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Palladium-catalyzed 'on-water' tandem cyclization reactions for the synthesis of biologically important 4-arylquinazolines

Shuo Yuan,[a] Bin Yu*[a] and Hong-Min Liu*[a]

Abstract: The privileged quinazoline scaffold is prevalent in pharmaceutically relevant molecules that show diverse biological activities. Herein we report an efficient palladium-catalyzed 'on-water' tandem cyclization reactions from commercially available arylboronic acids and benzonitriles that enable rapid access to the 4-arylquinazoline scaffolds in good to excellent yields (45 examples, up to 98% yield). This protocol has shown good functional group tolerance and broad substrate scope. The reaction was also performed on a gram scale and successfully applied to the synthesis of highly potent and selective PI3Kδ inhibitor **N11**, showing the practicability and synthetic utility of the protocol. In this reaction, the quinazoline scaffold is efficiently constructed with one C-C bond and one C-N bond formed simultaneously. Collectively, the protocol could serve as an alternative strategy to synthesize biologically important quinazoline scaffolds.

Water is widely used as green solvent in organic synthesis due to its environmentally friendly nature and unique reactivity.[1] Especially, under 'on water' conditions, a remarkable phenomenon of substantial rate acceleration is observed when insoluble reactants are stirred in aqueous suspension.[2] In this context, Lemal and co-workers demonstrated an efficient 'on water' protocol that enabled the construction of 1,2-diazetidines from quadricyclane and azodicarboxylates via [2σ+2σ+2π] cycloaddition.[3] Rideout and Breslow reported the Diels-Alder reactions between nonpolar compounds, which showed much higher reactivity in water than those performed in organic solvents, and the rate acceleration was mostly ascribed to the hydrogen bonding and micellar catalysis of water.[4] Grieco et al. reported that water could promote the Claisen rearrangement in an efficient manner.[5] Moreover, the unique characters of water such as poor solubility, high polarity and heat capacity as well as extensive H-bond donating (HBD) ability make water an attractive medium for organic reactions.[6]

Quinazolines are one of the privileged nitrogen containing heterocycles that are prevalent in natural products and synthetic molecules with diverse pharmacological properties, including anti-inflammatory, anticonvulsant, antiviral, anticancer, and antimicrobial activities.[7] In particular, the 4-phenylquinazolines (highlighted in red in Figure 1) have been found in some bioactive molecules such as **AM-2099** (selective $Na_V1.7$ inhibitor for the treatment of chronic pain),[8] **NTRC-808** (novel NTS2 agonist for the treatment of visceral pain and psychosis),[9] **N11** (selective PI3Kδ inhibitor developed by Novartis, efficacious *in vivo* for the treatment of inflammatory diseases),[10] and translocator protein (**TSPO**) ligand (regulation of cellular processes for the treatment of neuroinflammation) (Figure 1).[11] Because of unique structural features and interesting biological properties of 4-phenylqunazolines, the design of new protocols for the construction of this privileged scaffold has attracted considerable interest.[12]

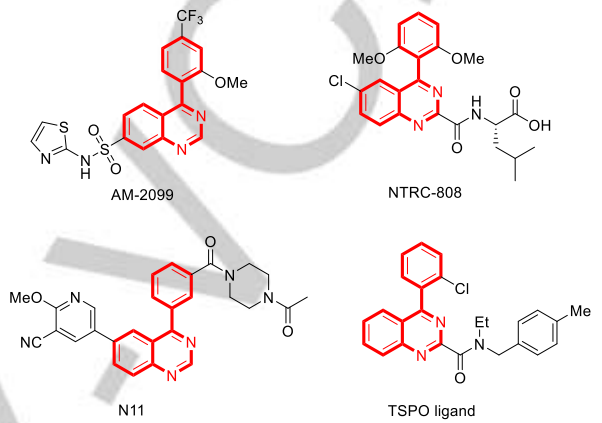

Figure 1. Representative bioactive 4-phenylquinazolines.

Although some methods for constructing the quinazoline scaffolds have been documented, strategies that enable efficient access to the 4-phenylquinazolines from benzonitriles are still rare.[13] Chen and Liu groups described a single-step procedure for the synthesis of 4-phenylquinazolines via the [2+2+2] cascade annulation of benzonitriles with diaryliodonium salts (or aryldiazonium salts) (Scheme 1a).[14] The Chen group developed a palladium-catalyzed three-component tandem addition/cyclization reactions of 2-aminobenzonitriles, aldehydes and arylboronic acids (Scheme 1b).[15] Recently, He and co-workers demonstrated the synthesis of 4-aryl quinazolines by the iron-catalyzed C(sp3)-H oxidation and intramolecular C-N bond formation in the presence of *tert*-BuOOH (Scheme 1c).[16] In 2018, the Chen group reported a tandem procedure for the preparation of diverse 4-phenylqunazolines from *N*-(2-cyanoaryl)benzamides and arylboronic acids via the sequences of carbopalladation and intramolecular cyclization (Scheme 1d).[17] Although these methods successfully achieved the synthesis of 4-arylquinazolines, the development of efficient and practical methodologies for the construction of 4-arylquinazoline scaffolds remains highly desirable.[18] Herein, we report the Pd-catalyzed tandem cyclization reactions for the construction of new 4-arylquinazolines from readily available phenylboronic acids and (*E*)-*N*'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamides, in which water is employed as the green reaction medium (Scheme 1e). In comparison with previously reported methods, our method could efficiently generate quinazoline scaffolds in good to excellent yields (up to 98% yield) under mild conditions and has been successfully applied to the synthesis of a highly potent and selective PI3Kδ inhibitor **N11**.

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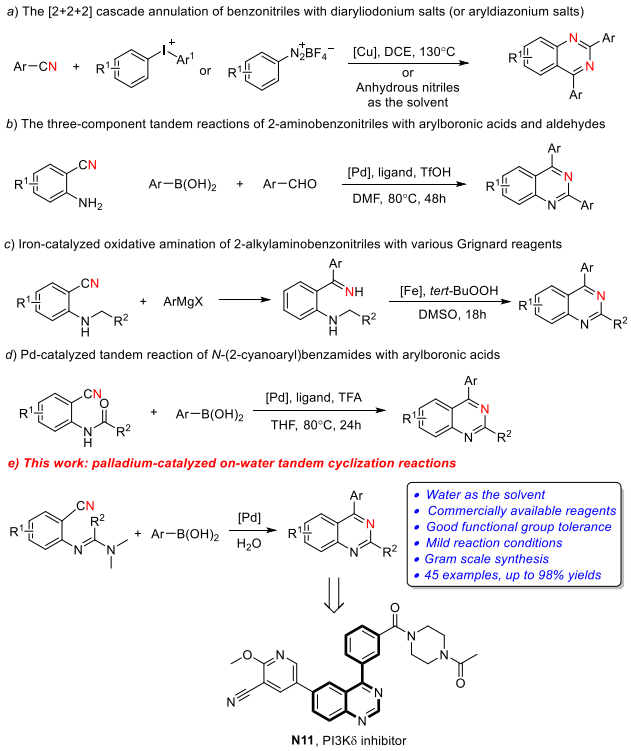
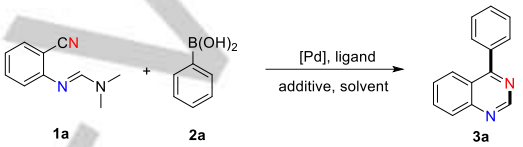


Scheme 1. Construction of 4-arylquinazoline skeletons from benzonitriles.

Initially, (*E*)-*N*'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamide **1a** (1 mmol) and phenylboronic acid **2a** (3 mmol) were chosen as model substrates to examine the reactivity in the presence of $Pd(acac)_2$ as catalyst (10 mol%), 2,2'-bipyridine (bpy, 20 mol%) as ligand, and trifluoromenthanesulfonic acid (TfOH) as additive (10 equiv.) in DMF (2 mL) at 60 ℃. Interestingly, the desired 4-phenylquinazoline **3a** was obtained in 33% yield (Table 1, entry 1). Encouraged by this result, we further optimized the reaction conditions of the model reaction, and the results are summarized in Table 1. We firstly screened several commonly used solvents (Table 1, entries 2-6). To our delight, compound **3a** was generated in 91% yield when the reaction was carried out in water (Table 1, entry 6). Only a trace amount of **3a** was obtained when the reaction was performed in dioxane and acetonitrile (Table 1, entries 2 and 3). No product was formed in dichloromethane (Table 1, entry 4). While in methanol, **3a** was generated in 60% yield (Table 1, entry 5). Next, different palladium catalysts were used to explore their catalytic capability (Table 1, entries 7-11), the results revealed that $Pd(acac)_2$ was the best one for catalyzing this cascade reaction, only a trace amount of by-product was formed. Compound **3a** was afforded in only 43% yield when $Pd(OAc)_2$ was utilized. Other catalysts such as $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $PdCl_2(dppf)$, and $Pd_2(dba)_3$ failed to deliver the desired compounds. Moreover, replacement of 2,2'-bipyridine (bpy) with other ligands, including triphenylphosphine (PPh_3) and BINOL, resulted in relatively lower yields (Table 1, entries 12 and 13). The yield was extremely low in the absence of ligand (Table 1, entry 14). Unfortunately, decreasing or increasing the reaction temperature reduced the yields (Table 1, entries 15 and 16), it was probably due to that the low temperature reduced the reaction efficiency, and high temperature caused the formation of by-products. Compared to TfOH, other acids including *p*-toluenesulfonic acid, acetic acid, benzoic acid and trifluoroacetic acid (TFA) were less efficient to promote this reaction (Table 1, entries 17-20). Interestingly, the results showed that the transformation of these reactions depended on the acidity of additives. No desired product was observed without the acid additive (Table 1, entry 21). Furthermore, when the catalyst loading decreased to 5 mol%, the yield of compound **3a** was 83%, lower than that for 10 mol% of catalyst loading (Table 1, entry 22). Similarly, the corresponding yield was 80% when 10 mol% of ligand was used (Table 1, entry 23). When 1 mmol amount of **2a** was used, the yield of the product was 76% (Table 1, entry 24). Based on above optimization, the best reaction condition was that substituted (*E*)-*N*'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamide (1 mmol) and arylboronic acid (3 mmol) were stirred in H_2O (2 mL) at 60 °C for 6 h in the presence of $Pd(acac)_2$ (10 mol%), bpy (20 mol%), and TfOH (10 equiv.) (Table 1, entry 6).

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a

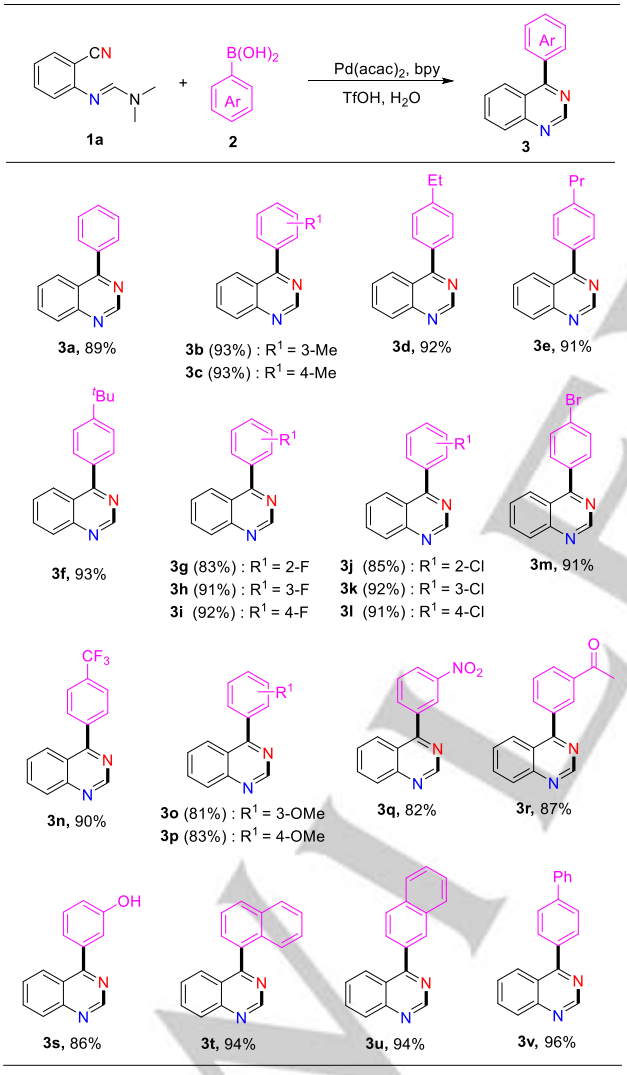
Entry	Catalyst	Ligand	Additive	Solvent	**3a** (%)[b]
1	$Pd(acac)_2$	bpy	TfOH	DMF	33
2	$Pd(acac)_2$	bpy	TfOH	Dioxane	Trace
3	$Pd(acac)_2$	bpy	TfOH	MeCN	Trace
4	$Pd(acac)_2$	bpy	TfOH	DCM	N.D.[c]
5	$Pd(acac)_2$	bpy	TfOH	MeOH	60
6	$Pd(acac)_2$	bpy	TfOH	H_2O	91
7	$Pd(OAc)_2$	bpy	TfOH	H_2O	43
8	$Pd(PPh_3)_2Cl_2$	bpy	TfOH	H_2O	N.D.
9	$Pd(PPh_3)_4$	bpy	TfOH	H_2O	N.D.
10	$PdCl_2(dppf)$	bpy	TfOH	H_2O	N.D.
11	$Pd_2(dba)_3$	bpy	TfOH	H_2O	Trace
12	$Pd(acac)_2$	PPh_3	TfOH	H_2O	48
13	$Pd(acac)_2$	BINOL	TfOH	H_2O	Trace
14	$Pd(acac)_2$	-	TfOH	H_2O	Trace
15[d]	$Pd(acac)_2$	bpy	TfOH	H_2O	38
16[e]	$Pd(acac)_2$	bpy	TfOH	H_2O	33
17	$Pd(acacc)_2$	bpy	TsOH	H_2O	70
18	$Pd(acac)_2$	bpy	AcOH	H_2O	7%
19	$Pd(acac)_2$	bpy	$PhCO_2H$	H_2O	4%
20	$Pd(acac)_2$	bpy	TFA	H_2O	79%
21	$Pd(acac)_2$	bpy	-	H_2O	N.D.
22[f]	$Pd(acac)_2$	bpy	TfOH	H_2O	83
23[g]	$Pd(acac)_2$	bpy	TfOH	H_2O	80
24[h]	$Pd(acac)_2$	bpy	TfOH	H_2O	76

[a] Reaction conditions: **1a** (1 mmol), **2a** (3 mmol), catalyst (10 mol%), ligand (20 mol%), additive (10 equiv.), solvent (2 mL), 6 h, 60 ℃. [b] NMR yields determined by ^1H NMR using the triphenylmethane as an internal standard. [c] N.D. means Not Detected. [d] At room temperature. [e] At 100 ℃. [f] 5 mol% amount of catalyst was used. [g] 10 mol% amount of ligand was used. [h] 1 mmol amount of **2a** was used.

With this optimal condition in hand, we next explored the scope of this reaction. As shown in Table 2, the corresponding products **3a-v** were obtained in good to excellent yields (81-

98%) regardless of the electronic nature and position of substitutions attached to the phenyl ring of boronic acids. For the halogen substituted arylboronic acids, the corresponding products **3g-m** were also generated in good yields (83-92%), although the halogen attached atom may undergo further Pd-catalyzed cross-coupling reactions. For the substrates bearing the electron-rich methoxy group, the products **3o-p** were obtained in relatively lower yields (81% and 83%, respectively). Similarly, the NO_2 substituted boronic acid also gave compound **3q** in 82% yield. Interestingly, for substrates bearing the acetyl and hydroxy groups at the 3-position of the phenyl ring, the corresponding products **3r** and **3s** were also formed in 87 and 86%, respectively under the optimized condition. Compounds **3t-v** were afforded in excellent yields (up to 96% yield) when the bulky 1-naphthaleneboronicacid, *β*-naphthylboronic acid, and 4-biphenylboronic acid were used.

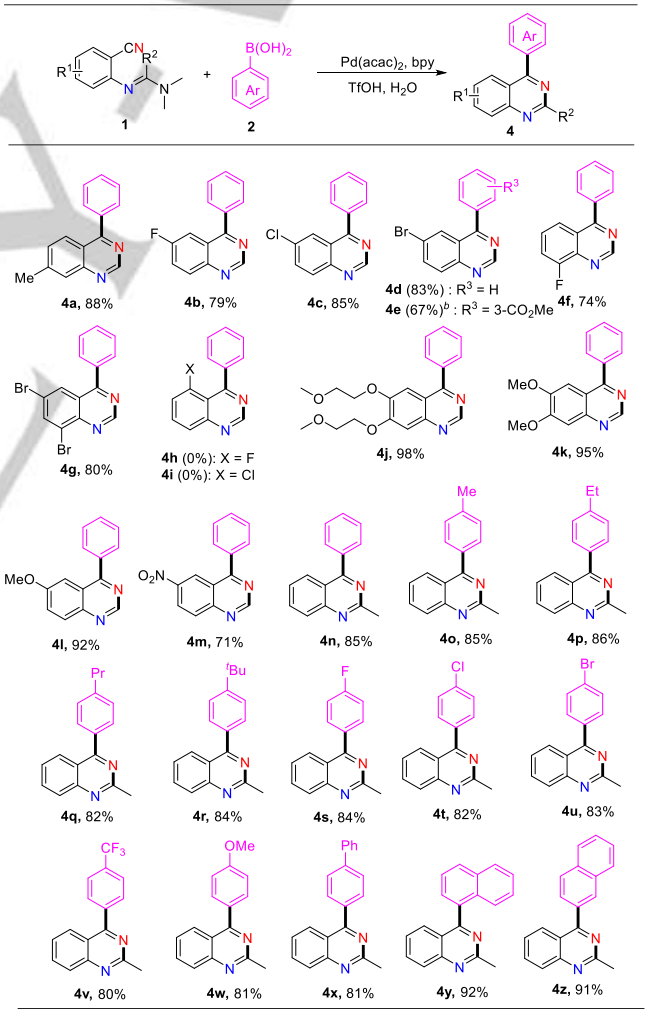
Table 2. Scope of arylboronic acids [a]



[a] Reaction conditions: **1a** (1 mmol), **2** (3 mmol), $Pd(acac)_2$ (10 mol%), bpy (20 mol%), TfOH (10 equiv.), H_2O (2 mL), 60 ℃, 6 h.

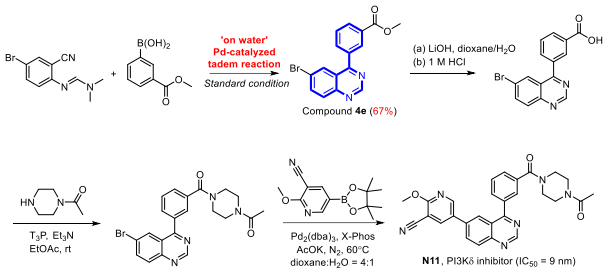
Given the good reactivity of compound **1a** with diverse arylboronic acids, we further investigated the scope of other (*E*)-*N*'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamides and arylboronic acids. As shown in Table 3, except for compounds **4h** and **4i**, other 4-arylquinazolines were generated in good to excellent yields (74-98%) under the optimized conditions. For substrates bearing the electron-donating groups, the corresponding products **4j-l** were obtained in excellent yields (92-98%). For the NO_2 substituted substrate, the product **4m** was formed in 71% yield. The results suggest that the electronic nature of substitutions attached to the phenyl ring of (*E*)-*N*'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamides is crucial for the reactivity. For substrates bearing halogen atoms or alkyl groups, the corresponding products were obtained in good yields as well. To our surprise, for substrates bearing halogen atoms adjacent to the CN group, no desired products were formed. We speculate that the steric hindrance of the halogen atom hampered the formation of the desired products. To prove the synthetic practicality of this method, the reaction was performed on a 1.0 gram scale under slightly modified conditions, the corresponding compound **4e** was formed in 67% yield.

Table 3. Scope of (*E*)-*N*'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamides [a]



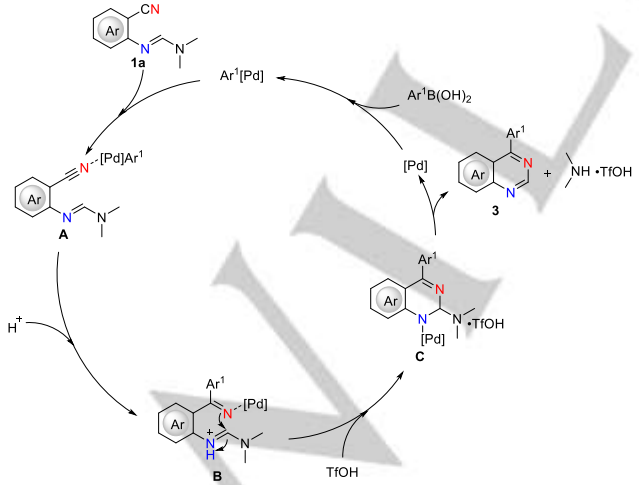
[a] Reaction conditions: **1a** (1 mmol), **2** (3 mmol), $Pd(acac)_2$ (10 mol%), bpy (20 mol%), TfOH (10 equiv.), H_2O (2 mL), 60 ℃, 6 h. [b] Conditions: 1a (1.01g, 4 mmol), 2 (3.6 g, 20 mmol), $Pd(acac)_2$ (10 mol%), bpy (20 mol%), TfOH (15 equiv.), H_2O (8 mL), 80℃, 12 h.

To further illustrate the synthetic utility, this method was then applied to the synthesis of **N11** (Figure 1), which is a highly potent and selective PI3Kδ inhibitor developed by Novartis for the treatment of inflammatory diseases.[10] Under the slightly modified condition, the key intermediate **4e** was efficiently synthesized in 67% yield on a gram scale. In contrast, Compound **4e** had been previously synthesized in an overall yield of 48%, which involved four consecutive steps and harsh reaction conditions.[10, 19] With the key intermediate **4e** in hand, **N11** was efficiently obtained through the reported routine methods as shown in Scheme 2.[10, 20] Conceivably, our protocol could also be applicable to the synthesis of other 4-phenylquinazoline derivatives, such as **AM-2099**, **NTRC-808** and **TSPO** ligand (Figure 1).



Scheme 2. Synthesis of selective PI3Kδ inhibitor **N11**.

Based on the aforementioned results, a plausible mechanistic pathway is depicted in Scheme 3. Intermediate **A** was formed from **1a** by the coordination of the arylpalladium species generated *in situ* from the palladium catalyst and arylboronic acid. Next, through carbopalladation of the cyano group and protonation of the imine, a palladium ketamine complex **B** was provided. The complex **B** then underwent protonation and intramolecular nucleophilic addition to generate species **C**, which was then subjected to aromatization, affording the desired quinazoline **3**. Clearly, through the palladium-catalyzed on-water tandem cyclization reactions, the quinazoline scaffold was efficiently constructed with one C-C bond and one C-N bond formed simultaneously.



Scheme 3. Purposed reaction mechanism for the formation of 4-arylquinazolines.

In summary, we have developed an efficient palladium-catalyzed 'on-water' tandem cyclization reactions from readily available arylboronic acids and benzonitriles that enable rapid access to the quinazoline scaffolds in good to excellent yields (45 examples, up to 98% yield). This protocol has shown well functional group tolerance and broad substrate scope. The reaction was also performed on a gram scale, affording compound **4e** in 67% yield. The protocol was successfully applied to the synthesis of highly potent and selective PI3Kδ inhibitor **N11**, showing the practicability and synthetic utility of the protocol. In this reaction, the quinazoline scaffold was efficiently constructed with one C-C bond and one C-N bond formed simultaneously. Compared with previously reported methods, the method presented in this work has several advantages such as mild reaction conditions, short reaction time, ease of product isolation, particularly the use of water as the solvent. To conclude, the protocol developed could serve as an efficient alternative strategy to synthesize biologically active 4-phenylquinazoline derivatives.

Acknowledgements

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Keywords: Palladium catalysis • On-water synthesis • Cascade reactions • Quinazolines

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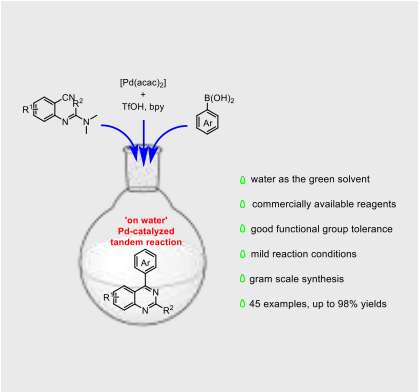
An efficient palladium-catalyzed 'on-water' tandem cyclization reactions from readily available arylboronic acids and benzonitriles has been developed to offer rapid access to the quinazoline scaffolds in good to excellent yields (up to 98% yield). This protocol is also performed on a gram scale and successfully applied to the synthesis of a highly potent and selective PI3Kδ inhibitor **N11**.



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Palladium-catalyzed ' on-water' tandem cyclization reactions for the synthesis of biologically important 4-arylquinazolines