specific articles on microwave effects see: (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199-9223; (b) Loupy, A.; Varma, R. S. *Chimica Oggi* **2006**, *24*, 36-40; (c) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36-47; (d) Irfan, M.; Fuchs, M.; Glasnov, T. N.; Kappe, C. O. *Chem. Eur. J.* **2009**, *15*, 11608-11618; (e) Schmink, J. R.; Leadbeater, N. E. *Org. Biomol. Chem.* **2009**, *7*, 3842-3846; (f) Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* **1992**, *57*, 7099-7102; (g) Baghurst, D. R.; Mingos, D. M.

P. *J. Chem. Soc., Chem. Commun.* **1992**, 674-677; (h) Robinson, J.; Kingman, S.; Irvine, D.; Licence, P.; Smith, A.; Dimitrakis, G.; Obermayerb, D.; Kappe, C. O. *Phys. Chem. Chem. Phys.* **2010**, *12*, 4750-4758.

6. Dressen, M. H. C. L.; van de Kruijs, B. H. P.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Proc. Res. Dev.* **2007**, *11*, 865-869.

7. (a) Bren, M.; Janezic, D.; Bren, U. *J. Phys. Chem. A* **2010**, *114*, 4197-4202; (b) Bren, U.; Krzan, A.; Mavri, J. *J. Phys. Chem. A* **2008**, *112*, 166-171 (c) Miklavc, A.; Perdih, M.; Smith, I. W. *J. Chem. Phys.* **2000**, *112*, 8813-8818.

8. (a) Jacob, J. J.; Chia, L. H. L.; Boey, F. Y. C. *J. Mater. Sci.* **1995**, *30*, 5321-5327; (b) Binner, J. G. P.; Hassine, N. A.; Cross, T. E. *J. Mater. Sci.* **1995**, *30*, 5389-5392; (c) Shibata, C.; Kashima, T.; Ohuchi, K. *Jpn. J. Appl. Phys.* **1996**, *35*, 316-319.

9. (a) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363-2366; (b) Lewis, D. A.; Summers, J. D.; Ward, T. C.; McGrath, J. E. *J. Polym. Sci. Part A* **1992**, *30*, 1647-1653.

10. Loupy, A.; Maurel, F.; Sabatié-Gogová, A. *Tetrahedron* **2004**, *60*, 1683-1691.

11. (a) Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565-3585; (b) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417-1424.

12. Leadbeater, N. E.; Schmink, J. R. *Tetrahedron* **2007**, *63*, 6764-6773.

13. Stadler, A.; Pichler, S.; Horeis, G.; Kappe, C. O. *Tetrahedron* **2002**, *58*, 3177-3183.

14. Razzaq, T.; Kappe, C. O. *Tetrahedron Lett.* **2007**, *48*, 2513-2517.

15. For recent articles on microwave chemistry scale-up: (a) Damm, M.; Glasnov, T. N.; Kappe, C. O. *Org. Proc. Res. Dev.* **2010**, *14*, 215-224; (b) Lehmann, H.; La Vecchia, L. *Org. Proc. Res. Dev.* **2010**, *14*, 650-656; (c) Schmink, J. R.; Kormos, C. M.; Devine, W. G.; Leadbeater, N. E. *Org. Proc. Res. Dev.* **2010**, *14*, 205-214; (d) Strauss, C. R. *Org. Proc. Res. Dev.* **2009**, *13*, 915-923; (e) Bowman, M. D.; Schmink, J. R.; McGowan, C. M.; Kormos, C. M.; Leadbeater, N. L. *Org. Proc. Res. Dev.* **2008**, *12*, 1078-1088; (f) Moseley, J. D.; Lenden, P.; Lockwood, M.; Ruda, K.;

Sherlock, J.-P.; Thomson, A. D.; Gilday, J. P. *Org. Proc. Res. Dev.* **2008**, *12*, 30-40; (g) Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E. *Org. Proc. Res. Dev.* **2008**, *12*, 41-57; (h) Kremsner, J. M.; Stadler, A.; Kappe, C. O. *Topics in Curr. Chem.* **2006**, *266*, 233-278; (i) Wolkenberg, S. E.; Shipe, W. D.; Lindsley, C. W.; Guare, J. P.; Pawluczyk, J. M. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 701-708; (j) Glasnov, T. N.; Kappe, C. O. *Macromol. Rapid Commun.* **2007**, *28*, 395.

16. (a) Razzq, T.; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321-1325; (b) Irfan, M.; Petricci, E.; Glasnov, T. N.; Taddei, M.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1327-1334.

17. (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 2000; (b) Anastas, P. T.; Williamson, T. C. *Green Chemistry: Frontiers in Benign Chemical Syntheses and Proc.es*; Oxford University Press: Oxford, 1998.

18. (a) Adams, D. J.; Dyson, P. J.; Tavener, S. J. *Chemistry in Alternative Reaction Media*; Wiley: Chichester, 2004; (b) Tundo, P.; Perosa, A.; Zecchini, F. *Methods and Reagents for Green Chemistry: An Introduction*; Wiley: Chichester, 2007.

19. For some books and reviews on water as a solvent see: (a) Li, C.-J.; Chan, T.-H. *Comprehensive Organic Reactions in Aqueous Media*; Wiley: Hoboken, New Jersey, 2007; (b) Lindström, U. M. *Organic Reactions in Water*; Blackwell Publishing: Oxford, 2007; (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095-3165; (d) Hailes, H. C. *Org. Proc. Res. Dev.* **2007**, *11*, 114-120; (e) Lindström, U. M.; Andersson, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 548-551.

20. For some reviews on microwave-assisted synthesis in water see: (a) Dallinger, D.; Kappe, C. O. *Chem. Rev*. **2007**, *107*, 2563-2591; (b) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev*., **2008**, *37*, 1546-1557; (c) Polshettiwar, V.; Varma, R. *Aqueous Microwave Assisted Chemistry: Synthesis and Catalysis*; Royal Society of Chemistry: Cambridge, 2010.

21. For some general reviews on microwaves-assisted transition metal-catalyzed reactions: (a) Nilsson, P.; Olofsson, K.; Larhed, M. *Top. Curr. Chem.* **2006**, *266*, 103-144;

22. For some general reviews and books on microwaves-assisted heterocyclic synthesis see: (a) Polshettiwar, V.; Varma, R. S. *Pure Appl. Chem.* **2008**, *80*, 777-790; (b) Jindal, R.; Bajaj, S. *Curr. Org. Chem.* **2008**, *12*, 836-849; (c) Polshettiwar, V.; Varma, R. S. *Curr. Opin. Drug Discov. Develop.* **2007**, *10*, 723-737; (d) van der Eycken, E.; Kappe, C. O.; Almqvist, F. *Topics in Heterocyclic Chemistry, Vol.1: Microwave-assisted synthesis of heterocycles*; Springer: Berlin, 2006; (e) Besson, T.; Brain C. T. *Heterocyclic Chemistry Using Microwave-Assisted Approaches*. In: Lidström, P,; Tierney, J.P. (eds); *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, 2004; (f) Bougrin, K.; Loupy, A.; Soufiaoui, M. J. *Photochem. Photobiol. C: Photochem. Rev.* **2005**, *6*, 139-167; (g) Suna, E.; Mutule, I. *Top Curr. Chem.* **2006**, *266*, 49-101.

23. (a) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672-3679; (b) Nolen, S. A.; Liotta, C. L.; Eckert, C. A.; Gläser, R. *Green Chem.* **2003**, *5*, 663-669.

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

25. Vasudevan, A.; Verzal, M. K. *Synlett* **2004**, *4*, 631-634.

26. (a) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193-198; (b) Varma, R. S. *Green Chem.* **1999**, *1*, 43-55; (c) Bogdal, D.; Loupy, A. *Org. Proc. Res. Dev.* **2008**, *12*, 710-722.

27. (a) Varma R. S. *Tetrahedron* **2002**, *58*, 1235-1255; (b) Polshettiwar, V.; Molnár, Á. *Tetrahedron* **2007**, *63*, 6949-6976.

28. (a) Chandrasekhar, S.; Narsihmulu, C.; Shameem Sultana, S.; Ramakrishna Reddy, N. *Org. Lett.* **2002**, *4*, 4399-4401; (b) Corma, A.; García, H.; Leyva, A. *Tetrahedron* **2005**, *61*, 9848-9854; (c) Li, J.-H.; Liu, W.-J.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 5409-5412; (d) Wasserscheid, P.; Welton, T. *Ionic liquids in synthesis*; Wiley-VCH: Wenheim, 2008.

29. Patai, S. *Patai Chemistry of the Carbon-Carbon Triple Bond - Patai's Chemistry of Functional Groups 1*, Wiley-Blackwell: London, 2010.

30. (a) Togni, A.; Grützmacher, H. *Catalyc Heterofunctionalization* Wiley-VCH Verlag GmbH: Weinheim, 2001; (b) Ide, D. M.; Eastlund, M. P.; Jupe, C. L.; Stockland Jr., R. A. *Curr. Org. Chem.* **2008**, *12*, 1258; (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079-3159; (d) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407-1420; (e) Ide, D. M.; Eastlund, M. P.; Jupe, C. L.; Stockland, R. A. *Curr. Org. Chem.* **2008**, *12*, 1258-1278.

31. (a) Joule, J. A. *Indole and its Dervatives*. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations;* Thomas, E. J., Ed.; George Thieme Verlag: Stuttgart, Germany, **2000;** Category 2, Vol.10, Chapter 10.13; (b) Sundberg, R. J. *Indoles;* Sundberg, R. J., Ed.; Academic Press: London, 1996; (c) Higasio, Y. S.; Shoji, T. *Applied Catalysis, A: General* **2001**, *221*, 197-207; (d) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761-793.

32. For some recent general reviews: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873-2920; (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875-2911; (c) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153-2167; (d) Russel, J. S.; Pelkey, E. T. In *Progress in Heterocyclic Chemistry*; Gribble, G. W. and Joule, J. A., Eds.; Elsevier Science: New York, 2008; Vol. 20, pp 122-151; (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644-4680; (f) Patil, S.; Patil, R. *Curr. Org. Synth.* **2007**, *4*, 201-222; (g) Patil, S.; Buolamwini, J. K. *Curr Org. Synth.* **2006**, *3*, 477-498; (h) Ziegert, R. E.; Knepper, K; Braese, S. In *Targets in Heterocyclic Chemistry*; Attanasi O. and Spinelli D., Eds.; Società Chimica Italiana: Roma, 2006; Vol. 9, pp 230-256.

33. (a) Harcken, C.; Ward, Y.; Thomson, D.; Riether, D. *Synlett* **2005**, 3121-3125; (b) Hopkins, C. R.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 8087-8090; (c) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488-2490; (d) Majumdar, K. C.; Mondal, S. *Tetrahedron Lett.* **2007**, *48*, 6951-6953; (e)

McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307-3310; (f) Cacchi, S.; Fabrizi, G.; Parisi, L. M.; Bernini, R. *Synlett* **2004**, 287-290; (g) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355-5358.

34. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467-4470; (b) Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834-871; (c) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874-922; (d) Arcadi, A.; Cacchi S.; Marinelli F. *Tetrahedron Lett.* **1989**, *30*, 2581-2584; (e) Takahashi, S.; Kuroyama, Y.; Sonogashira K.; Hagihara, N. *Synthesis* **1980**, 627-630; (f) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527-1530.

35. (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571-1587; (b) Stoll, A. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 113-116; (c) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255-1261; (d) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron* **2008**, *64*, 7301-7306.

36. (a) Ye, S.; Ding, Q.; Wang, Z.; Zhou, H.; Wu, J. *Org. Biomol. Chem.* **2008**, *6*, 4406-4412; (b) Ambrogio, I.; Cacchi, S.; Fabrizi G. *Tetrahedron Lett.* **2007**, *43*, 7721-7725; (c) Abbiati, G.; Arcadi, A.; Beccalli, E.; Bianchi, G.; Marinelli F.; Rossi, E. *Tetrahedron* **2006**, *62*, 3033-3039; (d) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Heterocycles* **2004**, *64*, 475-482; (e) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289-296; (f) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Adv. Synth. Catal.* **2006**, *348*, 1301-1305; (g) Tyrrell, E.; Whiteman, L.; Williams, N. *Synthesis* **2009**, *5*, 829-835; (h) Capelli, L.; Manini, P.; Pezzella, A.; Napolitano, A.; d'Ischia, M. *J. Org. Chem.* **2009**, *74*, 7191-7194.

37. a) Lee, J.-Y.; Lee, M. H.; Jeong, K.-S. *Supramol. Chem.* **2007**, *19*, 257-263; (b) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126-1136; (c) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277-1280; (d) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958-10964.

38. (a) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, *4*, 610-618; (b) Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2007**, *11*, 1775-1779; (c) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B. *Tetrahedron Lett.* **2008**, *49*, 7213-7216; (d) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627-630; (e) Miyazaki, Y.; Kobayashi, J. *J. Comb. Chem.* **2008**, *10*, 355-357.

39. Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546-10547.

40. McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687-7690.

41. Lai, R.-Y.; Hayashi, A.; Ozawa, F.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Organometallics* **2007**, *26*, 1062-1068.

42. (a) Ebrahimi, D.; Kemedi, D. F.; Messerla, A. B.; Hibbert, D. B. *Analyst* **2008**, *133*, 817-822; (b) Trost, B. M.; McClory, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2074-2077; (c) Dabb, S. L.; Ho, J. H. H.; Hodgson, R.; Messerle, B. A.; Wagler, J. *Dalton Trans.* **2009**, 634-642; (d) Boyer, A.; Isono, N.; Lackner, S.; Lautens, M. *Tetrahedron* **2010**, *66*, 6468-6482.

43. (a) Okuma, K.; Seto, J.; Sakaguchi, K.; Ozaki, S.; Nagahora, N.; Shioji, K. *Tetrahedron Lett.* **2009**, *50*, 2943-2945; (b) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731-5736.

44. (a) Namba, K.; Nakagawa, Y.; Yamamoto, H.; Imagawa, I.; Nishizawa, M. *Synlett* **2008**, 1719-1723; (b) Kurisaki, T.; Naniwa, T.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2007**, *48*, 1871-1874.

45. Terrasson, V.; Michaux, J.; Gaucher, A.; Wehbe, J.; Marque, S.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 5332-5335.

46. (a) Sakai, N.; Annaka, K.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 631-634; (b) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160-4165; (c) Murai, K.; Hayashi, S.; Takaichi, N.; Nobuhiro, K.; Fujioka, H. *J. Org. Chem* **2009**, *74*, 1418-1421.

47. Arcadi A.; Bianchi G.; Inesi, A.; Marinelli, F.; Rossi L. *Eur. J. Org. Chem.* **2008**, 783-787.

48. Wang, H.; Liu, L.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 6841-6843.

49. (a) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017-8028; (b) Chen, Y.; Markina, N. A.; Larock, R. C. *Tetrahedron* **2009**, *65*, 8908-8915; (c) Pearson, S. E.; Nandan, S. *Synthesis* **2005**, *15*, 2503-2506; (d) Hopkins, C. R.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 8631-8633; (e) Binet, J.; Boubia, B.; Dodey, P.; Legendre, C.; Barth, M. FR 2890071 A1 20070302 Application: FR 2005-8858 20050830; (f) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535-3538; (g) Ye, D.; Wang, J.; Zhang, X.; Zhou, Y.; Ding, X.; Feng, E.; Sun, H.; Liu, G.; Jiang, H.; Liu, H. *Green Chem.* **2009**, *11*, 1201-1208; (h) Dabb, S. L.; Ho, J. H. H.; Hodgson, R.; Messerle, B. A.; Wagler, J. *Dalton Trans.* **2009**, 634–642; (i) Sanz, R.; Guilarte, V.; Castroviejo, M. P. *Synlett* **2008**, *19*, 3006-3010.

50. (a) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 351; (b) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453; (c) Hiroya, K.; Suzuki, N.; Yasuhara, A.; Egawa, Y.; Kasano, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4339; (d) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815; (e) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280; (f) Schreiber, F. G.; Stevenson, R *J. Chem. Soc., Perkin Trans. 1*. **1977**, 90; (g) Russo, O.; Messaoudi, S.; Hamze, A.; Olivi, N.; Peyrat, J.-F.; Brion, J.-D.; Sicsic, S.; Berque-Bestela, I.; Alami, M. *Tetrahedron* **2007**, *63*, 10671–10683; (h) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235-2239.

51. (a) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652–1658; (b) Nakamura I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473 –4475.

52. (a) Houpis, I. N.; Choi, W.B.; Reider, P. J.; Molina, A.; Churchill, H.; Lynch, J. E.; Volante, R.P. *Tetrahedron Lett.* **1994**, *35*, 9355-9358; (b) Houpis, I. N.; Molina, A.; Lynch, J. E.; Churchill, H.; Volante, R. P.; Reider, P. J.; Choi, W. B. W002100878A1, 15111995, Appl. Number 95089967.

53. (a) Santín, E. P.; Khanwalkar, H.; Voegel, J.; Collette, P.; Mauvais, P.; Gronemeyer, H.; de Lera, Á. R. *ChemMedChem* **2009**, *4*, 780-791; (b) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron Lett.* **2001**, *42*, 6049-6051; (c) Corfield, J. A.; Grimes, R. M.; Harrison, D.; Hartley, C. D.; Howes, P. D.; Le, J.; Meeson, M. L.; Mordaunt, J. E.; Shah, P.; Slater, M. J.; White, G. V. WO2007071434 A1 28062007, Int. Appl. Number PCT EP2006 012442; (d) Le Bras, G.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2006**, *47*, 5497–5501; (e) Olivi, N.; Thomas, E.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Synlett* **2004**, *12*, 2175–2179; (f) Jacubert, M.; Hamze, A.; Provot, O.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 3588–3592.

54. (a) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135-156; (b) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017-3020; (c) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7599-7602; (d) Rossi, R.; Bellina, F.; Biagetti, M., Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7799-7802; (e) Rossi, R.; Bellina, F.; Catanese, A.; Mannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479-488; (f) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533-2545; (g) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. *J. Org. Chem.* **1995**, *60*, 3270-3271; (h) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770-8779; (i) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067-2081.

55. (a) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517-5520; (b) Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 933-935.

56. Hellal, M.; Bourguignon, J.-J.; Bihel, F. J.-J. *Tetrahedron Lett.* **2008**, *49*, 62-65.

57. Le Bras, G.; Hamze, A.; Messaoudi, S.; Provot, O.; Le Calvez, P.-B.; Brion, J.-D.; Alami, M. *Synthesis* **2008**, *10*, 1607-1611.

58. (a) Tougerti, A.; Negri, S.; Jutand, A. *Chem. Eur. J.* **2007**, *13*, 666-676; (b) Consorti, C. S.; Flores, F. R.; Rominger, F.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 133-141; (c) Yi, C.; Hua, R. *J. Org. Chem.* **2006**, *71*, 2535-2537; (d) Ljungdahl, T.; Bennur, T.; Dallas, A.; Emtenäs, H.; Mårtensson, J. *Organometallics* **2008**, *27*, 2490-2498; (e) Ruiz, J.; Cutillas, N.; Lopez, F.; Lopez, G.; Bautista, D. *Organometallics* **2006**, *25*, 5768.

59. (a) Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428; (b) Gelman, D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 5993; (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.

60. (a) Elangovan, A.; Wang, Y.-H.; Ho, T.-I. *Org. Lett.* **2003**, *5*, 1841; (b) Kotora, M.; Takahashi, T. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Neghishi, E.-I.; de Meijere, A., Eds.; Wiley Interscience: New York, **2002**; pp 973.

61. (a) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253-257; (b) Heck, F. R.; Dieck, H. A. *J. Organomet. Chem.* **1975**, *93*, 259-263; (c) Cacchi, S.; Marena, E.; Ortar, G. *Synthesis*, **1986**, 320; (d) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403; (e) Shirakawa, E.; Kitabata, T.; Otsuka, H.; Tsuchimoto, T. *Tetrahedron* **2005**, *61*, 9878-9885.

62. (a) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679-3681; (b) Tyrrell, E.; Al-Saardi, A.; Millet, J. *Synlett*, **2005**, 487-488; (d) Li, J. H.; Zhang, X. D.; Xie, Y. X. *Synthesis*, **2005**, 804-808.

63. (a) Djakovoch, L.; Rollet, P. *Adv. Synt. Catal.* **2004**, *346*, 1782; (b) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365-9368; (c) Arques, A.; Auñon, D.; Molina, P. *Tetrahedron Lett.* **2004**, *45*, 4337-4340; (d) Rau, S.; Lamm, K.; Görls, H.; Schöffel, J.; Walther, D. *J. Organomet. Chem.* **2004**, *689*, 3582-3592.

64. (a) Rollet, P.; Kleist, W.; Dufaud, V.; Djakovitch, L. *J. Molecular Catal. A: Chemical* **2005**, *241*, 39-51; (b) Lamblin, M.; Nassar-Hardy, L.; Hierso, J.-C.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2010**, *352*, 33-79; (c) Yin, L.; Liebscher, J. Chem. Rev. **2007**, *107*, 133-173; (d) Pal, M. *Synlett* **2009**, *18*, 2896-2912; (e) Prechtl, M. H. G.; Scholten, J. D.; Dupont, J. *Molecules* **2010**, *15*, 3441-3461; (f) Islam, S. M.; Mondal, P.; Roy, A. S.; Mondal, S.; Hossain, D. *Tetrahedron Lett.* **2010**, *51*, 2067-2070; (g) Suzuka, T.; Okada, Y.; Ooshiro, K.; Uozumi, Y. *Tetrahedron* **2010**, *66*, 1064-1069; (h) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Mihanparast, S. *Tetrahedron Lett.* **2009**, *50*, 6418-6420; (i) Sotiriou-Leventis, C.; Wang, X.; Mulik, S.; Thangavel, A.; Leventis, N. *Synthetic Commun.* **2008**, *38*, 2285-2298; (j) Li, P.-H.; Wang, L. *Adv. Synth. Catal.* **2006**, *348*, 681-685.

65. Heidenreich, R. G.; Kohler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118-1122.

66. Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Sreedhar, M. L. *J. Am. Chem. Soc.* **2002**, 124, 14127-14136.

67. (a) Van der Eycken, E. *Eur. J. Org. Chem.* **2003**, 4713; (b) Leadbeater, N. *Org. Lett.* **2003**, *5*, 3919-3922; (c) Luque, R.; Macquarrie, D. J. *Org. Biomol. Chem.* **2009**, 7, 1627-1632.

68. Lohmann, S.; Andrews, S. P.; Burke, B. J.; Smith, M. D.; Attfield, J. P.; Tanaka, H.; Kaneko, K.; Ley, S. V. *Synlett* **2005**, 1291-1295.

69. (a) Pitts, M. R. *Platinum Metals Rev.* **2008**, *52*, 64; (b) Pears, D. A.; Smith, S. C. *Aldrichim. Acta* **2005**, *38*, 23; (c) Yu, J.-Q.; Wu, H.-C.; Ramarao, C.; Spencer, J. B.; Ley, S. V. *Chem. Commun.* **2003**, 678; (d) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134; (e) Ramarao, C.; Ley, S. V.; Smith, S. C.; Shirley, I. M.; DeAlmeida, N. *Chem. Commun.* **2002**, 1132.

70. (a) Leeke, A. G.; Santas, R. C. D.; Al-Duri, B.; Seville, J. P. K.; Smith, C. J.; Connie, C. K.; Holmes, A. B.; McConvey, J. F.; Ian, F. *Org. Proc. Res. Dev.* **2007**, *11*, 144;

(b) Sharma, A. K.; Gowdahalli, K.; Krzeminski, J. *J. Org. Chem.* **2007**, *72*, 8987; (c) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem. Eur. J.* **2006**, *12*, 4407.

71. (a) Schweizer, S.; Becht, J.-M; Le Drian, C. *Adv. Synth. Catal.* **2007**, *349*, 1150; (b) Gil-Molto, J.; Karlström, S.; Nájera, C. *Tetrahedron* **2005**, *61*, 12168.

72. Carpita, A.; Ribecai, A. *Tetrahedron Lett.* **2009**, *50*, 204-207.

73. Sedelmeier, J.; Ley, S. V.; Lange, H.; Baxendale, I. R. *Eur. J. Org. Chem.* **2009**, 4412-4420.

74. Kuang, Y.-Y.; Chen, F.-E. *Helvetica Chim. Acta* **2009**, *92*, 897-902.

75. Jutand, A. *Pure Appl. Chem.* **2004**, *76*, 565-576.

76. The first cycloisomerization trials with **1a** (described in Table 14) employed a material purchased form Sigma-Aldrich. However, the same results were obtained when substrate **1a** was prepared in our laboratories using the copper-free Sonogashira method described in the experimental section 7.2.3.

77. Carpita, A; Ribecai, A. *Tetrahedron Lett.* **2009**, *50*, 6877–6881.

78. Carpita, A.; Ribecai, A.; Stabile, P. *Tetrahedron* **2010**, *66*, 7169-7178.

79. Maligres, P. E.; Humphrey, G. R.; Marcoux, J.-F.; Hillier, M. C.; Zhao, D.; Krska, S.; Grabowski, E. J. J. *Org. Proc. Res. Dev.* **2009**, *13*, 525-534.

80. (a) Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595-596; (b) Bajwa, J. S.; Chen, G.-P.; Prasad, K.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425-6427; (c) Liu, Y.; Shen, L.; Prashad, M.; Tibbatts, J.; Repič, O.; Blacklock, T. J. *Org. Proc. Res. Dev.* **2008**, *12*, 778-780; (d) Kraus, G. A. *Tetrahedron* **2005**, *61*, 9502-9505.

81. Ren, T.; Zhang, Y.; Zhu, W.; Zhou, J. *Synth. Commun.* **2007**, *37*, 3279-3290.

82. Ding, Q.; Wu, J. *J. Comb. Chem.* **2008**, *10*, 541-545.

83. Sun, K.; Sachwani, R.; Richert, K. L.; Driver, T. G. *Org. Lett.* **2009**, *11*, 3598-3601.

84. Fleckenstein, C. A.; Plenio, H. *Green Chem.* **2008**, *10*, 563-570.

85. Lu, X.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2002**, *67*, 5412-5415.

86. Isobe, A.; Takagi, J.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2008**, *10*, 2657-2659.

87. Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391-393.

88. Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716-4721.

89. Sørensen, U. S.; Pombo-Villar, E. *Tetrahedron* **2005**, *61*, 2697-2703.

90. Allen, A. D.; Ji, R.; Lai, W.-Y.; Ma, J.; Tidwell, T. *Heteroatom Chemistry* **1994**, *5*, 235-244.

91. Rudisill, D. E.; Stille, J. E. *J. Org. Chem.* **1989**, *54*, 5856-5866.

92. Schoenebeck, F.; Murphy, J. A.; Zhou, S.-Z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* **2007**, *129*, 13368-13369.

93. Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428-7431.

94. Bazile, Y.; Bras, J.-P.; De Cointet, P.; Nanthavong, S.; Pigerol, C.; Broll, M.; Eymard, P.; Werbenec, J.-P.; Fournier, J. *Eur. J. Med. Chem.* **1977**, *12*, 525-530.

95. McKew, J. C.; Foley, M. A.; Thakker, P.; Behnke, M. L.; Lovering, F. E.; Sum, F.-W.; Tam, S.; Wu, K.; Shen, M. W. H.; Zhang, W.; Gonzalez, M.; Liu, S.; Mahadevan, A.; Sard, H.; Peang Khor, S.; Clark, J. D. *J. Med. Chem.* **2006**, *49*, 135-158.

96. Sakai, H.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. *Adv. Synth. Catal.* **2008**, *350*, 2498-2502.

97. Kuzmich, D.; Mulrooney, C. *Synthesis* **2003**, *11*, 1671-1678.

98. Mahanty, J. S.; De, M.; Das, P.; Kundu, N. G. *Tetrahedron* **1997**, *53*, 13397-13418.

99. Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* **2008**, 5946-5951.

100. Choy, J.; Jaime-Figueroa, S.; Jiang, L.; Wagner, P. *Synth. Commun*. **2008**, *38*, 3840-3853.

101. Whelligan, D. K.; Thomson, D. W.; Taylor, D.; Hoelder, S. *J. Org. Chem.* **2010**, *75*, 11-15.