C–H Carbonylation

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Synthesis of Dibenzopyranones through Palladium-Catalyzed Directed C–H Activation/Carbonylation of 2-Arylphenols**

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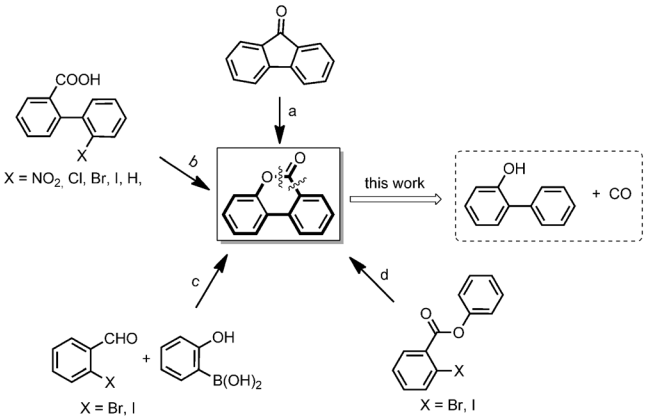
The dibenzopyranone scaffold is found in many natural products and biologically active molecules, and was considered as a privileged structure, which is of great importance as intermediate for the synthesis of various pharmaceutically interesting compounds.[1] Traditionally, major methods for the synthesis of dibenzopyranone derivatives include: 1) Baeyer–Villiger oxidation of fluorenone (Scheme 1, path a);[2] 2) lactonization of 2-halobiarylcarboxylic acid derivatives;[3]



Scheme 1. Synthesis of dibenzopyranone.

3) cross-coupling from 2-halobenzaldehydes and *o*-hydroxyarylboronic acids, followed by lactonization (path c);[4] 4) intramolecular C–C bond formation of aryl 2-halobenzoate (path d).[5] Although these present methods exhibited their individual advantages, they generally involved multistep procedures, sometimes harsh reaction conditions, starting materials that are not readily available, and the requirement of prefunctionalization. From the point of view of atom- and process-economical chemistry, to develop an efficient and general synthetic route with less waste is highly desirable. In view of recent advances in C–H bond carbonylation, we envisaged that the dibenzopyranone scaffold might be easily constructed from 2-phenylphenol through palladium-catalyzed C–H activation/carbonylation.

Indeed, C–H functionalization is the most sustainable and straightforward method to construct complicated molecules and has received significant attention during the past decades.[6] On the other hand, transition-metal-catalyzed carbonylation of organic halides with CO in the presence of various nucleophiles has been demonstrated to be a powerful approach to carbonyl compounds.[7] With the combination of these two important transformations, direct carbonylation of C–H bonds is an ideal strategy to introduce carbonyl group into molecules. For the numerous C–H carbonylation reactions reported to date, directing groups are usually required to achieve selectivity of these transformations. Various functional groups, such as N-containing heterocycles,[8] amides,[9] amidines,[10] aliphatic amines,[11] carboxylic acids,[12] hydroxy groups,[13] and free amines,[14] have been used as directing groups. However, a C–H carbonylation reaction using a phenolic hydroxy group as a directing group to prepare lactones has never been approached. The main challenge of this transformation is the incompatibility of phenols with the oxidative reaction conditions. Herein, we reported the first successful and efficient protocol for the synthesis of dibenzopyranones through Pd-catalyzed phenol-directed C–H activation/carbonylation of 2-phenylphenol derivatives in the presence of CO.

Our evaluation started with the reaction of 2-phenylphenol (**1a**) in the presence of the $Pd(OAc)_2$ catalyst and K_2CO_3 as a base under an atmospheric pressure of CO in mesitylene at 120 °C (Table 1). Different weak oxidants were tested first, and the desired product dibenzopyranone (**2a**) was obtained in a low yield when either AgOAc, $Cu(OAc)_2$, or air were used as oxidant. The product **2a** was produced in 16% yield when the reaction proceeded in the presence of a catalytic amount of $Cu(OAc)_2$ (10 mol%) without inert-gas protection.[15] Further studies indicated that the addition of pivalates improved the reaction slightly, while PivOH was the most effective one. Further optimization was conducted with different bases. Na_2CO_3 provided the best result, and **2a** could be isolated in 91% yield. When the loading of $Pd(OAc)_2$ was lowered to 5 mol%, the reaction did not lose efficiency. No product was formed in the absence of $Pd(OAc)_2$.

With the optimized conditions in hand, we further examined the scope of the phenol-directed C–H activation/carbonylation/lactonization (Figure 1). A variety of 2-aryl

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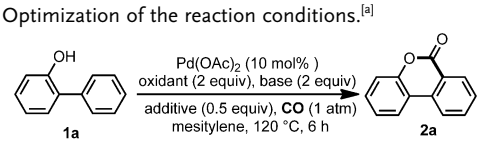
Table 1: Optimization of the reaction conditions.[a]



Entry	Oxidant	Base	Additive	Yield [%][b]
1	AgOAc	K_2CO_3	–	14
2	benzoquinone	K_2CO_3	–	0
3	$K_2S_2O_8$	K_2CO_3	–	0
4	air	K_2CO_3	–	6
5	$Cu(OAc)_2$	K_2CO_3	–	9
6[c]	$Cu(OAc)_2$/air	K_2CO_3	–	16
7[c]	$Cu(OAc)_2$/air	K_2CO_3	PivONa	21
8[c]	$Cu(OAc)_2$/air	K_2CO_3	PivOK	20
9[c]	$Cu(OAc)_2$/air	K_2CO_3	PivOH	25
10[c]	$Cu(OAc)_2$/air	K_2CO_3	MesCOOH	10
11[c]	$Cu(OAc)_2$/air	Cs_2CO_3	PivOH	22
12[c]	$Cu(OAc)_2$/air	Li_2CO_3	PivOH	38
13[c]	**$Cu(OAc)_2$/air**	**Na_2CO_3**	**PivOH**	**94 (91)**
14[c,d]	**$Cu(OAc)_2$/air**	**Na_2CO_3**	**PivOH**	**92 (89)**
15[c,e]	$Cu(OAc)_2$/air	Na_2CO_3	PivOH	0

[a] All the reactions were carried out on a 0.2 mmol scale in 2 mL mesitylene. PivOH = pivalic acid. [b] Yields were determined by using GC with *n*-dodecane as an internal standard. [c] $Cu(OAc)_2$ (10 mol%). CO/O_2 = 7:1 (see the Supporting Information). [d] $Pd(OAc)_2$ (5 mol%). [e] Without $Pd(OAc)_2$.

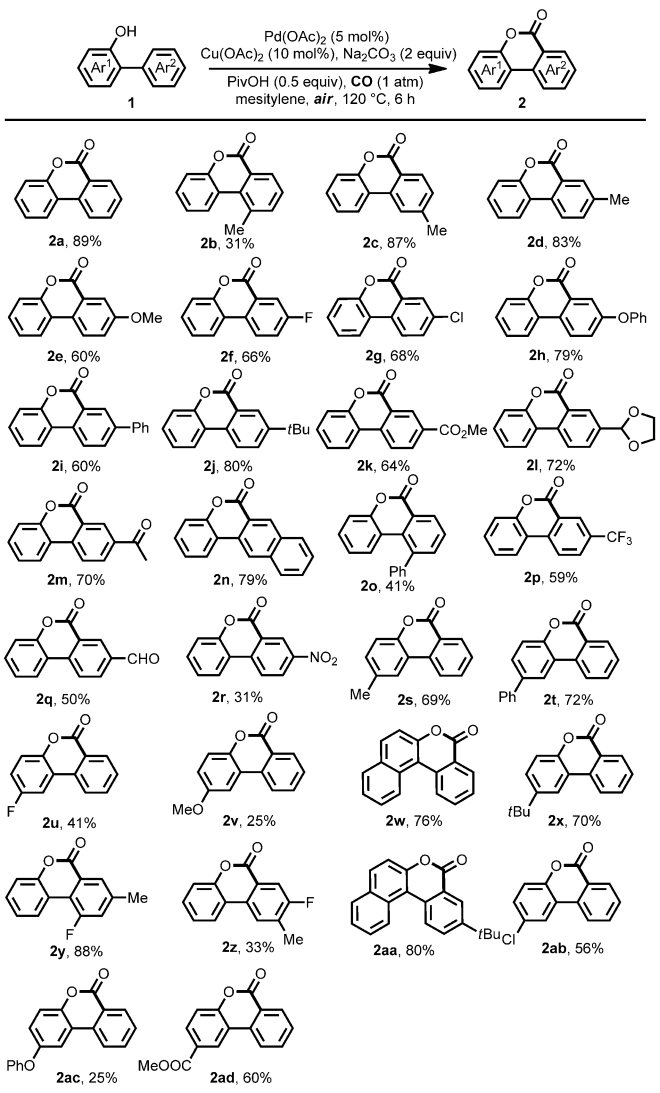
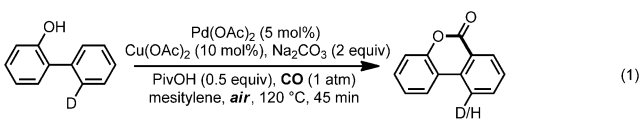


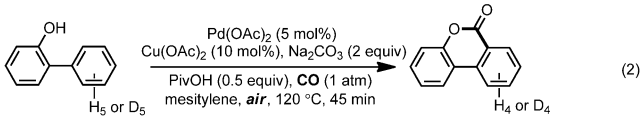
Figure 1. Investigation of the reaction scope. Reaction conditions: **1** (0.2 mmol), CO ballon (1 atm), mesitylene (2 mL). Yields of isolated products are shown.

phenols could be converted to the desired products in moderate to good yields. Various substituents at the Ar^2 aromatic ring were tolerated in this transformation, including electron-neutral or electron-donating groups, such as methyl (**2b**–**2d**), phenyl (**2i**, **2o**), *tert*-butyl (**2j**), methoxy (**2e**), phenoxy (**2h**), and ketal groups (**2l**), and electron-withdrawing groups such as ester (**2k**), ketone (**2m**), formyl (**2q**), trifluoromethyl (**2p**), and nitro groups (**2r**). Fluoride (**2f, 2y, 2z**) and chloride substituents (**2g**) were also compatible with the process. Substituents at the *ortho* position were unfavorable for product formation (**2b**, **2o**), which might arise from steric hindrance. The regioselectivity of this reaction favored the formation of the less sterically hindered products (**2c**, **2n**), while the other regioisomers were not observed. Notably, we did not recover the remaining starting material even when the yield was low (e.g., **2b**, **2o**, and **2r**). We proposed that phenols might decompose to intractable products owing to oxidative reaction conditions. Finally, the reaction was found to be more sensitive to the electronic nature of substituents on the Ar^1 aromatic ring. For example, electron-neutral groups, such as methyl (**2s**), phenyl (**2t**), *tert*-butyl (**2x**), and naphthyl (**2w**) gave higher yields than electron-withdrawing (**2u**, **2ab**, **2ad**) or -donating groups (**2v**, **2ac**).

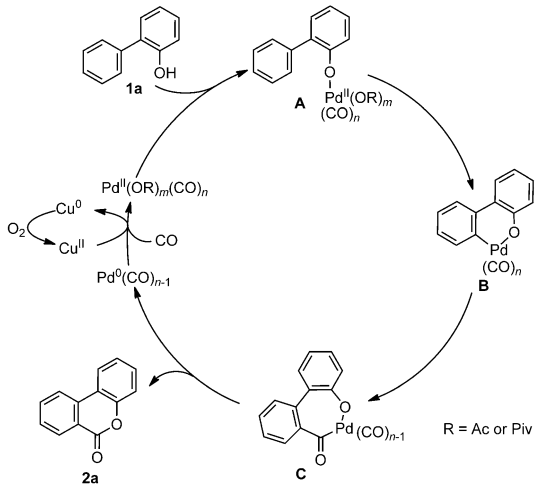
To gain preliminary insight into the reaction mechanism, we conducted a series of deuterium labeling experiments. First, the monodeuterated substrate [D_1]-**1a** was subjected to the standard condition for 45 min and afforded a mixture of [D_1]-**2a** and **2a** in a ratio of 1.38 [Eq. (1)]. Next, individual reactions of **1a** and [D_5]-**1a** under the standard conditions for 45 min were compared, and the KIE value was determined to be 1.36 [Eq. (2)]. Based on these kinetic results, together with the electronic nature of this reaction demonstrated above, we proposed that the C–H activation step might go through an S_EAr mechanism, rather than the concerted metalation—deprotonation (CMD) process, and the C–H activation might be involved in the rate-determining step.



(1)



(2)



Scheme 2. Proposed mechanism.

On the basis of the above results and previous studies, a plausible mechanism was proposed in Scheme 2. Intermediate **A** is formed by the chelation of the hydroxy group of **1a** with the CO-ligated palladium(II) complex. Subsequent C–H activation occurred through electrophilic cyclopalladation on the non-phenol ring, resulting in the six-membered palladocycle **B**. Then the migratory insertion of coordinated CO into the aryl–Pd bond forms the seven-membered palladacycle **C**. Reductive elimination from the intermediate **C** lead to the lactone **2a** and concurrent formation of a Pd^0 species, which is reoxidized to the active palladium(II) complex by $Cu(OAc)_2$ in the presence of O_2.

In summary, we have developed an efficient method for the synthesis of dibenzopyranones through Pd-catalyzed directed C–H activation/carbonylation of 2-phenylphenol derivatives in the presence of CO. Various dibenzopyranone derivatives could be synthesized in the presence of $Pd(OAc)_2$ as a catalyst and $Cu(OAc)_2$ as a catalytic oxidant under an atmospheric pressure of CO and O_2. Further studies on extending this transformation to the synthesis of biologically active compounds and surveying the detailed mechanism are currently underway.

Experimental Section

Typical procedure for the Pd-catalyzed phenol-directed C–H activation/carbonylation. A 25 mL Schlenk tube equipped with a stirrer bar was charged with 2-phenylphenol (**1a**, 34.0 mg, 0.20 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 5 mol%), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 10 mol%), Na_2CO_3 (42.0 mg, 0.40 mmol, 2.0 equiv), PivOH (10.0 mg, 0.1 mmol, 50 mol%), and mesitylene (2.0 mL). The Schlenk tube was attached to a balloon filled with CO. The Schlenk tube was sealed with a rubber stopper and then the reaction mixture was stirred at 120 °C for 6 h. Upon cooling to room temperature, the reaction mixture was directly subjected to flash chromatography on silica gel to afford dibenzopyranone (**2a**) as a white solid (PE/EA = 20:1, 35.0 mg).

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[15] The ratio of CO/air was determined by using GC. For details, please refer to the Supporting Information.

