



# Palladium-catalyzed three-component coupling reactions of 2-(cyanomethyl)phenol, aryl halides, and carbon monoxide



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## ABSTRACT

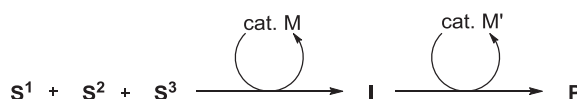
Three-component coupling reactions of 2-(cyanomethyl)phenol, aryl halides, and carbon monoxide (CO) in orthogonal–tandem catalysis were investigated. In the reactions, 2-(cyanomethyl)phenyl esters, which are produced through Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed alkoxycarbonylation of aryl halides with 2-(cyanomethyl)phenol, undergo cycloisomerization in situ catalyzed by Pd(PCy<sub>3</sub>)<sub>2</sub> as a co-catalyst to give 3-acyl-2-aminobenzofurans. Palladium species with homoleptic tertiary phosphines, such as Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd(PCy<sub>3</sub>)<sub>2</sub>, can catalyze the mechanistically distinct reactions in an orthogonal–tandem manner without interference. By switching the base used in this reaction, 3-acyl-2-(*N*-acylamino)benzofurans were obtained as major products instead of 3-acyl-2-aminobenzofurans. Given that 2-(cyanomethyl)phenols can be synthesized from commercially available salicylic acid derivatives in two steps, the present method thus provides facile access to synthetically useful 3-acyl-2-aminobenzofurans.

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## 1. Introduction

Cascade and tandem reactions provide efficient access to structurally complex molecules from simple and readily available starting materials.<sup>1</sup> Almost all such reactions involve both inter- and intramolecular multibond-forming processes and they are usually straightforward to perform. Ideally, these approaches can minimize the amount of reagent, cost, byproduct formation, time, and complexity of separation processes required for a desired transformation. The development of step-economic processes through the use of tandem reactions involving different types of reactions promoted by more than two catalysts is a challenging subject.<sup>2</sup> In this context, we have developed a number of transition metal-catalyzed cascade reactions.<sup>3,4</sup> We have recently reported the one-pot synthesis of hetero  $\alpha,\alpha'$ -dimers of heterocycles involving the Sonogashira reaction of acyclic coupling partners and subsequent cycloisomerization reactions catalyzed by Pd and Cu species.<sup>3</sup> These examples represent a strategy that has been classified as orthogonal–tandem catalysis (Scheme 1).<sup>2d</sup> We have also developed palladium-catalyzed cycloisomerization reactions based on intramolecular

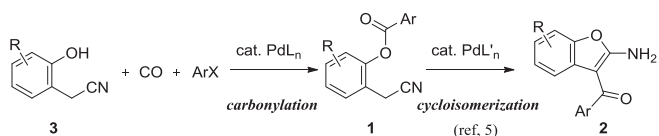
oxypalladation to a C–N triple bond of 2-(cyanomethyl)phenyl esters **1** leading to 3-acyl-2-aminobenzofurans **2**<sup>5</sup> (the downstream reaction presented in Scheme 2).<sup>6</sup> In the course of our studies, we envisioned that the carbonylation reaction of aryl halides with 2-cyanomethylphenols **3** (the upstream reaction presented in Scheme 2) could be combined with such cycloisomerization reactions for the short step synthesis of 3-acyl-2-aminobenzofurans **2**. Ideally, the mechanistically discrete reaction cascade could be catalyzed by a single catalyst; however, when more than two catalysts are required, it is essential for efficient operation that there is no interference between catalysts. Here, we wish to report an efficient and straightforward synthesis of 3-acyl-2-aminobenzofurans **2** by employing three-component coupling reactions of 2-(cyanomethyl)phenol derivatives **3**, aryl halides, and CO, catalyzed by two homoleptic tertiary phosphine-ligated palladium(0) species (Scheme 2). Because 3-acyl-2-aminobenzofurans have both an amino and a carbonyl group, they are useful building blocks for the synthesis of a range of benzofuran-fused heterocycles.



Scheme 1. Orthogonal-tandem catalysis (M=M' or M≠M').

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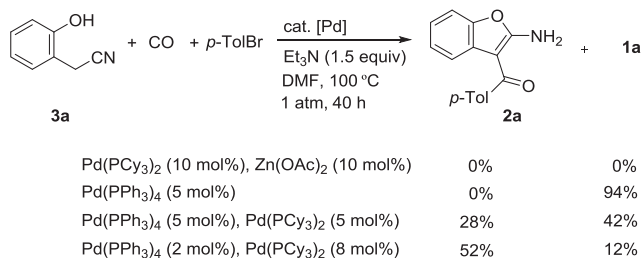
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**Scheme 2.** Palladium-catalyzed cycloisomerization (the downstream reaction) and carbonylation (the upstream reaction).

## 2. Results and discussion

Initially, the palladium-catalyzed, three-component coupling reaction of 2-(cyanomethyl)phenol **3a** and 4-bromotoluene (1.5 equiv) in the presence of Et<sub>3</sub>N (1.5 equiv) in DMF at 100 °C under a CO atmosphere (1 atm) for 40 h was examined.<sup>7</sup> Although Pd(PCy<sub>3</sub>)<sub>2</sub> was effective for the cycloisomerization of 2-(cyanomethyl)phenyl ester **1a** into 3-acyl-2-aminobenzofuran **2a**,<sup>5</sup> it was ineffective in the three-component coupling reaction even in the presence of Zn(OAc)<sub>2</sub> (10 mol%) as an additive (Scheme 3). The use of Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) led to the selective formation of **1a** (94%) with none of **2a**.<sup>8</sup> However, when the reaction was carried out in the presence of both Pd(PCy<sub>3</sub>)<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol% each), **2a** was obtained in 28% yield along with **1a** (42% yield). Having found that two types of palladium catalysts are effective for the three-component synthesis of 3-acyl-2-aminobenzofuran, we then optimized the reaction conditions by using 4-bromotoluene with **3a** and CO. Gratifyingly, we found that the three-component coupling reaction led to the formation of **2a** in 52% yield in the presence of palladium catalysts, Pd(PPh<sub>3</sub>)<sub>4</sub> (2 mol%) and Pd(PCy<sub>3</sub>)<sub>2</sub> (8 mol%).<sup>9</sup>

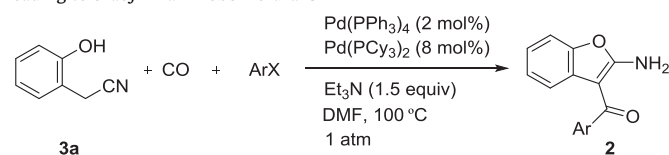


**Scheme 3.** Palladium-catalyzed three-component coupling.

Under the optimized reaction conditions [aryl bromide (1.5 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (2 mol%), Pd(PCy<sub>3</sub>)<sub>2</sub> (8 mol%), and Et<sub>3</sub>N (1.5 equiv) in DMF at 100 °C under 1 atm CO], the substrate scope of the reaction was examined by using a range of aryl halides. The results are summarized in Table 1. The reactions with aryl bromides having an electron-withdrawing group, such as a trifluoromethyl or a chloro group at the *para*-position, afforded the corresponding 3-acyl-2-aminobenzofurans **2b** and **2c** in 84 and 74% yields, respectively (entries 1 and 2). The presence of a substituent such as a chloro group at an *ortho*-position was also tolerated in the reaction (entry 3). The three-component cascade reaction was also applicable to aryl halides having either moderately electron-withdrawing or electron-donating substituents, although extended reaction times were required for these reactions to reach completion (entries 4–6). The reaction using 4-bromoanisole was sluggish, giving a small amount of 3-acyl-2-aminobenzofuran **2h**, whereas the reaction using 4-iodoanisole afforded **2h** in 42% yield (entries 7 and 8).<sup>10</sup>

The substrate scope of the reaction with respect to variation of 2-(cyanomethyl)phenols was also examined. As shown in Table 2, 2-(cyanomethyl)phenols **3** possessing a range of substituents participated in the cascade reactions to give the corresponding 3-acyl-2-aminobenzofuran derivatives **2i–l** in moderate to good yield (entries 1–4). It should be noted that a remote ester group of **2m**

**Table 1**  
Pd-catalyzed three-component coupling reactions using aryl halides, **3a**, and CO leading to 3-acyl-2-aminobenzofurans **2**<sup>a</sup>



Entry	Ar	X	Time	Product	Yield <sup>b</sup>
1	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Br	20 h	<b>2b</b>	84%
2	4-ClC <sub>6</sub> H <sub>4</sub>	Br	30 h	<b>2c</b>	74%
3	2-ClC <sub>6</sub> H <sub>4</sub>	Br	30 h	<b>2d</b>	71%
4	4-FC <sub>6</sub> H <sub>4</sub>	Br	40 h	<b>2e</b>	60%
5	2-Naph	Br	40 h	<b>2f</b>	71%
6	Ph	Br	40 h	<b>2g</b>	57%
7	4-MeOC <sub>6</sub> H <sub>4</sub>	Br	40 h	<b>2h</b>	7%
8	4-MeOC <sub>6</sub> H <sub>4</sub>	I	40 h	<b>2h</b>	42%

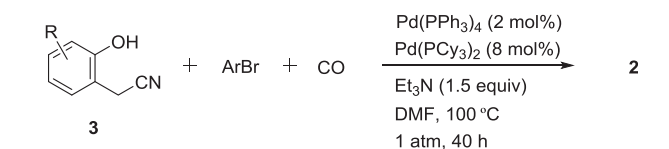
<sup>a</sup> Reaction conditions: **3a** (0.30 mmol), ArX (0.45 mmol), Et<sub>3</sub>N (0.45 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.006 mmol), and Pd(PCy<sub>3</sub>)<sub>2</sub> (0.024 mmol) in DMF (1.2 mL) under CO (1 atm).

<sup>b</sup> Isolated yield.

remained intact under the reaction conditions (entry 5). Silyloxy and methoxymethoxy groups were compatible with the reaction conditions, affording **2n** and **2o** in 70 and 72% yields, respectively (entries 6 and 7).<sup>11</sup>

The most plausible catalytic cycle leading to 3-acyl-2-aminobenzofurans **2** is shown in Fig. 1. The Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed alkoxy carbonylation of an aryl halide, CO, and 2-(cyanomethyl)phenol **3a** produces 2-(cyanomethyl)phenyl ester **1** (cycle A).<sup>7</sup> The latter then

**Table 2**  
Pd-catalyzed three-component coupling reactions leading to 3-acyl-2-aminobenzofurans **2**<sup>a</sup>



Entry	Product (2)	Yield <sup>b</sup>
1	<b>2i</b>	55%
2	<b>2j</b> (Ar=4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )	86%
3	<b>2k</b> (Ar=Ph)	71%
4	<b>2l</b>	66%
5	<b>2m</b> (R=OBz)	54%
6	<b>2n</b> (R=OTBDMS)	70%
7	<b>2o</b> (R=OMOM)	72%

<sup>a</sup> Reaction conditions: **3** (0.30 mmol), ArBr (0.45 mmol), Et<sub>3</sub>N (0.45 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.006 mmol), and Pd(PCy<sub>3</sub>)<sub>2</sub> (0.024 mmol) in DMF (1.2 mL) under CO (1 atm).

<sup>b</sup> Isolated yields.

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