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Direct Lactonization of 2-Arylacetic Acids through Pd(II)-Catalyzed C–H Activation/C–O Formation

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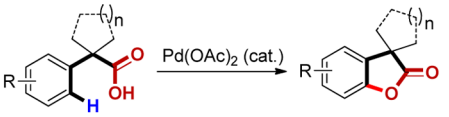
ABSTRACT



R = aryl, alkyl, alkoxyl, Cl, Br; n = 0, 1, 2; 24 examples, 17%- 89% yields

Palladium-catalyzed direct lactonization of 2-arylacetic acids through a reaction sequence that includes C–H activation/C–O formation is reported. This method provides a concise and efficient pathway to synthesize fully functionalized benzofuranone derivatives, which are highly relevant to bioactive natural and synthetic products.

Benzofuranone is an important structural motif in many biologically active natural products and pharmaceutical compounds (Figure 1).[1] It also serves as a synthon for the synthesis of bioactive products, such as aplysin, sesquiterpene, and isolaurinterol.[2] General methods for the preparation of the benzofuranone framework include (1) the condensations of 2-(2-hydroxyphenyl)acetic acid derivatives;[2c,3] (2) the Friedel–Crafts/lactonization reaction of α-hydroxy acid esters and phenols;[4] and (3) transition-metal-catalyzed coupling reactions.[5] These methods, to some extent, require tedious prefunctionalization steps, which induce the high consumption of both time and cost, limiting their application. Thus, new developments in constructing functionalized benzofuranone scaffolds are highly appealing. Recently, Gu and co-workers reported a beautiful example to produce benzopyranones through an

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oxidative cyclization, but the substrate is still limited to electron-rich arenes[6] and such a method could not be applied to synthesize benzofuranones. Obviously, the development of a transition-metal-catalyzed direct cyclization to synthesize benzofuranones from easily available carboxylic acids could be desirable and has never been approached.

Over the past decade, extensive efforts have been made to develop methods to functionalize aromatic C−H bonds directly to construct C−C,[7] C−N,[8] and C−O[9] bonds. Many of these reactions were assisted by directing groups, which played dual roles to assist chelation and subsequently promote further functionalization. Especially, the use of carboxylic acid as a directing group for C−H activation, developed by Yu[9] and other research groups,[10] has shown its advantages. Recently, Liu and Yoshikai first reported a Pd-catalyzed cyclization to approach the dibenzo[*b*,*d*]furan[11a,b] and dihydrobenzofuran[11c] through the C−H activation/intramolecular C−O formation sequence. However, the Pd-catalyzed intermolecular carboxylation of C−H bonds has been well developed. Yet, the carboxyl directed C−H bond activation and subsequent intramolecular cyclization offer a distinct challenge, because of (1) the large energy gap between the highest occupied molecular orbital (HOMO) of the Pd−O bond of carboxylate and the lowest unoccupied molecular orbital (LUMO) of the Pd−C bond, (2) the substantial ionic character of the Pd−O bond, and (3) the stability of palladacycles.[12] We report herein the first successful example of a straightforward and versatile method to obtain functionalized benzofuranones through palladium-catalyzed intramolecular oxidative aromatic C−O bond formation from readily available 2-arylacetic acids.

We began our study with **1a** as the model substrate (Table 1). The first attempt was conducted with the

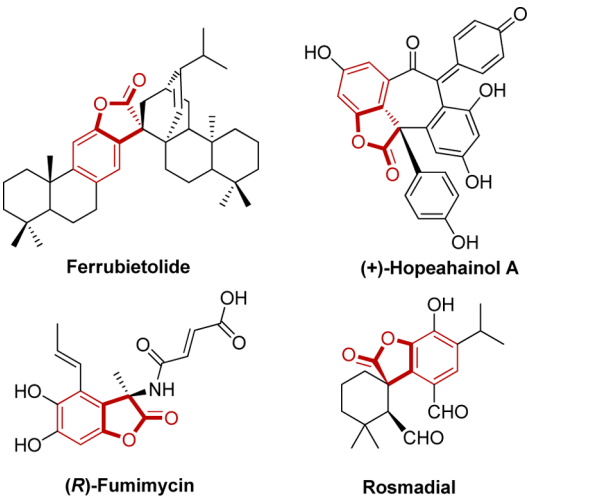

Figure 1. Natural bioactive products containing benzofuranone rings.

combination of $Pd(OAc)_2$ and K_2HPO_4, which was regarded as an efficient catalytic system in the carboxyl directed C−H/C−O cyclization.[12] We surveyed a wide range of oxidants to promote C−O reductive elimination from putative Pd(II), Pd(III),[13] or Pd(IV)[14] intermediates. However, no desired product **2a** was observed (entries 1−6). We further tested $PhI(OAc)_2$, a generally effective oxidant for the Pd(II)−Pd(IV) catalytic pathway.[15] To our delight, 53% of the desired product was obtained (entry 7). Encouraged by this result, we extensively screened various bases and found that CsOAc was the most effective one (entries 8−13). The extra addition of AgOAc further increased the yield to 65% (entry 14). Other silver salts, such as Ag_2O and Ag_2CO_3, were not efficient (entries 16−17). The combination of NaOAc and CsOAc supplied the best result in the presence of AgOAc (entry 15). Obviously, without Pd catalysis, the reaction did not work (entry 18), showing a completely different pathway from the previously reported work, through the oxidative cyclization pathway.[6]

With the optimized conditions in hand, we explored the substrate scope (Scheme 1). Significant steric and electronic effects of the substituents on the reactivity were observed. For biaryl substrates, electron-neutral groups, such as Me, ^{i}Pr, and ^{t}Bu (**2a**−**e**), afforded the corresponding products in good yields. Both electron-donating groups (MeO, **2f**) and electron-withdrawing groups (CF_3, **2g**) were tolerated on the substituted aryl ring. *Ortho*-substituted normal phenyl acetic acid is also efficient (**2l**). Moreover, the reaction could be conducted in the presence of halo substituents, thus allowing further functionalization through

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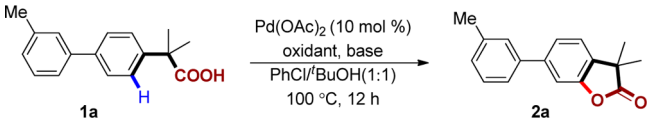
conventional cross-coupling reactions (**2r**−**s**). The naphthyl acetic acids are also efficient for the transformation (**2v**−**w**). Remarkably, the effect of substitutions at the α-positions of the acids are obvious. Both five- and six-member rings are much better than the four-member ring (**2h**−**j**), which could be explained by the Thorpe−Ingold effect (or dialkyl effect).[11c] Unfortunately, the presence of the α-hydrogen of 2-arylacetic acids blocked such lactonization (**2y**−**2z**).

Table 1. Optimization of Reaction Conditions[a]

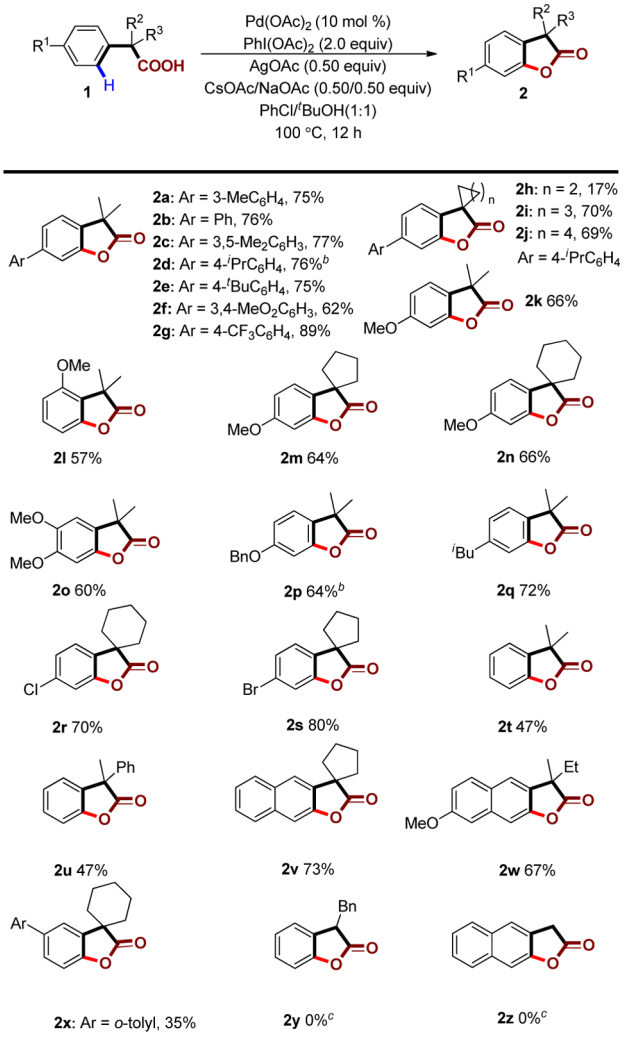


entry	oxidant (equiv)	base (equiv)	additive (equiv)	yield (%)[d]
1	$Cu(OAc)_2$ (2.0)	K_2HPO_4 (1.0)	–[c]	0[e]
2	$K_2S_2O_8$ (2.0)	K_2HPO_4 (1.0)	–[c]	0[e]
3	Ag_2CO_3 (2.0)	K_2HPO_4 (1.0)	–[c]	0[e]
4	BQ (2.0)	K_2HPO_4 (1.0)	–[c]	0[e]
5	MnO_2 (2.0)	K_2HPO_4 (1.0)	–[c]	0[e]
6	O_2 (1.0 atm)	K_2HPO_4 (1.0)	–[c]	0[e]
7	$PhI(OAc)_2$ (2.0)	K_2HPO_4 (1.0)	–[c]	53
8	$PhI(OAc)_2$ (2.0)	NaO^{t}Bu (1.0)	–[c]	43
9	$PhI(OAc)_2$ (2.0)	Na_2CO_3 (1.0)	–[c]	42
10	$PhI(OAc)_2$ (2.0)	NaOAc (1.0)	–[c]	47
11	$PhI(OAc)_2$ (2.0)	KOAc (1.0)	–[c]	49
12	$PhI(OAc)_2$ (2.0)	CsOAc (1.0)	–[c]	56
13	$PhI(OAc)_2$ (2.0)	CsOPiv (1.0)	–[c]	42
14	$PhI(OAc)_2$ (2.0)	CsOAc (1.0)	AgOAc (0.50)	65
15[b]	$PhI(OAc)_2$ (2.0)	CsOAc/NaOAc (0.50/0.50)	AgOAc (0.50)	75
16	$PhI(OAc)_2$ (2.0)	CsOAc/NaOAc (0.50/0.50)	Ag_2O (0.50)	32
17	$PhI(OAc)_2$ (2.0)	CsOAc/NaOAc (0.50/0.50)	Ag_2CO_3 (0.50)	39
18[f]	$PhI(OAc)_2$ (2.0)	CsOAc/NaOAc (0.50/0.50)	AgOAc (0.50)	0[e]

[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.10 mmol), $Pd(OAc)_2$ (0.010 mmol, 10 mol %), oxidant (0.20 mmol, 2.0 equiv), additive (0.050 mmol, 0.50 equiv), base (0.10 mmol, 1.0 equiv), PhCl/^{t}BuOH(0.75/0.75 mL), 100 °C, 12 h. [b] 0.2 mmol scale of **1a**. [c] No additive. [d] Isolated yield. [e] Detected by GC-MS. [f] Without Pd catalyst.

To gain insight into the mechanism, we performed deuterium-labeling experiments [Scheme 2, eqs 1−3]. The intermolecular and intramolecular kinetic isotopic effects were determined as 3.6 and 2.2, respectively, thus suggesting that C−H cleavage was involved in the rate-determining step (eqs 1 and 2). Further studies were also conducted in deuterated solvent, and scrambling of the H/D was not observed; thus, the C−H cleavage under this condition is not in equilibrium (eq 3). According to these studies and previous reports,[12] the catalytic pathway was proposed in Scheme 3. The deprotonation of carboxylic acids resulted in the formation of carboxy salts, which could further coordinate with Pd species to initiate the catalytic cycle. Followed by the concerted metalation deprotonation

Scheme 1. Pd(II)-Catalyzed C−H Activation/C−O Cyclization[a]



[a] Reaction conditions were as follows: **1a** (0.20 mmol), $Pd(OAc)_2$ (0.020 mmol, 10 mol %), $PhI(OAc)_2$ (0.40 mmol, 2.0 equiv), AgOAc (0.05 mmol, 0.50 equiv), CsOAc (0.10 mmol, 0.50 equiv), NaOAc (0.10 mmol, 0.50 equiv), PhCl/^{t}BuOH(1.5/1.5 mL), 100 °C, 12 h. [b] NaOAc (3.0 equiv) used as the base. [c] Determined by GC-MS.

(CMD) to achieve the C−H cleavage, the six-membered palladacycle II was generated. As previously reported by Yu and co-workers, the cation is very important in facilitating this step. Thus, different acetate salts might play critical roles.[16] After the oxidation of the Pd(II) species to the key Pd(IV) intermediate by $PhI(OAc)_2$,[14,17] reductive elimination took place to produce the desired product (path a, **2t**) and/or acetoxylation product (**3t**), which could further condense to afford **2t** (path b),[18] along with the release of the Pd(II) to facilitate the catalytic cycle.

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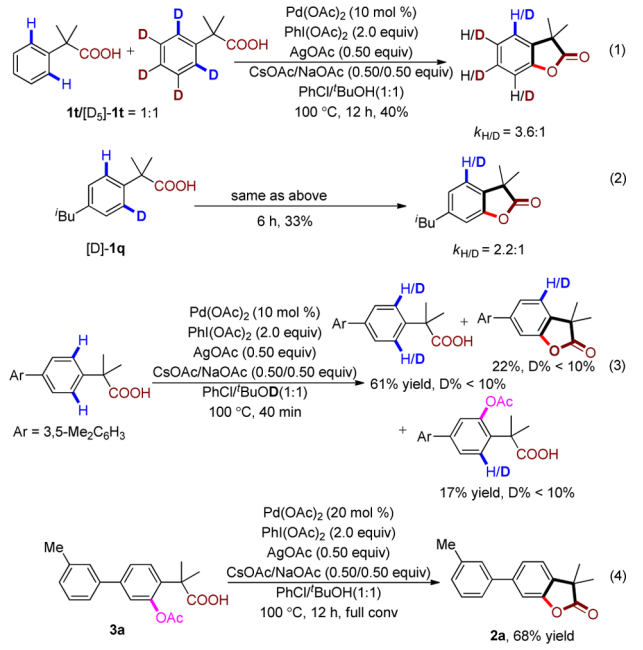
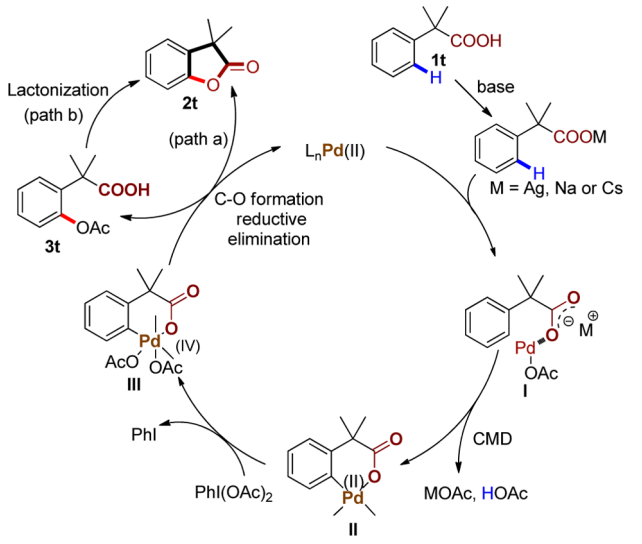
(18) For more details, please see the Supporting Information (SI).

Scheme 2. Experiments for Mechanism Research



Scheme 3. Plausible Mechanism



In conclusion, we have developed a palladium-catalyzed C−H activation/intramolecular C−O formation sequence with the carboxylic group as both a directing and a reacting group. This transformation provides a direct and efficient method for constructing benzofuranones from easily available linear β-aryl substituted carboxylic acids, which are potentially relevant to natural product synthesis and drug discovery. To discover potential applications of this reaction and to understand the corresponding catalytic cycle better, further investigations are underway.

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Supporting Information Available. Experimental procedures, as well as spectral data for lactonization products and mechanistic study experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.