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Tandem-type Pd(II)-catalyzed oxidative Heck reaction/intramolecular C–H amidation sequence: a novel route to 4-aryl-2-quinolinones†

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A novel catalytic method for synthesizing 4-aryl-2-quinolinones is reported. The process involves two mechanistically independent, sequential Pd(II)-catalyzed reactions—the oxidative Heck reaction and the intramolecular C–H amidation—both of which smoothly proceed in the presence of a single catalytic system in a one-pot manner.

2-Quinolinones are an important class of heterocycles, which have long been known to exhibit a range of biological properties.¹ In particular, there is increasing interest in several analogues of 4-aryl-2-quinolinones, including natural products² and compounds that are currently in clinical trials.³ Although various strategies have so far been developed to access 2-quinolinone structural motifs, there are only few reports on transition metal-catalyzed approaches, which would provide a more efficient and practical route.⁴ Noteworthy examples were recently reported by Kadnikov and Larock,^{4f} Cacchi and Fabrizi *et al.*,^{4d} and Willis *et al.*^{4b} who successfully developed palladium-catalyzed cyclization processes for preparing 2-quinolinones. Very recently, Yu *et al.* found that 3,3-diarylacrylamides can undergo palladium-catalyzed C–H functionalization followed by intramolecular amidation, providing a novel route to 4-aryl-2-quinolinones.^{4a,5–7}

On the other hand, the rapid construction of complex molecules through multiple bond-forming reactions in a single step, the so-called tandem process, can be a powerful tool for synthetic organic chemists. Such processes reduce the steps in the synthesis of certain molecules; thus, being attractive from the viewpoint of developing environmentally benign and economical synthetic methods. Inspired by the work of Cacchi and Fabrizi, who employed a Pd(0)-catalyzed tandem-type Mizoroki–Heck reaction/intramolecular Buchwald–Hartwig amidation sequence for the synthesis of 2-quinolinones [Fig. 1(a)],^{4d} and with the success of Yu's as well as ours in using catalytic C–H cyclization in the synthesis of 2-quinolinones [Fig. 1(b)],^{4a,5} we envisioned a tandem process consisting of the oxidative Heck reaction of cinnamamides with arylboron compounds^{8,9} followed by the intramolecular C–H amidation reaction. Both of the above can be catalyzed by Pd(II),

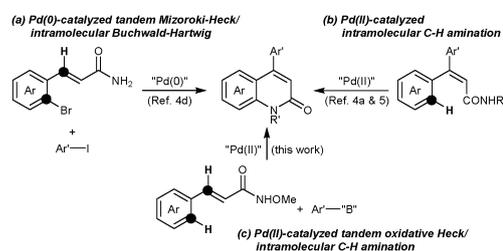


Fig. 1 Synthesis of 2-quinolinones via palladium-catalyzed processes.

leading to a facile and novel route to 4-aryl-2-quinolinone derivatives [Fig. 1(c)]. In this communication, we describe in detail the envisioned process in an effort to substantiate it.¹⁰

To probe the viability of the anticipated Pd(II)-catalyzed tandem process, we examined the reaction of *N*-methoxycinnamamide (**1a**) with 2,4,6-triphenylboroxin at 100 °C in the presence of 30 mol% of the Pd(OAc)₂/1,10-phenanthroline (1,10-phen) catalyst system (Table 1). Using AcOH as the solvent, we first evaluated the effect of the reoxidant. Interestingly, we found that the use of a copper salt as reoxidant delivered the 2-quinolinone compound, although the yields were low (entries 3–5). In these cases, demethoxylation unexpectedly occurred during the reaction, resulting in the formation of 2-quinolinone **3**, 3,3-diphenylacrylamide, resulting from Pd(II)-catalyzed oxidative Heck reaction followed by demethoxylation, was also formed as a minor product.¹¹ The subsequent screening revealed that the use of 1 equiv. of a silver salt as an additional reoxidant greatly enhanced the process. Among the silver salts tested (entries 6–8), Ag₂O gave the best results, providing 2-quinolinone **3** in 68% yield (entry 8). Although a reduced amount of the catalyst provided a decreased yield (entry 8 vs. entry 9), subsequent screening of the boron source (entries 9–12) indicated that phenylboronic acid showed better reactivity, generating **3** in fairly good yield (60%) in the presence of 10 mol% of the catalyst (entry 12). Further optimization studies resulted in another interesting finding. Namely, the use of increased amounts of Ag₂O (e.g., 4–10 equiv.) completely inhibited demethoxylation, leading to the formation of 2-quinolinone **2aa** (entries 13–16 vs. 12).¹² The best result was obtained when 8 equiv. of Ag₂O was employed, affording 2-quinolinone **2aa** in 76% yield (entry 15). With this catalyst system, carrying out the reaction first at 100 °C for 1 h and then at 120 °C for 10 h provided slightly better results (entry 17). The reaction under O₂ resulted in decreased yield (entry 18). The use of Ag₂O alone as reoxidant was not effective, and **2aa** (44%) and 3,3-diphenyl-*N*-methoxyacrylamide (Heck-product, 44%) were

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Table 1 Optimization of reaction conditions^a

Entry	Ph-B	X (mol%)	Reoxidant (equiv.)	Yield ^b (%)		
				2aa	3	1a
1	(PhBO) ₃	30	K ₂ S ₂ O ₈ (2)	0	0	0
2	(PhBO) ₃	30	Oxone (2)	0	4	0
3	(PhBO) ₃	30	Cu(OAc) ₂ (2)	0	19	0
4	(PhBO) ₃	30	Cu(OAc) ₂ · <i>n</i> H ₂ O (2)	0	22	0
5	(PhBO) ₃	30	Cu(TFA) ₂ · <i>n</i> H ₂ O (2)	0	31	0
6	(PhBO) ₃	30	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + Ag ₂ CO ₃ (2)	0	50	0
7	(PhBO) ₃	30	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + AgOAc (2)	0	53	0
8	(PhBO) ₃	30	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + Ag ₂ O (2)	0	68	0
9	(PhBO) ₃	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + Ag ₂ O (2)	0	49	0
10		10	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + Ag ₂ O (2)	0	48	0
11	PhBF ₃ K	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + Ag ₂ O (1)	0	55	0
12	PhB(OH) ₂ 10	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + Ag ₂ O (1)	0	60	0
13	PhB(OH) ₂ 10	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (2) + Ag ₂ O (4)	66	0	0
14	PhB(OH) ₂ 10	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (1) + Ag ₂ O (4)	64	0	12
15	PhB(OH) ₂ 10	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (1) + Ag ₂ O (8)	76	0	0
16	PhB(OH) ₂ 10	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (1) + Ag ₂ O (10)	65	0	0
17 ^c	PhB(OH) ₂ 10	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (1) + Ag ₂ O (8)	81	0	0
18 ^d	PhB(OH) ₂ 10	10	Cu(TFA) ₂ · <i>n</i> H ₂ O (1) + Ag ₂ O (8)	54	0	28
19	PhB(OH) ₂ 10	10	Ag ₂ O (8)	44	0	0
20	PhB(OH) ₂ 10	10	None	0	0	16 ^e
21	PhB(OH) ₂ 0	0	Cu(TFA) ₂ · <i>n</i> H ₂ O (1)	0	0	53 ^f
22	PhB(OH) ₂ 0	0	Ag ₂ O (8)	0	0	95

^a Reactions were carried out on a 0.11 mmol scale. ^b Isolated yield. ^c The reaction mixture was first stirred at 100 °C for 1 h and then stirred at 120 °C for 10 h. ^d Under an O₂ atmosphere. ^e 14% of demethoxylated cinnamamide was obtained. ^f 22% of demethoxylated cinnamamide was obtained.

obtained (entry 19). Essentially, the reaction without the reoxidant did not furnish any cyclized products (entry 20). Furthermore, performing the reaction without the palladium catalyst failed to produce any coupling or cyclized products (entries 21 and 22).¹³

To prove the generality of the method, the tandem process affording 2-quinolinones *via* the formation of symmetrical 3,3-diarylacrylamides was next examined (Table 2). Reactions of the substrate that has a methyl group or a halogen atom at the *para*-positions of the benzene rings proceeded efficiently (entries 3–5); whereas that of cinnamamide **1e**, possessing a methoxy group, resulted in the formation of the desired 2-quinolinone **2ee** only in 12% yield along with the recovery of the starting **1e** in 85% yield (entry 6). In the case of the reaction of **1f**, which possesses a methyl group at the *meta*-position of the

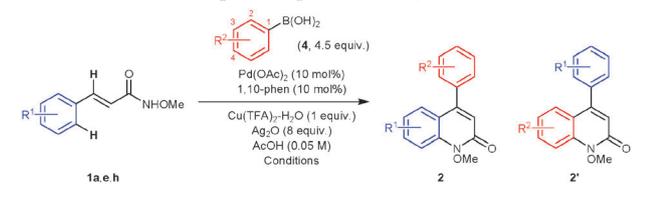
Table 2 2-Quinolinone synthesis *via* symmetrical 3,3-diarylacrylamides^a

Entry	Substrate 1	4 (R)	Conditions ^b	Product 2	Yield ^c (%)
1		4a (H)	A (<i>t</i> ¹ = 13)		76
2		4a (H)	B (<i>t</i> ¹ = 1, <i>t</i> ² = 10)		81
3		4b (4-Me)	A (<i>t</i> ¹ = 16)		76
4		4c (4-F)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 43)		59
5		4d (4-Cl)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 10)		61
6		4e (4-OMe)	A (<i>t</i> ¹ = 12)		12 ^d
7		4f (3-OMe)	A (<i>t</i> ¹ = 12)		68
8		4g (2-Me)	A (<i>t</i> ¹ = 13)		0 ^e

^a Reactions were carried out on a 0.11 mmol scale. ^b Conditions A: carried out at 100 °C for *t*¹ h. Conditions B: carried out at 100 °C for *t*¹ h and then 120 °C for *t*² h. ^c Isolated yield. ^d 85% of **1e** was recovered. ^e 34% of **1g** was recovered.

benzene ring, the C–H cyclization occurred at the less hindered site, exclusively affording 2-quinolinone **2ff** (entry 7). In contrast, the introduction of a methyl group at the *ortho*-position of the benzene ring did not result in the formation of the coupling or cyclized product (entry 8).

The substrate scope of the process was further examined using a variety of arylboronic acids (Table 3). Although 4-methoxyphenylboronic acid **4e** was not suitable for the process (entry 1), various arylboronic acids possessing a trifluoromethyl group, a methoxy-carbonyl group, or a halogen atom on the benzene ring (R²)

Table 3 Substrate scope of 2-quinolinone synthesis^a

Entry	Substrate 1	4 (R ²)	Conditions ^b	Yield of 2 + 2' (%) (2 : 2')
1		4e (4-OMe)	A (<i>t</i> ¹ = 9)	trace ^d
2		4h (4-CF ₃)	A (<i>t</i> ¹ = 12)	57 (57:0)
3		4i (3-CF ₃)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 48)	67 (67:0)
4		4j (4-CO ₂ Me)	A (<i>t</i> ¹ = 17)	64 (64:0)
5		4a (H)	A (<i>t</i> ¹ = 15)	69 (41:28)
6		4h (4-CF ₃)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 26)	60 (60:0)
7		4i (3-CF ₃)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 48)	48 (48:0)
8		4j (4-CO ₂ Me)	A (<i>t</i> ¹ = 17)	57 (57:0)
9		4c (4-F)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 43)	56 (40:16)
10		4d (4-Cl)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 48)	85 (59:26)
11		4k (4-Br)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 43)	66 (50:16)
12		4a (H)	A (<i>t</i> ¹ = 13)	62 ^e (62:0)
13		4h (4-CF ₃)	B (<i>t</i> ¹ = 3, <i>t</i> ² = 42)	53 ^e (53:0)
14		4d (4-Cl)	A (<i>t</i> ¹ = 15)	72 ^e (72:0)

^a Reactions were carried out on a 0.11 mmol scale. ^b Conditions A: carried out at 100 °C for *t*¹ h. Conditions B: carried out at 100 °C for *t*¹ h and then 120 °C for *t*² h. ^c Isolated yield. ^d 99% of starting **1a** was recovered. ^e 4-Aryl-6-methoxy-2-quinolinone was exclusively obtained.

successfully underwent reaction, affording different substituted 4-aryl-2-quinolinones generally in good to high yields (entries 2–14). When cinnamamide **1e** was employed, the reaction sometimes gave a mixture of 2-quinolinones **2** and **2'**, indicating that the *E*-/*Z*-isomerization could be occurring during the reaction course (entries 5 and 9–11).

In conclusion, we have reported a Pd(II)-catalyzed, tandem-type oxidative Heck reaction/intramolecular C–H amidation sequence, leading to a conceptually new, efficient method for the construction of 4-aryl-2-quinolinone scaffolds. Readily available, variously substituted cinnamamides and arylboronic acids were smoothly reacted in the presence of the PdCl₂/1,10-phen catalyst system along with the copper/silver reoxidant. Studies to improve the yields as well as to broaden the substrate scope are currently underway.

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