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Communication

Palladium-catalyzed oxidative homocoupling of 2-arylquinazolinones

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ABSTRACT

Pd-catalyzed oxidative homocoupling of 2-arylquinazolinones was successfully developed for the direct construction of biaryls *via* C—H bond activation. New well-defined structure that possessed two quinazolinone units was obtained with high efficiency and atomic economy. The protocols offer an efficient approach to the synthetically useful and functionalized biaryls in good yields using quinazolinone as a directing group.

Biaryls have attracted considerable attention in the fields of electrochemistry, photochemistry and biochemistry, because they are privileged π-conjugated cores in biologically active molecules, advanced functional materials, ligands, and synthetic intermediates [1]. Over the last decade, metal-catalyzed direct dehydrogenative coupling reactions *via* dual C–H bond activation have been developed as the most attractive and powerful approaches to biaryls, since the starting materials could be used directly without prior functionalization, and the sole byproduct would only be 2 equiv. of H^+ [2]. In 1965, van Helden and Verberg disclosed the first oxidative C—H/C—H coupling of aromatic compounds in the presence of stoichiometric amounts of $PdCl_2$ to synthesize biaryls [3]. Subsequently, in 2006, Lu and co-workers disclosed an intermolecular cross-coupling of simple arenes *via* C—H activation for synthesis of biaryls employing $Pd(OAc)_2$/TFA/$K_2S_2O_8$ as the catalytic system [4]. After that, the regioselective palladium-catalyzed homocoupling of indolizines was also demonstrated by You and co-workers in 2009 [5]. Recently, Zhou and Wang reported an efficient oxidative homocoupling of benzene to synthesize biaryls by using O_2 as the sole oxidant, in which low catalyst loading ($Pd(OAc)_2$, 0.07 mol%) was required [6]. Also noteworthy is a palladium-catalyzed oxidative homocoupling of 3-arylbenzo[*d*]-isoxazoles *via* direct C—H bond activation using benzoisoxazole as a new directing group reported by Ji group simultaneously [7].

As well-known, quinazolinone has become increasingly valuable framework because of its biological activities, such as antibacterial, antifungal, antimalarial, anticancer, antihypertensive, antitubercular, and anticonvulsant [8]. Logically, biaryls with two quinazolinone units could be potentially used for the development of new drugs or advanced functional materials. For example, compounds **I** and **II** (Fig. 1) show activity against Gram-positive and Gram-negative bacteria and yeasts [9].

Recently, our group has developed a series of easy methods for modification of arene *via* C–H bond activation, in which quinazolinones act as directing groups since there are two N atoms in the molecule [10]. However, to the best of our knowledge, no example was reported on the direct construction of biaryls with two 2-arylquinazolinone units. In our continuing effort to build new molecules through C–H bond activation [11], herein, we present a Pd-catalyzed oxidative homocoupling of 2-arylquinazolinones with O_2 as an oxidant using quinazolinone as a directing group (Scheme 1). New well-defined structure possessed two 2-arylquinazolinone units was obtained with high efficiency and atomic economy. This protocol features simple operation, easily available starting materials, high efficiency, environmental friendliness, and tolerance of a wide range of substrates.

Initially, 2-phenylquinazolin-4(3*H*)-one (**1a**) was chosen as a model substrate to examine the impact of various parameters on the reaction (Table 1). The results revealed that 2,2′-([1,1′-biphenyl]-2,2′-diyl)bis(quinazolin-4(3*H*)-one) (**2a**) was

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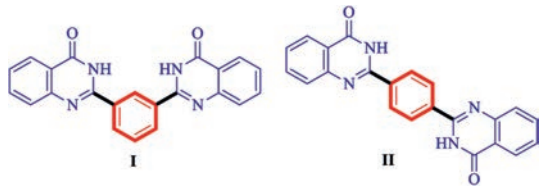
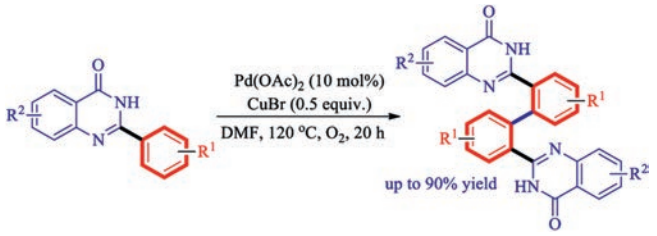


Fig. 1. Biologically active biaryls containing two quinazolinone units.

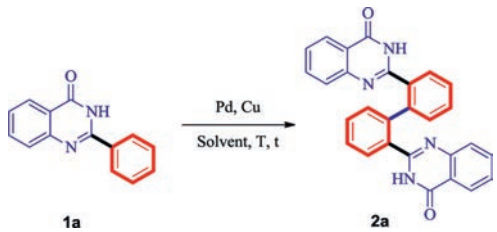


Scheme 1. Oxidative homocoupling of 2-arylquinazolinones.

obtained as a main product in 58% yield in DMF at 120 °C when $Pd(OAc)_2$ (10 mol%) was used as a catalyst with CuI (0.5 equiv.) under O_2 (1 atm) (Table 1, entry 1). Only 25% yield of the target product **2a** was achieved when the reaction was carried out under air atmosphere (Table 1, entry 2). No product was obtained under N_2 protection (Table 1, entry 3). Palladium salts, such as $PdCl_2$, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were screened. $Pd(OAc)_2$ gave the highest yield (Table 1, entry 1, entries 5–7). The reaction did not occur in the absence of Pd salt (Table 1, entry 4). Moreover, CuBr favors this reaction than other Cu salts (Table 1, entry 1, entries 8–13), and the yield of **2a** was increased to 90% in the presence of CuBr. DMF was demonstrated to be better than other solvents, such as DMA, DMSO, DCE and NMP (Table 1, entry 9 *vs.* entries 14–17). In addition, the yield of **3a** was decreased when the reaction temperature and reaction time were changed (Table 1, entries 18–21). However, when other oxidants were used in the reaction, such as oxone and TBHP, only 31% and 19% yields of **2a** were achieved, respectively (Table 1, entries 22–23). Based on the results, the optimal reaction conditions were identified as follows: DMF as solvent, at 120 °C, $Pd(OAc)_2$ (10 mol%) as a catalyst with CuBr (0.5 equiv.) under O_2 (Table 1, entry 9).

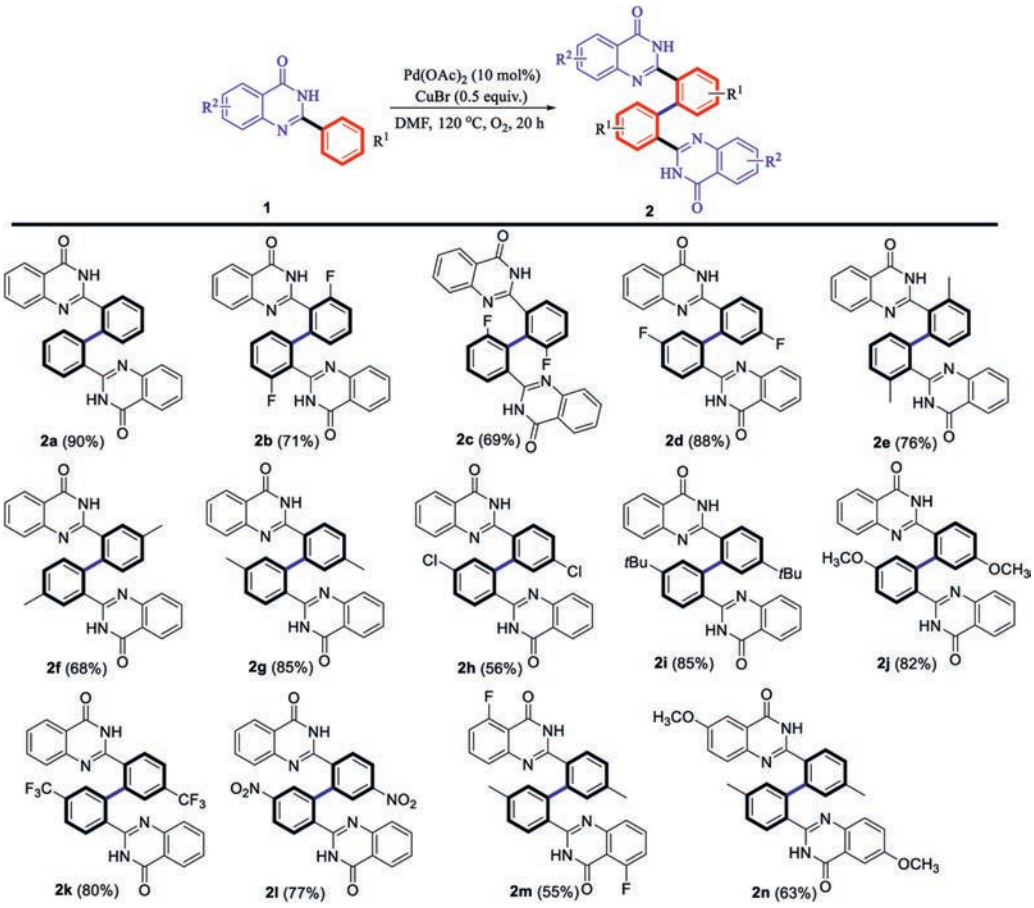
With the optimized reaction conditions in hand, the scope of the substrates was examined (Scheme 2). 2-Phenylquinazolin-4

Table 1
Optimization of the reaction conditions.[a]

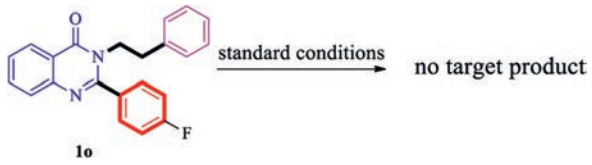


Entry	Pd	Cu	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	CuI	DMF	120	20	58
2[c]	$Pd(OAc)_2$	CuI	DMF	120	20	25
3[d]	$Pd(OAc)_2$	CuI	DMF	120	20	nd
4	–	CuI	DMF	120	20	nd
5	$PdCl_2$	CuI	DMF	120	20	trace
6	$Pd(PPh_3)_4$	CuI	DMF	120	20	nd
7	$Pd_2(dba)_3$	CuI	DMF	120	20	nd
8	$Pd(OAc)_2$	–	DMF	120	20	nd
9	$Pd(OAc)_2$	CuBr	DMF	120	20	90
10	$Pd(OAc)_2$	CuCl	DMF	120	20	46
11	$Pd(OAc)_2$	$Cu(NO_3)_2$	DMF	120	20	21
12	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	120	20	45
13	$Pd(OAc)_2$	$CuSO_4$	DMF	120	20	39
14	$Pd(OAc)_2$	CuBr	DMA	120	20	63
15	$Pd(OAc)_2$	CuBr	DMSO	120	20	nd
16	$Pd(OAc)_2$	CuBr	DCE	120	20	nd
17	$Pd(OAc)_2$	CuBr	NMP	120	20	trace
18	$Pd(OAc)_2$	CuBr	DMF	110	20	65
19	$Pd(OAc)_2$	CuBr	DMF	130	20	87
20	$Pd(OAc)_2$	CuBr	DMF	120	18	62
21	$Pd(OAc)_2$	CuBr	DMF	120	22	85
22[e]	$Pd(OAc)_2$	CuBr	DMF	120	22	31
23[f]	$Pd(OAc)_2$	CuBr	DMF	120	22	19

nd = not detected.
[a] Reaction conditions: **1a** (0.20 mmol), Pd (10 mol%), Cu (0.5 equiv.), solvent (2.0 mL), O_2 (1 atm).
[b] Isolated yields.
[c] Air.
[d] N_2.
[e] Oxone was used as oxidant.
[f] TBHP was used as oxidant.

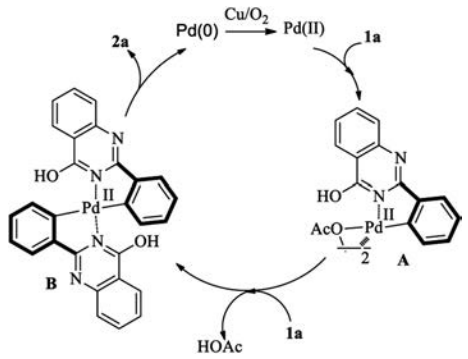


Scheme 2. Scope of substrates. Reaction conditions: **1a** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), CuBr (0.5 equiv.), DMF (2.0 mL), O_2 (1 atm). Isolated yields.



Scheme 3. Control experiments.

(3*H*)-one (**1a**) and its derivatives could react smoothly to give biarlys (**2a**-**2n**) in moderate to good yields (55%–90%). F or methy at the *ortho*-, *meta*-, and *para*-position of 2-phenyl in 2-aryl-quinazolin-4(3*H*)-ones provided the corresponding products **3b**-**3g** in 71%, 69%, 88%, 76%, 68%, and 85% yields, which indicated that steric effect of 2-aryl group slightly impacted this transformation. Other groups, such as Cl, *t*-butyl, methoxyl, trifluoromethyl, and nitryl could be well tolerated and gave the corresponding products in satisfactory yields (**3h**–**3L**) (56%–85%). These results indicated that the electron density on the moiety of the phenyl did not significantly influence the efficiency of the coupling reaction. 2-(*meta*-Fluoro)phenylquinazolin-4(3*H*)-one gave the hindered C2-coupling product **2c**, isolated with 69% yield, perhaps due to the *ortho*-directing effect of the F atom, in which C3 fluoro atom enhances the acidity of C2 proton. While, C6-coupling product **2f** at less hindered position was obtained in 68% yield as sole isomer. Moreover, the reaction of 5-fluoro-2-(*p*-tolyl)quinazolin-4(3*H*)-one and 6-methoxy-2-(*p*-tolyl)quinazolin-4(3*H*)-one proceeded smoothly under the standard reaction conditions to give the corresponding products **2m** and **2n** in 55% and 63% yields. However, when two different 2-arylquinazolinones were loaded in the reaction, such as 2-phenylquinazolin-4(3*H*)-one (**1a**) and 2-(*p*-tolyl)quinazolin-4(3*H*)-one (**1g**), the reaction was complex and gave the mixture of homo- and cross- coupling products.



Scheme 4. Proposed reaction mechanism.

To confirm which N atom of quinazolinone playing as the directing group, NH-protected quinazolinone was used as the substrate. No target product was obtained when 2-(4-fluoro-phenyl)-3-phenethylquinazolin-4(3*H*)-one (**1o**) was treated under the optimized reaction conditions (Scheme 3). The result suggested that nitrogen (NH) of quinazolinones might act as a directing group to coordinate with Pd(II).

Based on the results obtained and the literatures [12], a plausible reaction mechanism is proposed for the direct homocoupling of 2-

phenylquinazolin-4(3*H*)-one (Scheme 4). Firstly, the dimeric cyclopalladated intermediate **A** was formed through the coordination of Pd(II) with **1a**, followed by C—H bond activation/cleavage. Then, the single-core intermediate **B** was enabled through the second C—H bond activation of another substrate molecule (**1a**). Finally, intermediate **B** underwent a subsequent reductive elimination to give the homo-coupled product **2a** as well as Pd(0) species, which was oxidated into the active Pd(II) species for next catalytic cycle.

In summary, we have demonstrated a Pd-catalyzed aerobic oxidative homocoupling of 2-arylquinazolinones to synthesize 2,2′-([1,1′-biphenyl]-2,2′-diyl)bis(quinazolin-4(3*H*)-one), in which quinazolinone acts as a directing group. The well-defined products that possessed two quinazolinone units were obtained with high efficiency and atomic economy. This approach provided a fast pathway for atom/step economical syntheses of useful biaryls. Further study on the applications of this reaction is ongoing in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.03.080.

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