



Palladium/copper-catalyzed cross-coupling reactions for the synthesis of 4-heteroaryl quinolinone



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ABSTRACT

A convenient and efficient approach for the synthesis of 4-heteroaryl quinolinones was developed via palladium/copper-catalyzed coupling reactions between 4-quinolinonyl triflates with benzothiazole/benzoxazole/thiazole/oxazole/benzimidazole. Biological evaluation revealed that some of the obtained products exhibited in vitro antiproliferative activities on human-derived live cancer cell lines.

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The family of quinolinones constitutes an important class of naturally occurring compounds and privileged medicinal scaffolds.¹ The characteristics of the substituents on a quinolinone core profoundly affect the biological activity. Among them, 4-substituted quinolinones have been extensively investigated because of their wide activities as antibacterial,² anticancer³ as well as enzyme inhibitor.⁴ Significant efforts have been directed toward developing efficient synthetic approaches to 4-substituted quinolinones in the past decades.⁵ Recently, we discovered that 4-indolyl substituted quinolinones displayed good antiproliferative activity against MCF7 with IC₅₀ values of 4.47 μM.⁶ Inspired by this result, we are interested in the development of a more straightforward synthetic route to various 4-heteroaryl substituted quinolinones and their related library construction.

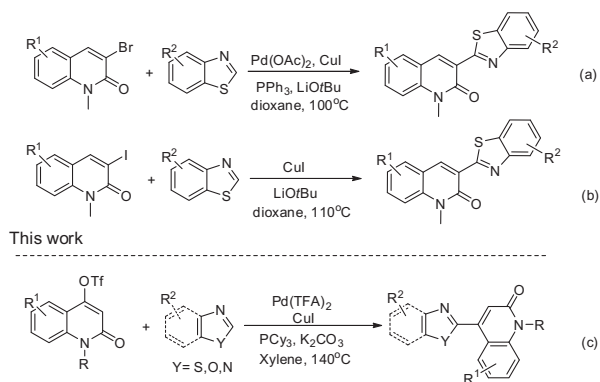
Benzothiazole are widely found in medicinal agents and are considered as privileged scaffolds.⁷ Recently various research groups have paid considerable attention to incorporate the benzothiazole unit into the quinolinone molecule to synthesize valuable biheteroaryls. For instance, the heteroarylation of 3-bromoquinolinones with benzothiazoles using Pd(OAc)₂/CuI bimetallic catalytic system in the presence of base and ligand was reported by Alami and co-workers (Scheme 1a).⁸ Hong realized an easy access to 3-benzothiazolyl quinolinones through cop-

per-mediated cross-couplings between 3-iodoquinolinones and benzothiazoles (Scheme 1b).⁹ However, the limited availability of substituted 3-iodoquinolinones and 3-bromoquinolinones, and rather limited substrate scope narrow their range of use. Moreover, with respect to the synthesis of 3-benzothiazolyl quinolinones, the development of 4-benzothiazolyl quinolinones is much less studied. Therefore, a simple new approach that provides direct and efficient access to 4-benzothiazolyl quinolinones remains highly in demand (Scheme 1c).

Since 4-hydroxyquinolinones could be readily prepared in gram-scale according to the known procedures described in the literature,¹⁰ we conceived that 4-quinolinonyl triflates **1** would be the choice for reaction development. Initially, we focused on the coupling of 4-quinolinonyl triflates **1a** and benzothiazole **2a** as test substrates to optimize the reaction conditions. Some screening results are shown in Table 1. As summarized, among those catalysts tested, Pd(TFA)₂ was found to be the most effective catalyst in the presence of PCy₃ (20 mol%), and K₂CO₃ (1 equiv.) in Xylene at 100 °C. On the contrary, the reaction did not work under the same conditions using PdSO₄, PdCl₂, PdBr₂, and Pd(OAc)₂ as catalysts (entries 1–5). With an attempt to improve the yield of the reaction, further efforts related to the influence of solvents were examined. The reaction failed to afford the desired product when DMF and NMP were employed (entries 7–8). While with DMSO, only trace of the product **3a** was detected (entry 6). Dioxane as solvent provided **3a** in 28% yield (entry 9). Xylene was the most suitable solvent and resulted in the desired product **3a** being obtained

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Scheme 1. Construction of benzothiazolyl quinolinones with different strategies.

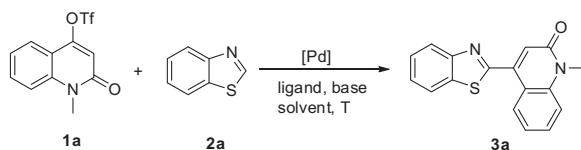
in 47% yield (entry 5). Ligands and bases, such as PPh₃, Dppe, Xantphos, Phen, Cs₂CO₃ or K₃PO₄, which have been used in Pd-catalyzed coupling reactions led to lower yields under the current reaction conditions (entries 10–15). The influence of temperature on the reaction was also investigated, and 140 °C was determined as optimum temperature for the formation of **3a** (entries 16–17). In addition, no beneficial effects were observed in the absence of base and decreasing the reaction concentration (entries 18–19). Of note, the use of CuI as cocatalyst led to a better yield (84%, entry 20). The reactions of decrease the amount of Pd(TFA)₂ or CuI were also conducted, but unfortunately, the yield was unsatisfactory although

the prolonged time was set. Therefore, we decided to use condition in entry 20 as the standard reaction conditions.

With the optimal conditions in hand, the scope of the transformation was investigated and the results are summarized in Table 2. As shown in Table 2, a series of 4-quinolinonyl triflates were screened. The reactions with 4-quinolinonyl triflates bearing either electron-rich or electron-deficient substituents (CH₃, OCH₃, Cl, F) at the phenyl moiety proceeded efficiently to afford the desired products (**3a–3e**) in moderate to good yields. Obviously, Substitution group (Et, Bn) on the quinolinone nitrogen core or N-H quinolinone had a little effect on the reaction efficiency. It was gratifying to find that polycyclic triflate **1f** also reacted smoothly with benzothiazole, leading to the corresponding product **3f** in 69% yield. To find the generality of this coupling reaction, a broad of benzothiazoles were further subjected to coupling with triflates. As can be seen, the presence of electron-donating groups (OMe) on benzothiazole leads to higher coupling yields than those with electron-withdrawing groups (Cl, Br) at the 5-position or 6-position. Moreover, this protocol could tolerate halides such as chloro and bromo moieties, which can offer versatile synthetic functionalization for further elaboration. 6-Cyanobenzothiazole was found to react with 4-quinolinonyl triflate to furnish the coupled product **3o** in 45% yield. Finally, expanding the scope from the benzothiazole core to a thiazole system was also possible, leading to the formation of **3p** in 85% yield (Table 3).

After exploring the versatility and diversity of the present palladium-catalyzed cross-coupling reaction of 4-quinolinonyl triflates with benzothiazoles, its application toward the synthesis of diverse 4-substituted quinolinone was explored. In this direction, a few

Table 1
Screening and optimization of the reaction conditions.



Entry ^a	[Pd]	Ligand/base	Solvent (mL)	Yield ^b (%)
1	PdCl ₂	PCy ₃ /K ₂ CO ₃	Xylene(2)	NR
2	PdBr ₂	PCy ₃ /K ₂ CO ₃	Xylene(2)	NR
3	PdSO ₄	PCy ₃ /K ₂ CO ₃	Xylene(2)	Trace
4	Pd(OAc) ₂	PCy ₃ /K ₂ CO ₃	Xylene(2)	Trace
5	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	Xylene(2)	47
6	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	DMSO(2)	Trace
7	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	DMF(2)	NR
8	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	NMP(2)	NR
9	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	Dioxane(2)	28
10	Pd(TFA) ₂	PPh ₃ /K ₂ CO ₃	Xylene(2)	14
11	Pd(TFA) ₂	Dppe/K ₂ CO ₃	Xylene(2)	Trace
12	Pd(TFA) ₂	Xantphos/K ₂ CO ₃	Xylene(2)	18
13	Pd(TFA) ₂	Phen/K ₂ CO ₃	Xylene(2)	NR
14	Pd(TFA) ₂	PCy ₃ /Cs ₂ CO ₃	Xylene(2)	Trace
15	Pd(TFA) ₂	PCy ₃ /K ₃ PO ₄	Xylene(2)	35
16 ^c	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	Xylene(1)	70
17 ^d	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	Xylene(1)	77
18 ^d	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	Xylene(2)	73
19 ^d	Pd(TFA) ₂	PCy ₃	Xylene(1)	56
20 ^{de}	Pd(TFA) ₂	PCy ₃ /K ₂ CO ₃	Xylene(1)	84

^a Reaction was performed with **1a** (0.25 mmol), **2a** (0.75 mmol), catalyst (5 mol%), ligand (20 mol%), base (0.25 mmol) at 100 °C for 12 h.

^b Isolated yield.

^c The reaction was performed at 120 °C.

^d The reaction was performed at 140 °C.

^e In the presence of 10 mol% CuI.

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