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Ohmic heating assisted synthesis of 3-arylquinolin-4(1*H*)-ones by a reusable and ligand-free Suzuki-Miyaura reaction in water

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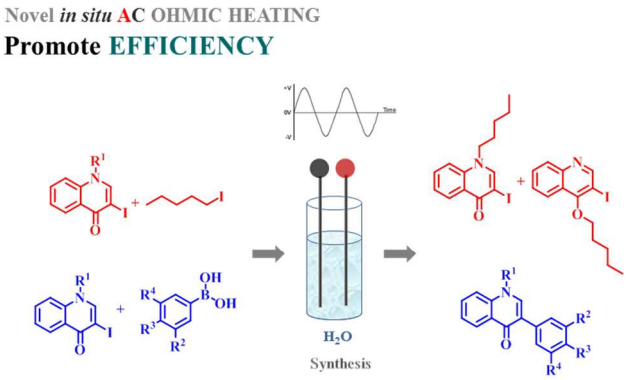
Abstract

Potential bioactive 3-arylquinolin-4(1*H*)-ones were synthesised under ohmic heating using an efficient, reusable and ligand-free protocol developed for the Suzuki-Miyaura coupling of 1-substituted-3-iodoquinolin-4(1*H*)-ones with several boronic acids in water using $Pd(OAc)_2$ as catalyst and TBAB as phase transfer catalyst. Good substrate generality, ease of execution, short reaction time and practicability make this method exploitable for the generation of libraries of B ring substituted 3-arylquinolin-4(1*H*)-ones. After a simple workup, Pd/catalyst-H_2O-TBAB system could be reused for at least seven cycles without significant loss in activity.



Introduction

Ohmic heating is an advanced thermal processing method where the reaction mixture or the medium, which serves as an electrical resistor, is heated by passing electricity through it (electrodes are in contact with the reaction medium).[1] The heating occurs in the form of internal energy transformation (from electric to thermal) within the reaction, being water the ideal green solvent to be used. In the ohmic heating methodology the thermal energy generation is due to the motion of the charged species in solution as result of the high frequency (25 kHz) AC electric current. The thermal energy transfer occurs mostly between the electrodes plates cross session region and the surroundings.[1] Thus, electrical energy is dissipated into heat with high efficiency, which results in a high speed heating rate allowing rapid and uniform heating (temperature homogeneity), leading to shorter reaction times and increased reaction yields. In a previous publication we presented ohmic heating as a new efficient process for organic synthesis in water and we described our reactor (Portuguese Patent 105908).[1] Now using this technology we prepared a library of 3-arylquinolin-4(1*H*)-ones for further biological evaluation.

Quinolin-4(1*H*)-one is a common scaffold found in natural products and is considered as a privileged structure, especially for anti-infective medicines.[2] Recently, the groups of Kyle,

Manestsch and Riscoe demonstrated that 3-substituted quinolin-4(1*H*)-ones display antimalarial activity at low to single digit nanomolar concentrations[3] while Kuo and co-workers discovered that 3-phenylquinolin-4(1*H*)-one has an excellent inhibitory effect against AA-induced platelet aggregation, superior to that of indomethacin and aspirin, which are well-known for their potent antiplatelet activity.[4] Other 3-arylquinolin-4(1*H*)-ones demonstrated good activity as anti-inflammatory agents.[5] 3-Chlorophenyl-5,7-dihydroxyquinolin-4(1*H*)-one and 3-chlorophenyl-5-hydroxy-7-methoxyquinolin-4(1*H*)-one, close analogues of the natural isoflavone genistein, possess potent EGFR tyrosine kinase inhibition activity.[6] Therefore an increasing interest in the synthesis of this kind of quinolin-4(1*H*)-ones has been observed. To optimize its pharmacological properties a considerable number of modifications have been made on the benzenoid ring (C-5 to C-8 positions) of the quinolin-4(1*H*)-one moiety, but the modifications on the pyridinone ring (C-2 to C-4) are still less common.

The Conrad-Limpach cyclization is the most used protocol for the preparation of 2- or 2,3-substituted quinolin-4(1*H*)-ones involving 2-substituted-β-ketoesters and anilines as starting materials.[7] Other reported methods to prepare 3-substituted-quinolin-4(1*H*)-ones involve the cyclization of 2-aryl-3-arylamino-4,4,4-trifluoro-2-butenenitriles hydrates with polyphosphoric acid,[8] the reverse Vilsmeier reaction of *N*-methylformanilide (MFA) with amides in $POCl_3$ followed by alkaline workup,[9] or ring closure of an appropriate ketone under modified Vilsmeier-Haack conditions ($POCl_3$, DMF) to give directly the 3-substituted quinolone in moderate yield.[6c] However, these methods commonly generate the desired quinolin-4(1*H*)-ones in poor yields requiring difficult purification procedures.

In the context of our recent studies on the application of ohmic heating in organic synthesis,[1] and connected with our ongoing research in the synthesis and transformation of

quinolin-4(1*H*)-ones,[10] we describe here a protocol for the synthesis of 3-arylquinolin-4(1*H*)-ones via Suzuki-Miyaura cross coupling reaction of *N*-substituted 3-iodoquinolin-4(1*H*)-ones with commercially available boronic acids using ohmic heating in water under phase transfer catalysis conditions.

Suzuki-Miyaura reaction has received much attention, chiefly due to its great versatility in the formation of C−C bonds.[11] The importance of this reaction has been documented by awarding the 2010 Nobel Prize in Chemistry to Professor Akira Suzuki.[12] The reaction is generally green, relatively easy to carry out, normally gives good yields and selectivities without much synthetic effort and is being increasingly applied in the synthesis of pharmaceuticals, natural products and advanced functional materials.[13] Developing aqueous systems for the Suzuki-Miyaura reactions has become also very attractive and is one of the latest challenges for modern chemists.[14-16] On the other hand the use of organoboron compounds is also compatible with aqueous reaction conditions since they are generally thermally stable and inert to water and oxygen.[15]

Now we report a ligand-free protocol for Suzuki-Miyaura reaction under ohmic heating using water as solvent and tetrabutylammonium bromide (TBAB) as additive.

Results and discussion

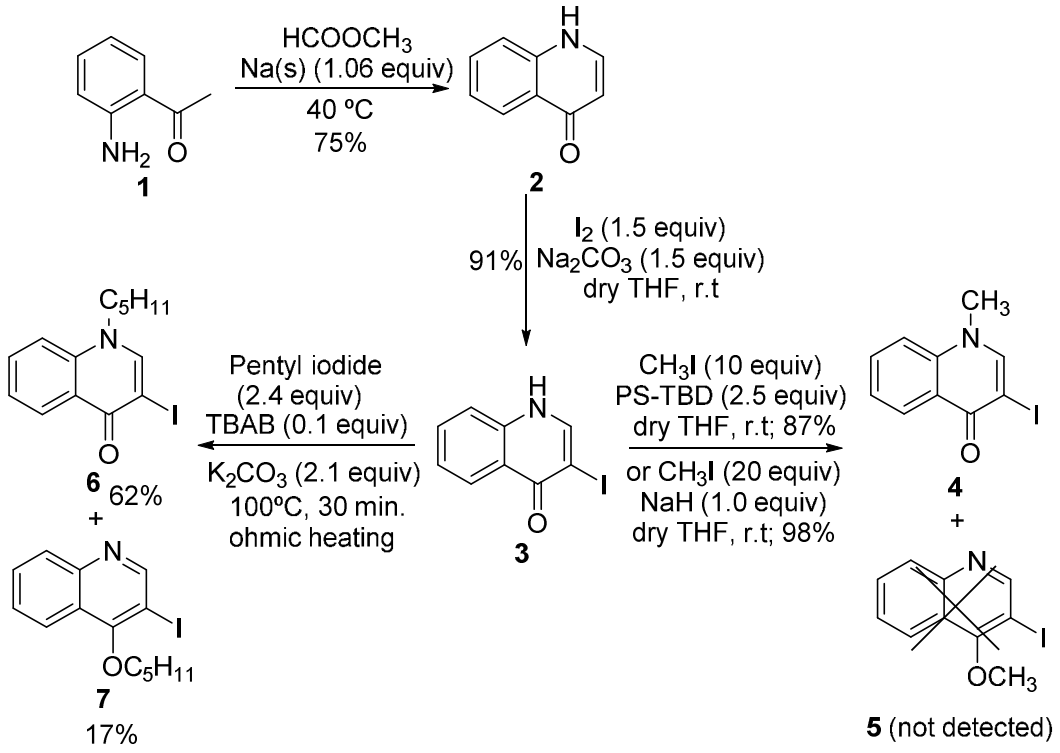
Synthesis of 3-iodoquinolin-4(1H)-ones used in the Suzuki-Miyaura cross coupling reaction

The 1-substituted-3-iodoquinolin-4(1*H*)-ones **4** and **6** were synthesised following the strategy depicted in Scheme 1. Following the published protocols[10b,c] for the synthesis of quinolin-4(1*H*)-one **3**, first we performed the reaction of 2'-aminoacetophenone **1** with methyl formate in the presence of sodium at 40ºC, and the quinolin-4(1*H*)-one **2** was

obtained with an improved yield of 75%. Next C-3 iodination was carried out using molecular iodine in dry THF in the presence of sodium carbonate at room temperature affording compound **3** in excellent yield (91%). C-3 bromination was also attempted with pyridinium tribromide (1 equiv) in AcOH at room temperature; however the reaction was not regioselective affording a complex mixture of products. Therefore we chose to use the iodinated compound in this work, since 3-iodoquinolin-4(1*H*)-ones proved to be more reactive (I > Br) in the Suzuki-Miyaura cross-coupling reaction.[17]

Methylation of quinolin-4(1*H*)-one **3** with methyl iodide and PS-TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene polystyrene) in dry THF afforded **4** in 87% yield. Alternatively compound **4** was obtained in excellent yield (98%) by methylation with methyl iodide in dry THF using sodium hydride (NaH) as base at room temperature. Both methods selectively afforded the desired *N*-methylated quinolin-4(1*H*)-one **4** in very good isolated yields without isolation of the corresponding isomer 4-methoxyquinoline **5**. The alkylation of **3**, to introduce the 1-pentyl group, was performed in the ohmic heating reactor, in water under phase transfer conditions, using TBAB as catalyst, pentyl iodide as alkylating agent and potassium carbonate as base, at 100ºC for 30 minutes. After that period 3-iodo-1-pentylquinolin-4(1*H*)-one **6** was isolated in 62% yield together with the isomer 3-iodo-4-pentyloxyquinoline **7** in 17% isolated yield.

Scheme 1. Synthesis of 3-iodoquinolin-4(1*H*)-ones 4 and 6 used in the Suzuki-Miyaura cross coupling reaction



In 2011, Corelli and co-workers[17b] reported the synthesis of 3-phenylquinolin-4(1*H*)-one **9a** through the reaction of 3-iodo-1-methylquinolin-4(1*H*)-one **4** with phenylboronic acid **8a** (1.2 equiv) using $Pd(OAc)_2$ as catalyst (10 mol%), PPh_3 as ligand (30 mol%), in the presence of Na_2CO_3 (2.0 M in H_2O) (2.5 equiv), in DME/EtOH (1.5:1), under microwave irradiation at 70ºC for 5 minutes. The 3-phenylquinolin-4(1*H*)-one **9a** was obtained in 75% isolated yield. Based on this protocol, we performed the reaction of **4** with phenylboronic acid **8a** (1.5 equiv) in water at 100ºC using sodium carbonate (1.0 equiv) as base and $Pd(OAc)_2$ (5 mol%) as catalyst under ohmic heating using TBAB (0.1 equiv) as phase transfer catalyst (PTC). PTC has long been recognized as a versatile

methodology for organic synthesis in industry, academia and in process chemistry and is particularly suitable when substrates are insoluble in the reaction medium as is the case of 1-substituted-3-iodoquinolin-4(1*H*)-ones **4** and **6**.[18] Under these conditions 3-phenylquinolin-4(1*H*)-one **9a** was obtained in 75% isolated yield after 30 minutes reaction time (Table 1, entry 1).

An extensive optimization of the reaction parameters led us to study: i) the effect of using the PTC (TBAB addition), ii) the effect of Pd catalyst addition, and iii) the reaction time. The base, solvent and the temperature used remain unchanged. Using the model reaction depicted in Table 1, our initial investigations focused on the study of the effect of the PTC (Table 1, entries 1 and 2). Lower yield (61%) was obtained without the addition of PTC (TBAB), demonstrating that TBAB played an important role in the efficiency of this ligand-free protocol in water. The product **9a** was isolated in very good yield (80%) when the reaction was performed without addition of $Pd(OAc)_2$ under ohmic heating (Table 1, entry 3), but no product was found when the reaction was performed under classical heating conditions without $Pd(OAc)_2$ (Table 1, entry 4). This result highlights that some contamination of the reaction media with palladium catalyst probably comes from the electrodes (made of 316 stainless steel) used in ohmic heating, in the first assay, and that such a small quantity of palladium seems to be sufficient to give the coupling product in very good yield. Indeed when we performed the reaction under classical heating conditions with the same electrodes immersed in the reaction medium, the product **9a** was obtained in 60% yield after 5.5 h (Table 1, entry 5). In order to clarify the effect of the electrodes in the reaction outcome we performed again the reaction under ohmic heating without addition of $Pd(OAc)_2$ using two new electrodes which were not in contact with palladium catalyst. In this case no product **9a** was isolated

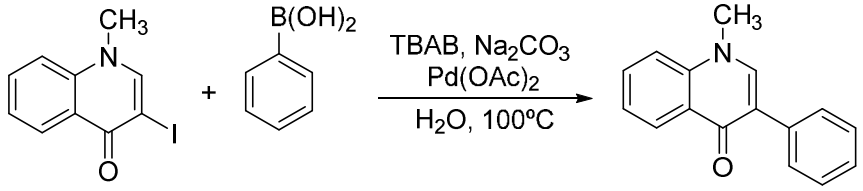
after 90 minutes of reaction time (Table 1, entry 6). The same result was obtained when the reaction was performed without addition of both catalysts [TBAB and $Pd(OAc)_2$] (Table 1, entry 7), as expected.

Finally we found that the optimal conditions for the reaction required the presence of $Pd(OAc)_2$ (5 mol%), Na_2CO_3 (1.0 equiv) and TBAB (0.1 equiv) as PTC, at 100ºC for 15 minutes, leading to the formation of the product **9a** in very good isolated yield (86%) (Table 1, entry 8). When compared to the yield reported by Corelli and co-workers for the synthesis of 3-phenylquinolin-4(1*H*)-one **9a** (yield 75%) our method led to a better yield (86%). No ligand was required, less amount of catalyst and base were used in the reaction which proceeds using exclusively water as solvent.

Based on the previous results we suspected that the high heating rate in the beginning of the reaction may be crucial for the higher yields found under ohmic heating although some "electrochemical effects" that may be involved in the deposition and the solubilisation of Pd-catalyst cannot be excluded.

In order to clarify this idea we performed the reaction under classical heating using the optimal conditions found (Table 1, entry 8) with electrodes immersed in the reaction without passing electric current. The reaction was monitored by TLC and after 240 minutes of reaction time the coupling product **9a** was isolated in 70% yield (Table 1, entry 9). Then we repeat the reaction without addition of $Pd(OAc)_2$ with the electrodes from the previous experiment immersed in the reaction medium to find if there was Pd-catalyst deposited in the electrodes to efficiently catalyse the reaction. After 240 minutes the reaction product **9a** was isolated in 4% yield (Table 1, entry 10). These results highlight that deposition of Pd-catalyst in the electrodes under classical conditions is not as efficient as under ohmic heating.

Table 1 Optimization of Suzuki-Miyaura cross-coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one 4 with phenylboronic acid 8a, under classical heating (CH) and ohmic heating (ΩH).



4 **8a** **9a**

Entry	Heating Method	TBAB (molar equiv)	$Pd(OAc)_2$ (molar equiv)	Time (min.)	Yield 9a (%)[a]
1	ΩH	0.1	0.05	30	75
2	ΩH	---	0.05	30	61
3	ΩH	0.1	---	30	80
4	CH	0.1	---	240	---[b]
5[c]	CH	0.1	---	330	60
6[d]	ΩH	0.1	---	90	---[b]
7[d]	ΩH	---	---	30	---[b]
8	ΩH	0.1	0.05	15	86
9	CH	0.1	0.05	240	70
10[e]	CH	0.1	---	240	4

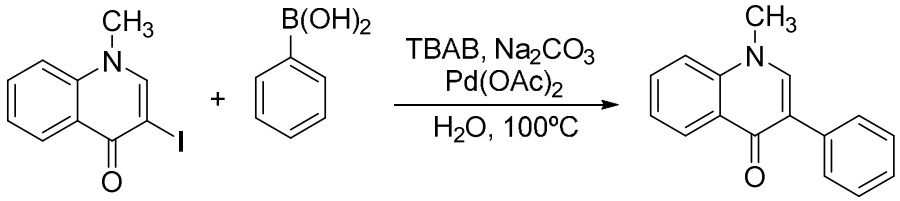
[a]Isolated yields. [b]Formation of **9a** was not observed. [c]The used electrodes of entry 3 were immersed in the reaction medium without passing electrical current. [d]New electrodes which were not in contact with Pd-catalyst were used. [e]The same electrodes of entry 9 were used and $Pd(OAc)_2$ was not added in this experiment.

In order to compare the three heating methods, the model reaction was performed under classical heating (oil bath), microwave and ohmic heating and the results are presented in Table 2.

These results show that for a reaction time of 15 minutes ohmic heating was the most efficient heating method leading to the highest yield of **9a** (Table 2, entry 1). There is a significant difference between the yields obtained under ohmic heating and under the other heating methods. It is important to note that, the reaction under microwave heating

gave lower yield, even when the reaction time is prolonged to 30 minutes (Table 2, entries 2 and 3). Our suspicion is that under ohmic heating the high heating rates in the beginning, may enhance the reduction of Pd(II) to Pd(0) which is the species involved in the catalytic cycle of the Suzuki reaction. Moreover it is very likely that the used iron-containing electrodes will readily reduce aqueous solutions of $Pd(OAc)_2$ to the pure metal Pd(0). The deposition mechanism under the ohmic heating process itself may enforce this phenomenon.

Table 2 The effect of the heating method on the cross-coupling of 3-iodo-1-methylquinolin-4(1*H*)-one 4 with phenylboronic acid 8a[a]



4 **8a** **9a**

Entry	Heating method	Time (min.)	Yield 9a[b](%)
1[c]	ΩH	15	86
2[d]	MW	15	35[e]
3[d]	MW	30	76
4	CH	15	4[f]

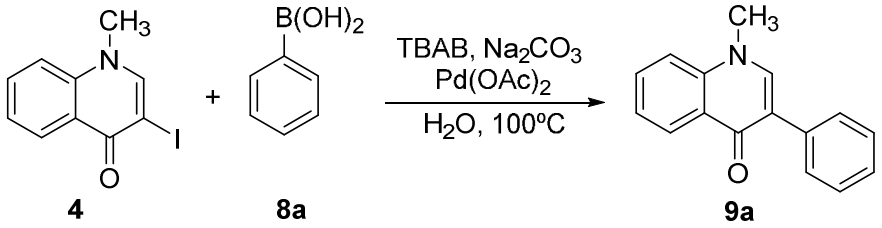
[a]Reaction conditions: 3-iodo-1-methylquinolin-4(1*H*)-one **4** (0.28 mmol), phenylboronic acid **8a** (1.5 equiv), $Pd(OAc)_2$ (5 mol%), Na_2CO_3 (1 equiv) and TBAB (0.1 equiv), H_2O (4 mL), 100ºC. [b]Isolated yield. [c]Model reaction for comparison. [d]Reactions were performed in a single-mode microwave reactor under open-vessel conditions (temperature was measured using an IR sensor). [e]62% of Starting material was recovered. [f]The round bottom flask was immersed into an oil bath at 100ºC.

According to the literature the Suzuki-Miyaura coupling reactions can be catalysed by unusual low Pd-loading.[19] De Vries and Reetz have shown that the Heck reaction can be

run with the addition of what they term "homeopathic" quantities of palladium catalysts (ideally 0.01-0.1 mol%), but they have found that when using very low metal concentrations the rate of reaction is too slow to be practical.[19a-c] De Vries and coworkers have also shown that the use of unusually low Pd-loading in the Suzuki reaction on aryl bromides is also possible.[19d]

Inspired in these findings we decided to study the effect of the palladium amount in the model reaction yield in order to find the lower threshold of synthetically viable Pd-catalyst concentration. The results obtained (Table 3) showed that for the ideally homeopathic quantities the reaction occurs with a very low yield even after a prolonged reaction time (Table 3, entries 2 and 3). However when using 0.5 mol% of Pd-catalyst the yield increased to 73% (Table 3, entry 4) and similar yields were obtained using 1, 3 and 5 mol% of catalyst (Table 3, entries 5-7). When using 5 mol% of catalyst the coupling product was obtained in 86% isolated yield after only 15 minutes showing that the increase of palladium concentration led to shorter reaction time.

Table 3 The effect of the amount of $Pd(OAc)_2$ on the cross-coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one 4 with phenylboronic acid (8a) using ohmic heating.[a]



4 **8a** **9a**

Entry	$Pd(OAc)_2$ (molar equiv)	Time (min.)	Yield 9a (%)[b]
1	---	90	---[c]
2	0.0001	120	6
3	0.001	120	11
4	0.005	30	73
5	0.01	30	74
6	0.03	30	80
7	0.05	30	75
8[d]	0.05	15	86

[a]Reaction conditions: 3-iodo-1-methylquinolin-4(1*H*)-one (0.28 mmol), phenylboronic acid **8a** (1.5 equiv), Na_2CO_3 (1 equiv) and TBAB (0.1 equiv), H_2O (4 mL), 100ºC. [b]Isolated yield. [c]No product was isolated. [d]Model reaction for comparison.

Since tetraalkylammonium halides are known to induce the formation and stabilization of nano-sized transition metal colloids,[20] we investigated the formation of Pd-colloids under the optimized reaction conditions. A solution of $Pd(OAc)_2$ (0.014 mmol), TBAB (0.028 mmol) as a stabilizer and the phenylboronic acid **8a** (0.42 mmol) in water (4 mL) was heated at reflux under ohmic heating. Once reached the reflux, the solution colour becomes dark brown, suggesting the formation of nano-sized Pd-colloids. The heating was continued for 10 minutes and the resulting mixture was monitored by UV-Vis

spectroscopy. The UV-Vis spectra obtained (see Figure S45 in Supplementary Information) also suggests the formation of nano-sized Pd-colloids as can be inferred from the observation of a small band in the near-UV. According to Creighton and coworkers[21] for small particles of most of the d-block metals the absorption in the UV-Vis range is continuous across the range, but in the case of colloidal Pd this absorption has some structure, giving broad or at least partly resolved absorption bands in the near-UV. However, in our case, these colloidal Pd particles might be very unstable under the experimental conditions used, leading to the formation of a dark precipitate at the end of the reaction. Similar observations were made by El-Sayed and coworkers[22] and by Herrmann and coworkers[23] for coupling reactions using palladium colloid as catalyst, suggesting that the instability of the colloid might be due to the use of high temperatures. In our case, it is very likely that the refluxing conditions used under ohmic heating leads to the Pd metal precipitation. Therefore it is not $Pd(OAc)_2$ that can be recycled but Pd(0). The high temperature and the presence of TBAB will initially lead to the formation of Pd colloids which then are deposited as thin film or Pd black on the electrodes thus explaining how the Pd on the electrodes (especially in the presence of TBAB) can catalyse the reaction so efficiently. According to the literature,[24] if a colloidal solution of Pd-nanoparticles is formed in this reaction, a process of this kind should not belong to the traditional area of homogeneous catalysis, instead it should be more closely related to heterogeneous catalysis.

Scope and limitations of substrates

With a viable coupling procedure in hand, attention was turned to generalize the process, and the substrate scope of the coupling reaction was studied in detail by varying the

substituents in the boronic acid coupling partner. To highlight the usefulness and flexibility of this protocol we employed boronic acids containing electron-withdrawing and electron donating substituents as well as sterically hindered boronic acids. All reactions were performed in water (4 mL) using $Pd(OAc)_2$ (5 mol%) as catalyst and TBAB as additive (0.1 equiv), in the presence of a base at 100ºC under ohmic heating conditions and the results are summarized in Table 4. Analysing the results, we concluded that the reaction is sensitive to the electronic effects of the boronic acid substituents. The yield of the reaction is higher for boronic acids bearing electron donating groups (EDG) (**9b**, $R^4 = OCH_3$ and **9c**, $R^4 = OH$, 83%) and for the neutral substituent (**9a**, $R^4 = H$, 86% and **9m**, $R^4 = H$, 90%) (Table 4, entries 1-3 and 13), and lower with those having electron withdrawing groups (EWG) (**9e**, $R^4 = CHO$, 67% and **9f**, $R^4 = NO_2$, 36%) (Table 4, entries 5 and 6), considering substitution at *para*-position. In the case of derivative **9f** another product, the 3-(4-aminophenyl)-1-methylquinolin-4(1*H*)-one **11** was isolated in 13% yield due to the reduction of the nitro group. Regarding to the substitution at *meta*-position, higher yields were obtained for derivative **9g** ($R^3 = OCH_3$, 86%) in comparison with **9h** ($R^3 = CHO$, 64%), when using K_3PO_4 as base for 5 minutes reaction time (Table 4, entries 7 and 8). Actually, the greater reactivity and higher reaction yields associated to EDG-substituted boronic acids were observed before in the synthesis of arylnaphthalenes by Suzuki-Miyaura cross-coupling reaction using a mixture of H_2O:DMF as solvent.[25] Our reaction conditions are similar since DMF is a solvent with bulk properties similar to those of water (high dielectric constant and high ability to stabilize ionic species).[26] The yield of the Suzuki-Miyaura reaction in the experimental conditions adopted in this work clearly have some dependency with the substituent electron donor strength, and with steric hindrance factors, however these are

not the only factors affecting the reaction outcome. Solubility aspects and competing undesirable side reactions may also play a role in defining the trend observed. For example, in the synthesis of the dimethylamino derivative **9d**, the strongest EDG, [R^4 = $N(CH_3)_2$, 40%], another reaction product, the 1-methyl-3-(4-methylaminophenyl)quinolin-4(1*H*)-one **10** was isolated in 10% yield and 12.5% of starting material was recovered (Table 4, entry 4). This is an indication that the yield of 1-methyl-3-(4-dimethylaminophenyl)quinolin-4(1*H*)-one **9d** may be lowered by the presence of a significant side-reaction, what could explain the deviation from the trend observed for EDG substituted compounds. In addition there are usually three pathways in Suzuki-Miyaura cross-coupling reaction: the main Suzuki reaction, and two important side reactions: homocoupling, and hydrolytic deboronation of the boronic acid. These side reactions were occasionally observed in this work, mainly when boronic acids presented EWG substituents.

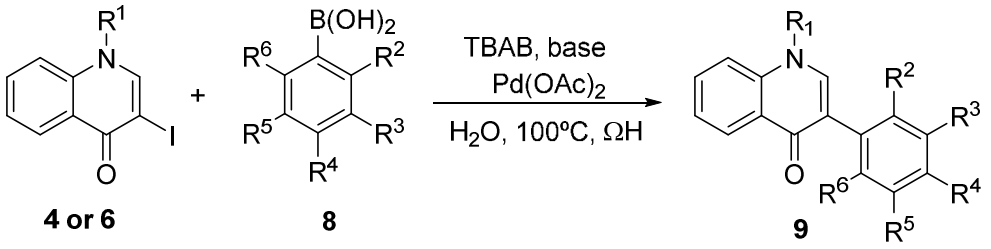
Concerning to the Suzuki-Miyaura reaction mechanism, these observations are consistent with the idea that increased nucleophilicity increases the transmetalation rate.[27] Reported *pKa* values indicate that boronic acids bearing EWGs (such as R^4 = 4-CHO and 4-NO_2) are by far the strongest acids and the ones substituted with EDGs (R^4 = OCH_3 and CH_3) the weakest and that *ortho*-substituted phenylboronic acids are generally less acidic.[15c,28] As the main role of the base in the Suzuki reaction mechanism under these conditions is to increase the reactivity of the boronic acid toward the Pd-halide complex[27] different bases, weak (Cs_2CO_3, K_3PO_4) or strong (NaOH), and amounts were tested for boronic acids containing EWGs. Water soluble inorganic bases such as K_3PO_4, Na_2CO_3, K_2CO_3, and NaOH have been successfully used in efficient ligand-free catalytic systems. In fact, when Cs_2CO_3 and K_3PO_4 were used in the reaction of **4** with phenylboronic acid

8j (R^3 = CHO, R^4 = OCH_3) the yield of the product **9j** was slightly better (42% and 49%, respectively) than when Na_2CO_3 was used (30%). In order to improve the yields of **9j** we also tried NaOH and Na_2CO_3 in DMF/H_2O as solvent but these conditions led to lower reaction yields (29% and 24%, respectively).

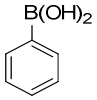
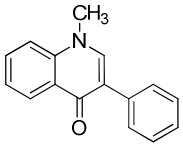
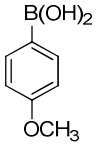
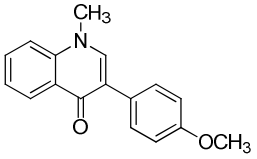
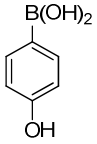
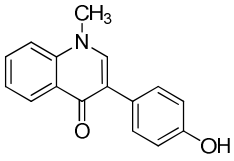
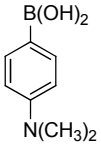
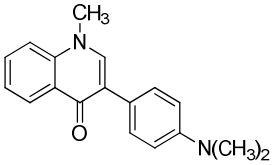
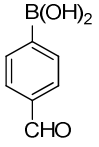
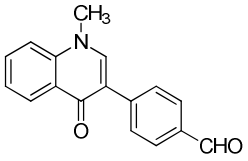
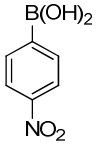
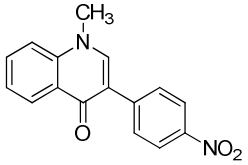
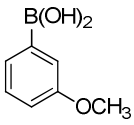
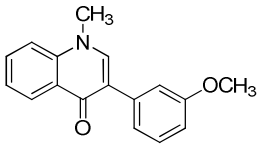
In some cases the reaction was faster or the yields were slightly better in the presence of K_3PO_4 as base, however previous studies on the role of the base in the Suzuki-Miyaura reaction showed that a few bases favour the reactivity of the boronic acids with lower reactivity (more acid).[27]

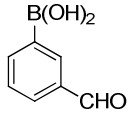
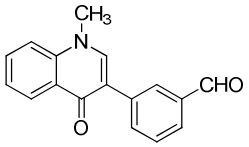
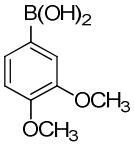
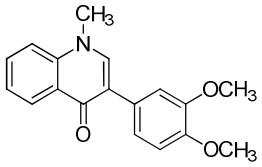
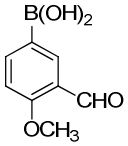
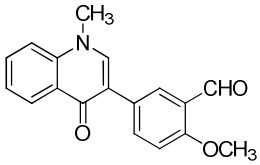
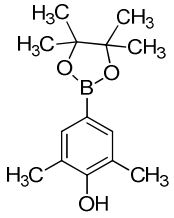
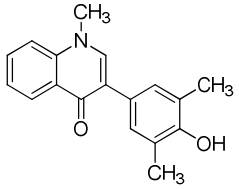
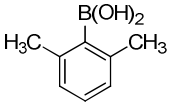
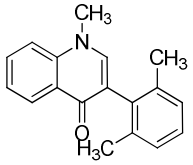
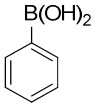
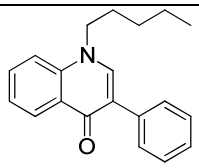
The reaction with the borate ester (pinacol) **8k** (R^3 = CH_3, R^4 = OH, R^5 = CH_3) afforded the coupling product **9k** in very low yield (20%) (Table 4, entry 11) while no reaction product was obtained in the case of 2,6-dimethylphenylboronic acid **8l** (R^2 = CH_3, R^6 = CH_3) (Table 4, entry 12). This result is not surprising since it is well-known that *ortho*-substituted phenylboronic acids were found to be generally less reactive than the other isomers probably due to steric hindrance.[29] However, when the reaction occurs with these steric hindered boronic acids generally lead to lower Suzuki reaction yields. The yields as well as coupling rates can be improved by using stronger bases like NaOH or $Ba(OH)_2$. However it is known that more extensive deboronation, which is expected to be favoured in highly basic media and for *ortho*-substituted boronic acids, tends to occur.[15a,c,30] This was the main reason why we did not try a stronger base in the reaction of 3-iodo-1-methylquinolin-4(1*H*)-one **4** with 2,6-dimethylphenylboronic acid **8l**. The substitution of the *N*-methyl group by the *N*-pentyl group in the quinolin-4(1*H*)-one moiety **6** did not affect the reaction yield being the corresponding product **9m** obtained in excellent yield (90%) (Table 4, entry 13).

Table 4 Synthesis of 3-arylquinolin-4(1*H*)-ones 9a-k,m by Suzuki-Miyaura cross-coupling reaction of 4 and 6 with arylboronic acids 8a-l: reaction scope and yields[a]



4 or 6 **8** **9**

Entry	Compound	Boronic acid	Time (min.)	Base (molar equiv)	Product	Yield 9 (%)[b]
1[c]	**9a**		15	Na_2CO_3/ 1.0		86
2	**9b**		15	Na_2CO_3/ 1.0		83
3	**9c**		15	Na_2CO_3/ 1.0		83
4	**9d**		30	Na_2CO_3/ 1.0		40 + 10[d]
5	**9e**		15 15	Na_2CO_3/ 1.0 K_3PO_4/ 1.0		67 66
6	**9f**		5 10	Na_2CO_3/ 1.0 K_3PO_4/ 1.0		36 + 13[e] 14
7	**9g**		30 5	Na_2CO_3/ 1.0 K_3PO_4/ 1.0		39 86

8	**9h**		15 5	Na_2CO_3/ 1.0 K_3PO_4/ 1.5		69 64
9	**9i**		15 15 5	Na_2CO_3/ 1.0 K_3PO_4/ 1.0 K_3PO_4/ 1.0		61 37 61[f]
10	**9j**		30 30 15 15 15	Na_2CO_3/ 1.0 NaOH/ 1.0 Na_2CO_3/ 1.0 in DMF/H_2O Cs_2CO_3/1.0 K_3PO_4/ 1.0		30 29 24 42 49
11	**9k**		15	Na_2CO_3/ 1.0		20
12	**9l**		30	K_3PO_4 / 1.5		No reaction
13	**9m**		30	Na_2CO_3/ 1.0		90

[a]Reaction conditions: For entries 1-12, 3-iodo-1-methylquinolin-4(1*H*)-one **4** (80.0 mg, 0.28 mmol), aryl boronic acid **8a-l** (0.42 mmol), base (see Table 4, for amount and base used), TBAB (9.02 mg, 0.028 mmol), $Pd(OAc)_2$ (3.15 mg, 0.014 mmol), H_2O (4 mL), 100 ºC. For entry 13, 3-iodo-1-pentylquinolin-4(1*H*)-one **6** (60.0 mg, 0.18 mmol), phenylboronic acid **8a** (32.92 mg, 0.27 mmol), Na_2CO_3 (19.07 mg, 0.18 mmol), TBAB (5.80 mg, 0.018 mmol), $Pd(OAc)_2$ (2.02 mg, $9x10^{-3}$ mmol), H_2O (4 mL), 100 ºC. [b]Isolated yield. [c]Model reaction for comparison. [d]1-Methyl-3-(4-methylaminophenyl)quinolin-4(1*H*)-one **10** was isolated as a by-product. [e]3-(4-Aminophenyl)-1-methylquinolin-4(1*H*)-one **11** was isolated as a by-product; the yield was calculated from the NMR mixture with **9f**. [f]Unreacted starting material was recovered (9.4%).

Reusability of the catalysts

The possible reduction of the amount of palladium catalyst to 0.5 mol%, as shown previously for the model reaction (Table 3, entry 4), that could also be catalysed by surface-deposits of Pd on the electrodes, led us to explore the possibility to reuse the catalyst. Moreover environmental and economic concerns (Pd is an expensive metal catalyst) corroborate this study. So, initially the reusability of the Pd-catalyst was investigated using as model reaction the Suzuki coupling of 3-iodo-1-methylquinolin-4(1*H*)-one **4** with phenylboronic acid **8a** in the presence of $Pd(OAc)_2$, Na_2CO_3 and TBAB at 100ºC for 15 minutes using water as solvent. After the first cycle the reaction mixture was removed from the reactor which was then charged with all the reactants in each run, except $Pd(OAc)_2$, which was not added in the following runs. The results were shown in figure 1.

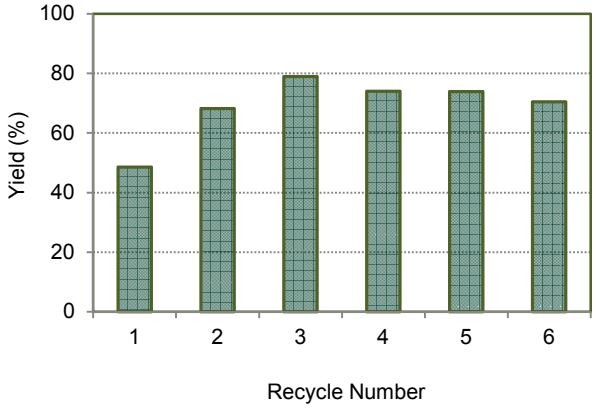


Figure 1. The reusability of Pd-catalyst in the Suzuki-Miyaura coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one **4** with phenylboronic acid **8a**.

It was clear that the Pd-catalyst could be reused for at least six times without significant loss in activity. In the first cycle the yield was lower than the expected (49%) probably due to the

loss of some product that remained adsorbed in the electrodes even after washing them abundantly with water. As we presume that some catalyst can also remain on the electrodes surface we do not clean them with organic solvents or by scraping. In the following cycles the yields were very good (68%, 79% 74%, 74% and 71%) and the starting material was completely consumed until the sixth cycle. When the last cycle was finished, the TLC of the reaction mixture showed some starting material, evidencing that consumption was not complete after 15 minutes probably due to the decrease of the catalyst efficiency or decrease of its amount in the reaction medium.

Then we decided to investigate the reusability of the reaction medium, more precisely of the mixture H_2O-TBAB-Pd/catalyst, thus envisioning the possibility of recovering both catalysts and also the solvent, aiming to achieve a more economic synthetic process and promoting the reduction of waste that will exist for further treatment at the end of the synthetic process. The results obtained are presented in figure 2. Once again it was clear that H_2O-TBAB-Pd/catalyst catalytic system could be reused at least seven times without loss of activity. In the last cycle we performed the reaction without adding base to the mixture and complete consumption of starting material occurred. The ohmic heating data showed an increase in the current intensity and heating rate for the last 3 assays (See Figure S46 of Supplementary Information). These data indicate an increase in the medium conductivity thus suggesting higher concentrations of reactants mainly of those that can contribute to increase the medium conductivity such as the base and boronic acid which were added in each experiment. So it seems that the increase in the concentration of these reactants may be due to the recovery of some amounts of base and acid when reusing the reaction medium.

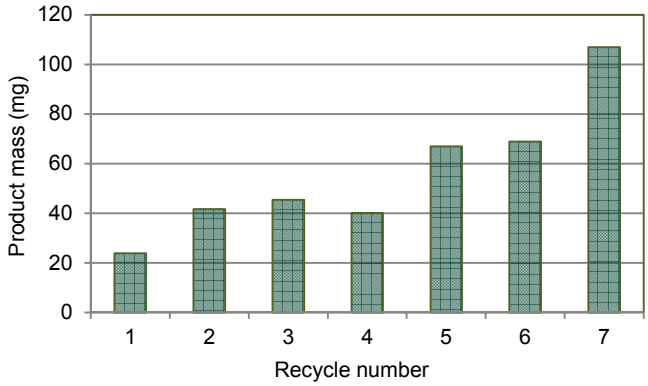


Figure 2 The reusability of H_2O-TBAB-Pd-catalyst in the Suzuki coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**4**) with phenylboronic acid (**8a**).

The yield was determined at the end of the seventh cycle applying the equation (1) where m is the mass of product obtained for each reaction from 1 to 7 cycles and m' is the theoretical mass of product expected for the same cycles. Curiously the global yield obtained was 86% the same yield we obtained when we performed the reaction during 15 minutes for the first time (see Table 1, entry 8).

% global yield = [(m1+m2+m3+m4+m5+m6+m7)/7]/[(m'1+m'2+m'3+m'4+m'5+m'6+m'7)/7] x100

(Equation 1)

Conclusion

From the standpoint of generating diversity, this protocol allows the rapid preparation of a multitude of 3-arylquinolin-4(1*H*)-one analogues, given the large number of commercially available boronic acids. The use of ohmic heating represents a significant improvement over existing synthetic approaches. The high heating rates achieved in the beginning of the reaction and the local energy generation seems to be crucial for the reaction efficiency and enhance the deposition of Pd-catalyst in the surface of the electrodes, allowing the reuse of the catalyst for

at least six catalytic cycles without significant loss of activity. It was found that using the ohmic heating reactor the reaction occurs successfully in water in a shorter time, in good to excellent yields, using ligand-free conditions. Moreover we have shown that the reaction can be run using 0.5 mol% of $Pd(OAc)_2$ which is a very low Pd catalyst amount when compared to the 10 mol% used by Corelli and coworkers. Good substrate generality, ease of execution, practicability, and the possibility of reusing the catalysts and the solvent make this synthetic methodology exploitable for the generation of libraries of potentially bioactive 3-arylquinolin-4(1*H*)-ones, with environmental and economic benefits.

Experimental section

All reactions were carried out in air without any protection of inert gases. 3-Iodo-1-metilquinolin-4(1*H*)-one **4** was prepared following the method reported in literature[10b,31] or using methyl iodide and NaH in dry THF being necessary in the latter case the use of a nitrogen atmosphere. Boronic acids, bases and TBAB were purchased and used without further purification. Preparative thin-layer chromatography was carried out with silica gel (60 DGF_{254}) plates. Melting points were determined on a melting point apparatus and are uncorrected. NMR spectra were recorded on 300 or 500 [300.13 MHz (^{1}H), 75.47 MHz (^{13}C) or 500.13 MHz (^{1}H), 125.77 MHz (^{13}C)] NMR spectrometers with TMS as internal reference and with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (δ) are quoted in ppm relative to TMS. Coupling constants (*J*) are quoted in Hz. Unequivocal ^{13}C assignments were made on the basis of 2D gHSQC (^{1}H/^{13}C) and gHMBC (delays for one bond and long-range $J_{C/H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. Mass spectra (EI, 70 eV) were measured. Positive-ion ESI mass spectra were acquired using nitrogen as nebulizer

gas and argon as collision gas. The needle voltage was set at 3000 V, with the ion source at 80 ºC and desolvation temperature at 150 ºC. Cone voltage was 35 V]. High resolution mass spectra (EI-HRMS, 70 eV) were also measured. For experiments carried out under ohmic heating, the 10 mL reactor was filled with the reaction mixture, closed and the mixture was heated to reflux. For 4 mL of reaction mixture the length of electrodes immersed in the reaction medium was 9 mm, the distance between the electrodes was 10 mm. Temperature measurement was done using a type J glass sheathed thermocouple located inside the reactor. Medium magnetic stirring speed (740 rpm) was used in all the experiments carried out in the ohmic heating reactor. For the experiments carried out in conventional heating (oil bath) under reflux conditions, the same reaction vessel used in the ohmic heating reactor was filled with the reaction mixture and was immersed into the oil bath at 100 ºC. Medium magnetic stirring speed (740 rpm) was used. Microwave-assisted reactions were carried out in a circular single-mode cavity instrument (300 W max magnetron power output). Reactions were carried out in an open-vessel using a 50 mL round-bottom flask filled with the reaction mixture and equipped with a condensator. The temperature measurement was done through an infrared sensor which monitors and controls the temperature conditions of the reaction vessel located in the instrument cavity. Medium stirring speed was used in the experiments performed. The conditions used for the experiments performed in classical heating were also described in tables 1 and 2 and those used in MW heating experiments were described in table 2.

General procedure for the synthesis of 3-iodo-1-pentylquinolin-4(1*H*)-one (6). The 10 mL ohmic heating reactor[1] was charged with 3-iodoquinolin-4(1*H*)-one **3** (125.2 mg, 0.44 mmol), pentyl iodide (0.14 mL, 1.07 mmol), potassium carbonate (127.8 mg, 0.92 mmol), TBAB (15.2 mg, 0.047 mmol) and H_2O (4 mL). The mixture was heated at reflux for 30 minutes.

After cooling to room temperature the aqueous mixture was extracted with ethyl acetate (4 x 10 mL) and the combined organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The obtained mixture was purified by thin layer chromatography (TLC) using ethyl acetate: hexane (3:2). Two products were isolated: 3-iodo-1-pentylquinolin-4(1*H*)-one **6** as the main product (62%) and 3-iodo-4-pentyloxyquinoline **7** as minor product (17%).

3-Iodo-1-pentylquinolin-4(1*H*)-one (6). 62% Yield (93.0 mg), yellow solid, m.p 117.3–117.6 ºC. ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ_H = 0.84 (t, *J* = 6.8 Hz, 3 H, C*H*$_3$,), 1.13- 1.33 (m, 2 H, H-3', 4'), 1.67-1.76 (m, 1 H, H-2'), 4.29 (t, *J* = 7.4 Hz, 1 H, H-1'), 7.42-7.47 (m, 1 H, H-6), 7.74-7.80 (m, 2 H, H-7,8), 8.20 (d, *J* = 7.9 Hz, 1 H, H-5), 8.66 (s, 1 H, H-2) ppm. ^{13}C NMR (125.77 MHz, DMSO-d$_6$): δ_C = 13.9 (C-5'), 21.8 (C-4'), 28.0 (C-3'), 28.3 (C-2'), 52.0 (C-1'), 80.4 (C-3), 117.0 (C-8), 123.3 (C-4a), 124.3 (C-6), 126.4 (C-5), 132.3 (C-7), 139.0 (C-8a), 149.0 (C-2), 172.7 (C-4) ppm. MS (EI) *m/z* (%): 341 ($M^{+\cdot}$, 74), 285 (6), 284 [$(M-C_4H_9)^+$, 100], 271 (10), 158 (6), 144 (10). HRMS (EI) *m/z* calcd for $C_{14}H_{16}NOI$ $(M)^{+\cdot}$: 341.0277, found: 341.0275.

3-Iodo-4-pentyloxyquinoline (7). 17% Yield (25.5 mg), dark yellow oil. ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ_H = 0.93 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.34-1.59 (m, 2 H, H-3',4'), 1.92 (quintet, *J* = 6.6 Hz, 1 H, H-2'), 4.14 (t, *J* = 6.6 Hz, 1 H, H-1'), 7.67 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 1 H, H-6), 7.82 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1 H, H-7), 8.04 (d, *J* = 8.3 Hz, 1 H, H-8), 8.08 (dd, *J* = 8.3, 1.3 Hz, 1 H, H-5), 9.06 (s, 1 H, H-2) ppm. ^{13}C NMR (125.77 MHz, DMSO-d$_6$): δ_C = 14.0 (C-5'), 22.0 (C-4'), 27.7 (C-3'), 29.5 (C-2'), 74.9 (C-1'), 86.1 (C-3), 121.8 (C-5), 124.4 (C-4a), 127.4 (C-6), 129.2 (C-8), 130.4 (C-7), 149.0 (C-8a), 157.6 (C-2), 162.6 (C-4) ppm.

MS (EI) *m/z* (%): 341 ($M^{+\bullet}$, 85), 285 (11), 284 [$(M-C_4H_9)^+$, 100], 255 (4), 236 (5), 214 [$(M-I)^+$, 4], 144 (8). HRMS (EI) *m/z* calcd for ($C_{14}H_{16}NOI$) $(M)^{+\bullet}$: 341.0277, found: 341.0279.

General procedure for the Suzuki-Miyaura cross-coupling reaction of 3-iodo-1-metilquinolin-4(1*H*)-one (4) with arylboronic acids (8a-l). The 10 mL ohmic heating reactor was charged with 3-iodo-1-methylquinolin-4(1*H*)-one **4** (80.0 mg, 0.28 mmol), the appropriate aryl boronic acid **8a-l** (0.42 mmol), base (see table 2, for amount and base used), TBAB (9.02 mg, 0.028 mmol), $Pd(OAc)_2$ (3.15 mg, 0.014 mmol) and H_2O (4 mL). The mixture was heated at reflux with stirring for the period described in table 2. Then the aqueous mixture was extracted with ethyl acetate (4 x 10 mL) and the combined organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The products **9a-k** were isolated after TLC using ethyl acetate: hexane (3:2) as eluent.

1-Methyl-3-phenylquinolin-4(1*H*)-one (9a). 86% Yield (56.6 mg), white solid, m.p. 119.8 - 120.2 ºC. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H = 3.83 (s, 3 H, NC*H*$_3$), 7.26-7.43 (m, 5 H, H-6,8,4',3',5'), 7.64-7.70 (m, 3 H, H-7,2',6'), 7.68 (s, 1 H, H-2), 8.56 (dd, *J* = 8.3, 1.6 Hz, 1 H, H-5) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C = 40.9 (N*C*H$_3$), 114.9 (C-8), 121.9 (C-3), 123.9 (C-6), 126.9 (C-4'), 127.1 (C-4a), 127.5 (C-5), 128.2 (C-3',5'), 128.8 (C-2',6'), 132.0 (C-7), 135.3 (C-1'), 139.8 (C-8a), 142.6 (C-2), 175.8 (C-4) ppm. MS (EI) *m/z* (%): 235 ($M^{+\bullet}$, 41), 234 [$(M-H)^+$, 100], 165 (6), 145 (10). HRMS (EI) *m/z* calcd for ($C_{16}H_{13}NO$) $(M)^{+\bullet}$: 235.0997, found: 235.0995.

3-(4-Methoxyphenyl)-1-methylquinolin-4(1*H*)-one (9b). 83% Yield (61.6 mg), white solid, m.p. 154.8-155.3 ºC. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H = 3.78 (s, 3 H, OC*H*$_3$), 3.90 (s, 3 H, NC*H*$_3$), 6.96 (d, *J* = 8.9 Hz, 2 H, H-3',5'), 7.42 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1 H, H-6), 7.66-7.68 (m, 1 H, H-8), 7.68 (d, *J* = 8.9 Hz, 2 H, H-2',6'), 7.74 (ddd, *J* = 9.3, 6.9, 1.5 Hz, 1 H, H-

7), 8.24 (s, 1 H, H-2), 8.30 (dd, J = 8.0, 1.5 Hz, 1 H, H-5) ppm. ^{13}C NMR (125.77 MHz, DMSO-d_6): δ_C = 40.0 (N*C*H$_3$), 55.0 (O*C*H$_3$), 113.3 (C-3',5'), 116.5 (C-8), 119.4 (C-3), 123.3 (C-6), 126.1 (C-5), 126.5 (C-4a), 128.1 (C-1'), 129.4 (C-2',6'), 131.8 (C-7), 139.7 (C-8a), 143.3 (C-2), 158.0 (C-4'), 174.3 (C-4) ppm. MS (EI) *m/z* (%): 265 ($M^{+\bullet}$, 100), 264 [$(M-H)^+$, 71], 251 (6), 250 [$(M-CH_3)^+$, 36], 249 (8), 235 (4), 222 (19). HRMS (EI) *m/z* calcd for ($C_{17}H_{15}NO_2$) $(M)^{+\bullet}$: 265.1103, found: 265.1101.

3-(4-Hydroxyphenyl)-1-methylquinolin-4(1*H*)-one (9c). 83% Yield (58.4 mg), white solid, m.p. 295.9-296.8 ºC. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H = 3.88 (s, 3 H, NC*H*$_3$), 6.79 (d, J = 7.4 Hz, 2 H, H-3',5'), 7.40 (ddd, J = 8.0, 6.8, 0.9 Hz, 1 H, H-6), 7.53 (d, J = 7.4 Hz, 2 H, H-2',6'), 7.66 (d, J = 8.5 Hz, 1 H, H-8), 7.73 (ddd, J = 8.5, 6.8, 1.5 Hz, 1 H, H-7), 8.18 (s, 1 H, H-2), 8.28 (dd, J = 8.0, 1.5 Hz, 1 H, H-5), 9.53 (br s, 1 H, O*H*) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C = 40.3 (N*C*H$_3$), 115.2 (C-3',5'), 116.7 (C-8), 119.8 (C-3), 123.6 (C-6), 126.2 (C-5), 126.5 (C-4a, 1'), 129.4 (C-2',6'), 132.1 (C-7), 139.8 (C-8a), 143.3 (C-2), 156.7 (C-4'), 174.4 (C-4) ppm. MS (EI) *m/z* (%): 251 ($M^{+\bullet}$, 66), 250 [$(M-H)^+$, 100], 235 (6), 208 (7), 185 (7), 120 (7). HRMS (EI) *m/z* calcd for ($C_{16}H_{13}NO_2$) $(M)^{+\bullet}$: 251.0946, found: 251.0942.

1-Methyl-3-[4-(dimethylamino)phenyl]quinolin-4(1*H*)-one (9d). 40% Yield (31.2 mg), yellow solid, m.p. 188.8-189.4 ºC. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H = 2.91 [s, 6 H, N(C*H*$_3$)$_2$], 3.90 (s, 3 H, NC*H*$_3$), 6.76 (d, J = 8.8 Hz, 2 H, H-3',5'), 7.40 (ddd, J = 8.0, 6.8, 0.9 Hz, 1 H, H-6), 7.60 (d, J = 8.8 Hz, 2 H, H-2',6'), 7.67 (d, J = 8.4 Hz, 1 H, H-8), 7.74 (ddd, J = 8.4, 6.8, 1.4 Hz, 1 H, H-7), 8.20 (s, 1 H, H-2), 8.29 (dd, J = 8.0, 1.4 Hz, 1 H, H-5) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C = 40.2 (N*C*H$_3$), 40.3 [N(*C*H$_3$)$_2$], 112.0 (C-3',5'), 116.5 (C-8), 120.1 (C-3), 123.2 (C-6), 123.7 (C-1'), 126.2 (C-5), 126.4 (C-4a), 129.0 (C-2',6'), 131.7 (C-7), 139.7 (C-8a), 142.7 (C-2), 149.3 (C-4'), 174.4 (C-4) ppm. MS (EI) *m/z* (%): 278 ($M^{+\bullet}$,

100), 277 [(M-H)$^+$, 58], 264 (16), 263 (35), 261 (18). HRMS (EI) *m/z* calcd for ($C_{18}H_{18}N_2O$) (M)$^{+\bullet}$: 278.1419, found: 278.1416.

1-Methyl-3-[4-(methylamino)phenyl]quinolin-4(1*H*)-one (10). 10% Yield, pale yellow residue. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H = 2.87 (s, 3 H, NHC*H*$_3$), 3.84 (s, 3 H, NC*H*$_3$), 6.77 (d, *J* = 8.7 Hz, 2 H, H-3',5'), 7.37-7.42 (m, 2 H, H-6,8), 7.53 (d, *J* = 8.7 Hz, 2 H, H-2',6'), 7.66 (m, 1 H, H-7), 7.66 (s, 1 H, H-2), 8.56 (dd, *J* = 8.2, 1.7 Hz, 1 H, H-5) ppm. MS (EI) *m/z* (%): 264 (M$^{+\bullet}$, 100), 263 [(M-H)$^+$, 56], 249 [(M-CH_3)$^+$, 21], 248 (7), 234 [(M-$NHCH_3$)$^+$, 12]. HRMS (EI) *m/z* calcd for ($C_{17}H_{16}N_2O$) (M)$^{+\bullet}$: 264.1263, found: 264.1262.

3-(4-Formylphenyl)-1-methylquinolin-4(1*H*)-one (9e).[32] 61% Yield (44.9 mg), white solid, m.p. 212.0 - 212.5 ºC. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ_H = 3.95 (s, 3H, NC*H*$_3$), 7.48 (dt, *J* = 7.6, 0.8 Hz, 1 H, H-6), 7.73 (d, *J* = 8.4 Hz, 1 H, H-8), 7.80 (ddd, *J* = 8.4, 7.6, 1.5 Hz, 1 H, H-7), 7.93 (d, *J* = 6.9 Hz, 2 H, H-2',6'), 8.06 (d, *J* = 6.9 Hz, 2H, H-3',5'), 8.33 (dd, *J* = 7.6, 1.5 Hz, 1 H, H-5), 8.50 (s, 1 H, H-2), 10.01 (s, 1 H, C*H*O) ppm. ^{13}C NMR (125.77 MHz, DMSO-d_6): δ_C = 40.3 (N*C*H$_3$), 116.8 (C-8), 117.9 (C-3), 124.0 (C-6), 126.2 (C-5), 126.7 (C-4a), 128.4 (C-3',5'), 129.2 (C-2',6'), 132.3 (C-7), 134.2 (C-1'), 139.8 (C-8a), 142.3 (C-4'), 145.0 (C-2), 174.1 (C-4), 192.6 (*C*HO) ppm. MS (EI) *m/z* (%): 263 (M$^{+\bullet}$, 58), 262 [(M-H)$^+$, 100], 257 (4), 234 (11), 233 (3), 190 (5), 164 (4). HRMS (EI) *m/z* calcd for ($C_{17}H_{13}NO_2$) (M)$^{+\bullet}$: 263.0946, found: 263.0946.

1-Methyl-3-(4-nitrophenyl)quinolin-4(1*H*)-one (9f). 36% Yield (28.2 mg), yellow solid, m.p. 242.2 - 244.3 ºC. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H = 3.97 (s, 3 H, NC*H*$_3$), 7.51 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1 H, H-6), 7.76 (dd, *J* = 8.2, 1.1 Hz, 1 H, H-8), 7.83 (ddd, *J* = 8.2, 6.8, 1.6 Hz, 1 H, H-7), 8.14 (d, *J* = 8.9 Hz, 2 H, H-2',6'), 8.28 (d, *J* = 8.9 Hz, 2 H, H-3',5'), 8.34 (dd, *J* = 8.0, 1.6 Hz, 1 H, H-5), 8.59 (s, 1 H, H-2) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C = 40.6 (N*C*H$_3$), 116.8 (C-3), 117.0 (C-8), 123.2 (C-3',5'), 124.3 (C-6), 126.2 (C-5),

126.8 (C-4a), 128.7 (C-2',6'), 132.5 (C-7), 139.8 (C-8a), 143.2 (C-1'), 145.48 (C-4'), 145.51 (C-2), 174.0 (C-4) ppm. MS (EI) *m/z* (%): 280 ($M^{+\bullet}$, 66), 279 [$(M-H)^+$, 100], 250 (85), 249 (91), 234 (35), 233 (33), 190 (17). HRMS (EI) *m/z* calcd for ($C_{16}H_{12}N_2O_3$) $(M)^{+\bullet}$: 280.0848, found: 280.0846.

3-(4-Aminophenyl)-1-methylquinolin-4(1*H*)-one (11): All the data of this compound were taken from a mixture of **11** with the expected reaction product **9f** (See SI): 13% Yield (9.1 mg), ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H = 3.09 (s, 3 H, NC*H*$_3$), 6.99 (d, *J* = 9.2 Hz, 2 H, H-3',5'), 7.46-7.54 (m, 2 H, H-6; H-8), 7.74-7-80 (m, 1 H, H-7), 8.12 (d, *J* = 9.2 Hz, 2 H, H-2',6'), 8.17 (s, 1 H, H-2), 8.48 (dd, *J* = 8.1, 1.5 Hz, 1 H, H-5) ppm. MS (EI) *m/z* (%): 250 ($M^{+\bullet}$, 100), 249 [$(M-H)^+$, 100], 235 [$(M-CH_3)^+$, 14], 234 [$(M-NH_2)^+$, 22], 233 (13), 207 (13). HRMS (EI) *m/z* calcd for ($C_{16}H_{14}N_2O$) $(M)^{+\bullet}$: 250.1106, found: 250.1105.

3-(3-Methoxyphenyl)-1-methylquinolin-4(1*H*)-one (9g). 86% Yield (63.9 mg), white solid, m.p. 209.4-210.3 ºC. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H = 3.80 (s, 3 H, NC*H*$_3$), 3.92 (s, 3 H, OC*H*$_3$), 6.87 (m, 1 H, H-4'), 7.31-7.34 (m, 1 H, H-5',6'), 7.38-7.39 (m, 1 H, H-2'), 7.45 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1 H, H-6), 7.69 (dd, *J* = 8.2, 1.1 Hz, 1 H, H-8), 7.77 (ddd, *J* = 8.2, 6.9, 1.6 Hz, 1 H, H-7), 8.32 (dd, *J* = 7.9, 1.6 Hz, 1 H, H-5), 8.33 (s, 1 H, H-2) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C = 40.3 (N*C*H$_3$), 55.0 (O*C*H$_3$), 112.0 (C-4'), 114.1 (C-2'), 116.6 (C-8), 119.3 (C-3), 120.7 (C-6'), 123.6 (C-6), 126.2 (C-5), 126.7 (C-4a), 128.9 (C-5'), 132.0 (C-7), 137.2 (C-1'), 139.8 (C-8a), 144.1 (C-2), 159.0 (C-3'), 174.2 (C-4) ppm. MS (ESI) *m/z* (%): 553 [$(2M+Na)^+$, 10], 288 [$(M+Na)^+$, 15], 266 [$(M+H)^+$, 100]. HRMS (EI) *m/z* calcd for ($C_{17}H_{15}NO_2$) $(M)^{+\bullet}$: 265.1103, found: 265.1102.

3-(3-Formylphenyl)-1-methylquinolin-4(1*H*)-one (9h).[32] 69% Yield (50.8 mg), white solid, m.p. 166.1-167.1 ºC. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H = 3.94 (s, 3 H, NC*H*$_3$), 7.47 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1 H, H-6), 7.63 (t, *J* = 7.8 Hz, 1 H, H-5'), 7.72 (dd, *J* = 7.6, 1.2 Hz, 1 H,

H-8), 7.78 (dd, *J* = 7.8, 1.5 Hz, 1 H, H-4'), 7.82 (ddd, *J* = 7.6, 6.8, 1.5 Hz, 1 H, H-7), 8.10 (dt, *J* = 7.8, 1.5 Hz, 1 H, H-6'), 8.31 (dd, *J* = 8.0, 1.5 Hz, 1 H, H-5), 8.34 (br s, 1 H, H-2'), 8.45 (s, 1 H, H-2), 10.06 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.47 MHz, DMSO-d6): δ_C = 40.3 (N*C*H$_3$), 116.8 (C-8), 118.2 (C-3), 123.9 (C-6), 126.2 (C-5), 126.7 (C-4a), 127.6 (C-4'), 128.8 (C-5'), 129.4 (C-2'), 132.2 (C-7), 134.3 (C-6'), 136.1 (C-3'), 136.8 (C-1'), 139.9 (C-8a), 144.4 (C-2), 174.2 (C-4), 193.4 (*C*HO) ppm. MS (EI) *m/z* (%): 263 ($M^{+\bullet}$, 52), 262 [$(M-H)^+$, 100], 234 [$(M-CHO)^+$, 15], 190 (6), 165 (6). HRMS (EI) *m/z* calcd for ($C_{17}H_{13}NO_2$) $(M)^{+\bullet}$: 263.0946, found: 263.0943.

3-(3,4-Dimetoxyphenyl)-1-methylquinolin-4(1*H*)-one (9i). 61% Yield (50.4 mg), pale yellow solid, m.p. 158.2-159.3 ºC. ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ_H = 3.78 (s, 3 H, 4'-OC*H*$_3$), 3.80 (s, 3 H, 3'-OC*H*$_3$), 3.92 (s, 3 H, NC*H*$_3$), 6.98 (d, *J* = 8.4 Hz, 1 H, H-5'), 7.30 (dd, *J* = 8.4, 2.0 Hz, 1 H, H-6'), 7.42 (d, *J* = 2.0 Hz, 1 H, H-2'), 7.43 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1 H, H-6), 7.69 (dd, *J* = 8.4, 1.1 Hz, 1 H, H-8), 7.76 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1 H, H-7), 8.28 (s, 1 H, H-2), 8.31 (dd, *J* = 8.0, 1.6 Hz, 1 H, H-5) ppm. ^{13}C NMR (75.47 MHz, DMSO-d$_6$): δ_C = 40.3 (N*C*H$_3$), 55.54 and 55.57 (2 x O*C*H$_3$), 111.5 (C-5'), 112.4 (C-2'), 116.6 (C-8), 119.4 (C-1'), 120.6 (C-6'), 123.4 (C-6), 126.2 (C-5), 126.6 (C-3), 128.5 (C-4a), 131.9 (C-7), 139.7 (C-8a), 143.5 (C-2), 147.7 (C-4'), 148.1 (C-3'), 174.3 (C-4) ppm. MS (EI) *m/z* (%): 295 ($M^{+\bullet}$, 100), 294 [$(M-H)^+$, 22], 280 [$(M-CH_3)^+$, 57], 274 (65), 259 (35), 249 (22), 209 (24), 208 (18). HRMS (EI) *m/z* calcd for ($C_{18}H_{17}NO_3$) $(M)^{+\bullet}$: 295.1208, found: 295.1208.

3-(3-Formyl-4-methoxyphenyl)-1-methylquinolin-4(1*H*)-one (9j).[32] 49% Yield (40.2 mg), pale yellow solid, m.p. 241.5-242.3 ºC. ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ_H = 3.93 (s, 3 H, NC*H*$_3$), 3.96 (s, 3 H, OC*H*$_3$), 7.29 (d, *J* = 6.9 Hz, 1 H, H-5'), 7.45 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H, H-6), 7.71 (dd, *J* = 8.2, 1.2 Hz, 1 H, H-8), 7.79 (ddd, *J* = 8.2, 6.8, 1.5 Hz, 1 H, H-7), 8.07 (d, *J* = 2.4 Hz, 1 H, H-2'), 8.10 (dd, *J* = 6.9, 2.4 Hz, 1 H, H-6'), 8.31 (dd, *J* = 8.1, 1.5 Hz, 1 H,

H-5), 8.37 (s, 1 H, H-2), 10.41 (s, 1 H, C*H*O) ppm. ^{13}C NMR (75.47 MHz, DMSO-d$_6$): δ_C = 40.3 (N*C*H$_3$), 56.1 (O*C*H$_3$), 112.4 (C-5'), 116.7 (C-8), 118.1 (C-3), 123.69 (C-3'), 123.72 (C-6), 126.1 (C-5), 126.5 (C-4a), 127.4 (C-6'), 128.3 (C-1'), 132.1 (C-7), 136.4 (C-2'), 139.9 (C-8a), 143.7 (C-2), 160.4 (C-4'), 174.2 (C-4), 189.2 (*C*HO) ppm. MS (EI) *m/z* (%): 293 [$M^{+\bullet}$, 100], 292 [$(M-H)^+$, 74], 278 (30), 264 (12), 250 (31), 249 (11), 235 (11), 222 (10). HRMS (EI) *m/z* calcd for ($C_{18}H_{15}NO_3$) $(M)^{+\bullet}$: 293.1052, found: 293.1053.

3-(4-Hydroxy-3,5-dimethylphenyl)-1-methylquinolin-4(1*H*)-one (9k). 20% Yield (15.6 mg), dark yellow solid, m.p. 310.2-310.9 ºC. ^{1}H NMR (500.13 MHz, DMSO-d$_6$): δ_H = 2.20 (s, 6 H, 3'-C*H*$_3$ and 5'-C*H*$_3$), 3.89 (s, 3 H, NC*H*$_3$), 7.29 (s, 2 H, H-2',6'), 7.41 (t, *J* = 7.6 Hz, 1 H, H-6), 7.67 (d, *J* = 8.3 Hz, 1 H, H-8), 7.74 (dd, *J* = 8.3, 7.6 Hz, 1 H, H-7), 8.18 (s, 1 H, H-2), 8.23 (br s, 1 H, O*H*), 8.28 (d, *J* = 7.6 Hz, 1 H, H-5) ppm. ^{13}C NMR (125.77 MHz, DMSO-d$_6$): δ_C = 16.9 (2 x *C*H$_3$), 39.7 (N*C*H$_3$), 116.6 (C-8), 120.2 (C-3), 123.3 (C-6), 123.6 (C-3',5'), 126.2 (C-5), 126.5 (C-1'), 126.6 (C-4a), 128.5 (C-2',6'), 131.8 (C-7), 139.8 (C-8a), 143.1 (C-2), 152.2 (C-4'), 174.4 (C-4) ppm. MS (EI) *m/z* (%): 279 ($M^{+\bullet}$, 66), 292 [$(M-H)^+$, 100], 257 (28), 237 (29), 236 (40), 194 (26), 165 (23), 152 (33), 139 (25), 138 (26), 125 (22), 124 (27), 123 (62), 114 (23), 111 (36), 110 (50), 97 (65), 96 (54). HRMS (EI) *m/z* calcd for ($C_{18}H_{17}NO_2$) $(M)^{+\bullet}$: 279.1259, found: 279.1254.

General procedure for the Suzuki-Miyaura cross coupling reaction of 3-iodo-1-pentylquinolin-4(1*H*)-one (6) with phenylboronic acid (8a). The 10 mL ohmic heating reactor was charged with 3-iodo-1-pentylquinolin-4(1*H*)-one **6** (60.0 mg, 0.18 mmol), phenylboronic acid **8a** (32.92 mg, 0.27 mmol), sodium carbonate (19.07 mg, 0.18 mmol), TBAB (5.80 mg, 0.018 mmol), $Pd(OAc)_2$ (2.02 mg, 9x10-3 mmol) and H_2O (4 mL). The mixture was heated at reflux with stirring for 30 minutes. Then the aqueous mixture was extracted with ethyl acetate (4 x 10 mL) and the combined organic layer was dried with

anhydrous sodium sulfate and concentrated under reduced pressure. The product **9m** was isolated after TLC using ethyl acetate: hexane (3:2) as eluent.

1-Pentyl-3-phenylquinolin-4(1*H*)-one (9m). 90% Yield (47.2 mg), light yellow oil. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ_H = 0.85 (t, J = 7.8 Hz, 3 H, H-5''), 1.14-1.32 (m, 4 H, H-3'',4''), 1.78 (quintet, J = 7.2 Hz, 2 H, H-2''), 4.36 (t, J = 7.2 Hz, 2 H, H-1''), 7.30 (ddd, J = 9.2, 5.5, 1.3 Hz, 1 H, H-4'), 7.39-7.42 (m, 3 H, H-3',5',6), 7.74-7.76 (m, 4 H, H-2',6',7,8), 8.33 (s, 1 H, H-2), 8.33 (dd, J = 8.2, 1.5 Hz, 1 H, H-5) ppm. ^{13}C NMR (125.77 MHz, DMSO-d_6): δ_C = 13.7 (C-5''), 21.6 (C-4''), 28.0 (C-3''), 28.1 (C-2''), 50.9 (C-1''), 116.3 (C-8), 119.5 (C-4a), 123.2 (C-6), 126.3 (C-3,5), 126.7 (C-4'), 127.7 (C-3',5'), 128.3 (C-2',6'), 131.8 (C-7), 135.6 (C-1'), 138.7 (C-8a), 143.2 (C-2), 174.0 (C-4) ppm. MS (EI) *m/z* (%): 291 ($M^{+\bullet}$, 86), 290 [$(M-H)^+$, 100], 284 (9), 248 [$(M-C_3H_7)^+$, 7], 235 (14), 234 [$(M-C_4H_9)^+$, 66], 220 [$(M-C_5H_{11})^+$, 34], 206 (10), 165 (7). HRMS (EI) *m/z* calcd for ($C_{20}H_{21}NO$) $(M)^{+\bullet}$: 291.1623, found 291.1621.

General procedure for the reusability of $Pd(OAc)_2$ in the Suzuki-Miyaura cross coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (4) with phenylboronic acid (8a). The 10 mL ohmic heating reactor was charged with 3-iodo-1-methylquinolin-4(1*H*)-one **4** (80.0 mg, 0.28 mmol), the phenylboronic acid **8a** (51.21 mg, 0.42 mmol), sodium carbonate (29.66 mg, 0.28 mmol), TBAB (9.02 mg, 0.028 mmol), $Pd(OAc)_2$ (3.15 mg, 0.014 mmol) and H_2O (4 mL). The mixture was heated at reflux with stirring for 15 minutes. After this period the aqueous mixture was extracted with ethyl acetate anhydrous sodium sulfate and concentrated under reduced pressure. The isolated product **9a** was obtained by TLC using ethyl acetate: hexane (3:2) as eluent. In the next run all reagents described above were added except the

catalyst $Pd(OAc)_2$. The work up and purification steps for the following runs were the same as the previously described for the first run. This procedure was performed for six runs.

General procedure for the reusability of $Pd(OAc)_2$-H_2O-TBAB in the Suzuki-Miyaura cross coupling reaction of 3-iodo-1-metilquinolin-4(1*H*)-one (4) with phenylboronic acid (8a). The 10 mL ohmic heating reactor was charged with 3-iodo-1-methylquinolin-4(1*H*)-one **4** (80.0 mg, 0.28 mmol), phenylboronic acid **8a** (51.21 mg, 0.42 mmol), sodium carbonate (29.66 mg, 0.28 mmol), TBAB (9.02 mg, 0.028 mmol), $Pd(OAc)_2$ (3.15 mg, 0.014 mmol) and H_2O (4 mL). The mixture was heated at reflux and stirred for 15 minutes. Then the mixture was allowed to cool at room temperature and the precipitate was filtered. The $Pd(OAc)_2$-H_2O-TBAB was recovered by filtration and subjected to the next runs after addition of the 3-iodo-1-methylquinolin-4(1*H*)-one **4**, boronic acid **8a**, sodium carbonate (the same quantities as described above for each one of these reactants) and water (1 mL). This procedure was carried out seven runs. In the last run the base, sodium carbonate, was not added. The isolated solids from each run were purified by TLC using ethyl acetate: hexane (3:2) as eluent. The work up and purification were the same as described above for the six first runs. In the seventh run the reaction mixture was extracted with ethyl acetate (4 x 10 mL) and both reactor and electrodes were washed with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The product **9a** was obtained pure after TLC using ethyl acetate:hexane (3:2) as eluent.

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Supporting Information. [^{1}H NMR and ^{13}C NMR spectral data for new compounds, MS and HRMS analysis of compound **11**, UV-vis spectrum of the experiment performed to investigate the formation of Pd-nanoparticles and results of real time monitoring the ohmic heating [Temperature (T), Power (P), AC Current (Iac) and AC Voltage (Vac)] along the reaction heating time (t) for each run from 1 to 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) According to the IUPAC nomenclature rules compounds **9e**, **9h** and **9j** should be named as 4-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)benzaldehyde **(9e),** 3-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)benzaldehyde **(9h)** and 2-methoxy-5-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)benzaldehyde **(9j)**. However the nomenclature presented in the experimental characterization of these compounds was adopted for convenience, allowing a more direct comparison with the other derivatives.