

A Simple Catalytic Synthesis of Condensed Pyridones from *o*-Bromoarylcarboxamides Involving *ipso* Substitution via Palladacycles

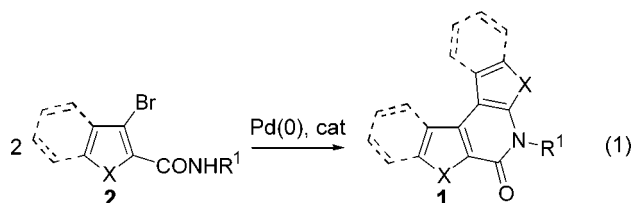
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Palladacycles are key intermediates in inter- and intramolecular cross-coupling reactions.¹ We recently described a catalytic procedure involving palladacycles,² which has been applied to the synthesis of condensed quinolin-4(5*H*)-ones shown in Scheme 1, starting from *o*-substituted iodoarenes and amides of *o*-bromo arene- and heteroarene-carboxylic acids.³ The reaction has been carried out in the presence of norbornene, Pd(OAc)₂/2-trifurylphosphine (TFP) and K₂CO₃ in DMF.

Surprisingly, in the absence of norbornene, coupling of two molecules of the *o*-bromoaromatic carboxamide followed an unpredictable pathway, which is the subject of this preliminary communication. Symmetrically condensed pyridones **1** were obtained simply starting from **2** (X = HC=CH, S, O, N-Me), in the presence of Pd(OAc)₂/TFP as the catalyst, K₂CO₃ as a base in DMF at 105 °C (eq 1). Under these conditions, compounds **1** were isolated in 23–86% yield (Table 1).



As shown in Table 1, the reaction readily occurs using secondary amides with N-bonded Me, PMB, and Ph, while the primary ones did not give the expected products (e.g., entry 6). In addition to **1a** (23%) and **1b** (30%) the reactions of **2a** and **2b** gave compounds **3** and **4** in 34% and 20% yield, respectively (Figure 1). As we shall see, these compounds derive from the same initial steps as for **1a** and **1b**.

Scheme 2 shows a possible reaction pathway (TFP ligand is omitted). Palladium(0) oxidatively adds to the Br-amide **2** in the first step. At this point, we suggest that complex **5** gives rise to a five-membered palladacycle **6**,⁵ in which the CONHR¹ group takes part in the construction of a metallacycle. This favors further reaction with a second molecule of **2** possibly through an oxidative addition process involving a palladium(IV) species⁶ leading to C–C bond formation in a new palladium complex **7** (Scheme 2). The latter then undergoes intramolecular *ipso* aromatic substitution at the carbon atom bearing the CONHR¹ with formation of **1**, amine, and CO₂.⁷ Accordingly the reaction of **2c** (R¹ = Ph) gave aniline (¹H NMR of the crude), which was isolated as 1-(PMB)-3-phenylurea (23% yield) after addition of an excess of PMBNCO to the crude. To account for this result we propose that the aminocarbonyl group is attacked by the palladium-bonded bicarbonate anion (formed by exchange of the Pd–Br bond with KHCO₃). This would lead to the unstable carbamic carbonic mixed anhydride HOCOOCONHPh, which decomposes to amine and two

Scheme 1

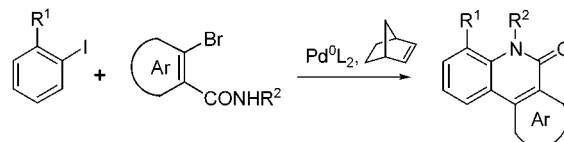


Table 1. Pd-catalyzed Synthesis of **1**^a

	2	R ¹	Time (h)	1 yield (%) ^b
1		Me	20	 1a , 23 ^c
2		Me	24	 1b , 30 ^d
3		Me	20	 1c , 75
4	2c	PMB ^e	48	1c , 50 (74) ^f
5	2c	Ph	24	1c , 86
6	2c	H	24	– ^g
7		Me	48	 1d , 71 ^h
8		Me	20	 1e , 52

^a Reaction conditions: **2** (0.45 mmol, 1 equiv), Pd(OAc)₂ (5 mol %), TFP (10 mol %), K₂CO₃ (2 equiv), DMF (10 mL) at 105 °C. Reaction conditions were not optimized. Unless otherwise indicated, conversion of **2** was complete. ^b Isolated yield. ^c 34% yield of **3** (see Figure 1). ^d 20% yield of **4** (see Figure 1). ^e *p*-Methoxybenzyl. ^f In parentheses the yield in the presence of aniline (0.5 equiv). ^g No trace of **1c** was observed; only **2c** and dehalogenated **2c** were isolated in ca. 25 and 9% yield. ^h 90% conversion. ⁱ 80% conversion.

molecules of CO₂.⁸ C–N bond-forming reductive elimination regenerates palladium(0), and the reaction turns out to be catalytic. To our knowledge this process is unprecedented.

The amine R¹NH₂ itself resulting from the *ipso*-substitution process can compete, if sufficiently nucleophilic, with the inorganic

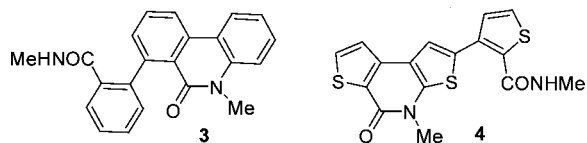
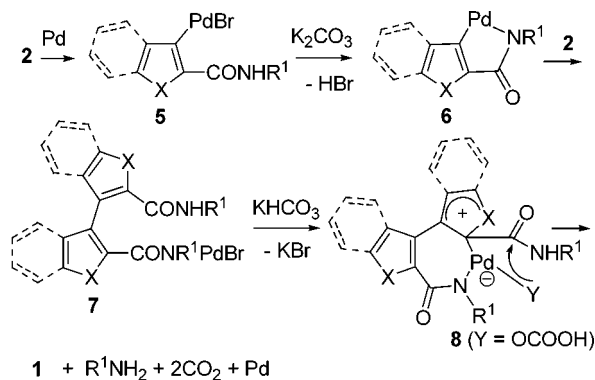
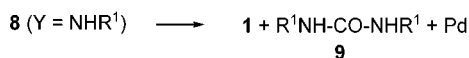


Figure 1. Other products of reaction 1.

Scheme 2



Scheme 3



base for the attack on the aminocarbonyl group leading to **1** and the symmetrically substituted urea **9** (Scheme 3).⁹

Since a possible alternative to the pathway shown in Scheme 3 could involve elimination of R^1NCO , followed by the reaction with a molecule of R^1NH_2 , we performed the reaction of **2c** ($R^1 = PMB$) (2 equiv) in the presence of aniline (1 equiv) to eventually trap the isocyanate. Under these conditions, no trace of the expected urea $PhNH-CO-NHPMB$ was observed, whereas **9** was isolated in 50% yield.¹⁰

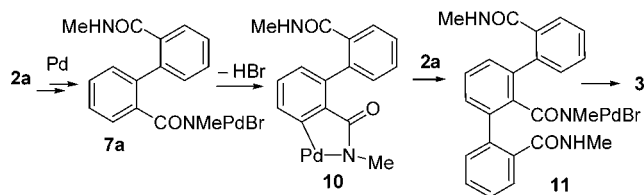
The absence of the mixed urea in this experiment also suggests that a scarcely nucleophilic amine such as aniline, is less prone to react with the $CONHR^1$ group. In fact, we were not able to get any evidence for *N,N*-diphenylurea formation in the reaction of **2c** ($R^1 = Ph$).

Further support to the proposed reaction course comes from the following observations: (a) bis-amides corresponding to hydrogenolysis of complex **7** were found as byproducts (ca. 10%) in reactions of **2c** and **2d**. They turned out to be stable under basic conditions in the absence of palladium (CS_2CO_3 , DMF, 105 °C), suggesting that the presence of the metal is needed for *ipso* substitution according to the mechanism of Scheme 2; (b) we prepared the hydrogenolysis product of complex **7a** ($R^1 = Ph$) and caused it to react with $PdCl_2(MeCN)_2$ to form **1a** ($R^1 = Ph$) via the palladium chloride complex corresponding to **7a** ($R^1 = Me$) (Scheme 2). A small but significant amount of **1a** was obtained (ca. 5% yield after 2 h at 105 °C) with palladium black separation and almost complete recovery of the starting compound; (c) the formation of compound **3**, which is the main product in the reaction of **2a** ($R^1 = Me$) (Figure 1, Table 1), implies the intermediacy of **7a** to give palladacycle **10** (Scheme 4).^{1b,11} The latter will allow the reaction of another molecule of **2a** to form **11** and finally **3** through *ipso* substitution, which is preferred to attack on one of the two aromatic C–H available.^{11a}

A different pathway leads to product **4** (Figure 1), the formation of which must be interpreted as deriving from further attack of **2b** to the thienopyridone **1b**.^{7,12}

Noteworthy, the selectivity of the reactions with benzocondensed *o*-bromo-heterocyclic amides **2c–e** increased, C–H activating arylation being not feasible (entries 3–8).

Scheme 4



In summary, a catalytic multistep process based on a novel reaction sequence combining the palladacycle-catalyzed homocoupling of **2** with intramolecular aromatic *ipso* substitution leads to **1** under mild conditions. They belong to the class of 6-phenanthridinones and their heterocyclic analogues, which show promising biological activity.¹³ We believe that the present work opens up the access to important classes of compounds through one-pot procedures much simpler than the conventional ones.^{3,13}

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Supporting Information Available: Experimental procedures and characterization for compounds **1–4** and hydrogenolysis product from **7c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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