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Novel Pd^{II}-Mediated Cascade Carboxylative Annulation to Construct Benzo[*b*]furan-3-carboxylic Acids

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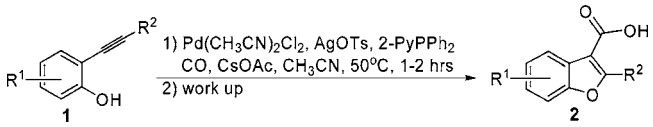
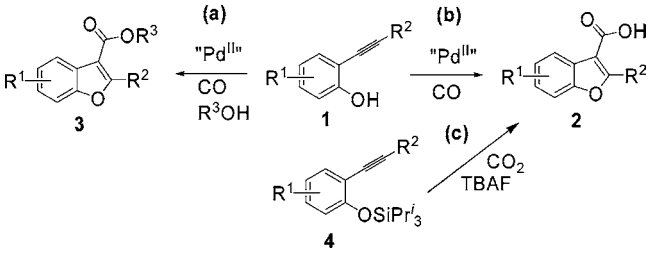
ABSTRACT



Benzo[*b*]furan-3-carboxylic acid (2) was generated from 1 by forming three new bonds in one step via a Pd^{II}-mediated cascade carboxylative annulation. The proposed mechanism was supported by the observation of an unusual acetylation of 1 as a side reaction together with an ^{18}O-labeling study.

Recently, the Pd^{II}-catalyzed/mediated cascade carbonylative annulation of the *o*-hydroxyarylacetylenes (**1**) has proved a highly efficient method for rapidly generating diverse benzo[*b*]furan-3-carboxylic esters (**3**) (**a**, Scheme 1).[1] However, similar metal-mediated transformations leading to benzo[*b*]furan-3-carboxylic acids (**2**) (**b**, Scheme 1) remain unprecedented, although Pd-promoted carboxylation of unsaturated carbon−carbon bonds is well documented especially via Reppe carbonylation.[2]

Scheme 1



From a drug discovery perspective, synthesis of benzofuran-based carboxylic acids could be more interesting because of their increased solubility in aqueous media and the potential enhancement of ionic interactions with basic residues in their association with biological receptors.[3] So far, there is only one example of a direct method for making **2** from **4** (**c**, Scheme 1, $R^1 = H$, $R^2 = Me$, 62% yield).[4] However, this method employed a strong reagent, TBAF, for success. Although molecules such as **2** can also be obtained by the hydrolysis of **3**, a strong base is necessary since **3** is already stabilized by the electron-rich benzofuran ring. Therefore, direct and mild methods to make structurally diverse molecules such as **2** still need to be developed.

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Our former endeavors[1c,d] in generating diverse benzo[*b*]-furan-3-carboxylic esters (**3**) (**a**, Scheme 1) using Pd chemistry encouraged us to further explore this cascade Pd^{II} chemistry for constructing the benzofuran-3-carboxylic acids (**2**) (**b**, Scheme 1) directly from the *o*-hydroxyarylacetylenes (**1**). This approach was initially investigated in a model study by using stoichiometric amounts of Pd reagent and ligand.

R^3OH (**a**, Scheme 1) could not simply be replaced by H_2O in order to generate carboxylic acids since the CO is readily oxidized into formic acid in the presence of H_2O, leading to the palladium bleeding,[5] which is indeed consistent with our observation.

In the absence of the alcohol, our most efficient conditions to generate benzo[*b*]furan-3-carboxylic esters (**3**) (**a**, Scheme 1) in the solution phase[1c] could not produce any acid **2a** (Table 1, entry 1), whereas the conditions we optimized for synthesis of the **3** (**a**, Scheme 1) on solid phase[1d] did result in the generation of the corresponding acid **2a** in a low yield (30%) with *o*-acetyloxyarylacetylene **3a** (29%) as an unusual byproduct (Table 1, entry 2). To increase the yield and suppress this side reaction, various Pd^{II} species, counter-anions, ligands, bases, and solvents were systematically investigated (Table 1).

The solvent effect was first studied (Table 1, entries 2−5), and CH_3CN was found to provide the best result in comparison with DMF, THF, or benzene.

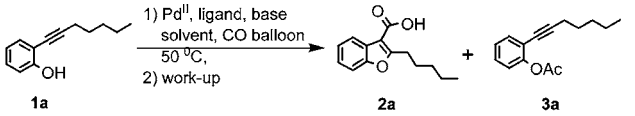
Notably, bases other than the CsOAc (Table 1, entries 1, 6−9), such as organic bases selected for avoiding side product **3a**, blocked the reactions.

Among various Pd^{II} species investigated (Table 1, entries 10−13), $Pd(CH_3CN)_2Cl_2$ was found to be the most reactive.

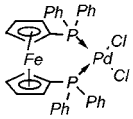
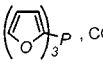
Various ligands were tested (Table 1, entries 14−19). Obviously, electron-rich ligands are not favorable for increasing the reactivity of the cationic Pd^{II} species. Finally, 2-$PyPPh_2$, a highly efficient ligand for Pd^{II}-catalyzed Reppe carbonylation,[6] proved outstanding in our case, the yield of **2a** dramatically being increased up to 70% and the byproduct **3a** notably being suppressed to less than 10% (Table 1, entry 19).

To make the Pd^{II} species more cationic so as to further increase its reactivity, AgOTs was added to extract Cl^- from the $Pd(CH_3CN)_2Cl_2$ by forming AgCl and exchange Cl^- with a noncoordinating OTs^-, which is a superior counteranion for Pd^{II}.[6,7] As a result, the side product **3a** was completely suppressed and the yield of **2a** was increased to 80% (Table 1, entry 20). Similarly, $AgBF_4$ was also tested, and a comparable result was obtained (Table 1, entry 21). Further reaction studies were performed by using a commercially available cationic $Pd(CH_3CN)_4(BF_4)_2$ in the absence of any silver salts, a satisfactory yield of 70% was achieved. However, 10% of byproduct **3a** was generated. Therefore, based on our investigation, silver salt did play an important role in suppressing the side reaction of acetylation.

Table 1. Optimization of the Conditions



1a **2a** **3a**

Entry	Conditions	2a / 3a	Yield of 2a (%)
1	PdI_2, thiourea, CO, Cs_2CO_3, CBr_4, CH_3CN		0
2	$Pd(PPh_3)_2Cl_2$, dppp, CO, CsOAc, DMF	1 / 1	30
3	$Pd(PPh_3)_2Cl_2$, dppp, CO, CsOAc, *THF*	1 / 1	28
4	$Pd(PPh_3)_2Cl_2$, dppp, CO, **CsOAc**, ***CH_3CN***	1 / 1	35
5	$Pd(PPh_3)_2Cl_2$, dppp, CO, CsOAc, *Benzene*	1 / 1	26
6	$Pd(PPh_3)_2Cl_2$, dppp, CO, *DIPEA*, CH_3CN		0
7	$Pd(PPh_3)_2Cl_2$, dppp, CO, *DBU*, CH_3CN		0
8	$Pd(PPh_3)_2Cl_2$, dppp, CO, *2,6-lutidine*, CH_3CN		0
9	$Pd(PPh_3)_2Cl_2$, dppp, CO, *NaOAc*, CH_3CN		trace
10	*$PdCl_2$*, CO, CsOAc, CH_3CN	1 / 1	41
11	*$Pd(OAc)_2$*, CO, CsOAc, CH_3CN	1 / 1	38
12	 , CO, CsOAc, CH_3CN	1 / 1	27
13	***$Pd(CH_3CN)_2Cl_2$***, CO, CsOAc, CH_3CN	3 / 2	54
14	$Pd(CH_3CN)_2Cl_2$, *dppp*, CO, CsOAc, CH_3CN	3 / 2	42
15	$Pd(CH_3CN)_2Cl_2$, *2,2′-bipyridyl*, CO, CsOAc, CH_3CN	3 / 2	36
16	$Pd(CH_3CN)_2Cl_2$, *t-Bu_3P*, CO, CsOAc, CH_3CN	3 / 1	38
17	$Pd(CH_3CN)_2Cl_2$, *n-Bu_3P*, CO, CsOAc, CH_3CN	1 / 1	21
18	$Pd(CH_3CN)_2Cl_2$,  , CO, CsOAc, CH_3CN	1 / 1	48
19	$Pd(CH_3CN)_2Cl_2$, ***2-$PyPPh_2$***, CO, CsOAc, CH_3CN	10 / 1	70
20	**$Pd(CH_3CN)_2Cl_2$, *AgOTs*, 2-$PyPPh_2$, CO, CsOAc, CH_3CN**	**80 / 0**	**80**
21	$Pd(CH_3CN)_2Cl_2$, ***AgBF4***, 2-$PyPPh_2$, CO, CsOAc, CH_3CN	14 / 1	75
22	***$Pd(CH_3CN)_4(BF_4)_2$***, 2-$PyPPh_2$, CO, CsOAc, CH_3CN	10 / 1	70

By using the optimized conditions (Table 1, entry 20), various *o*-hydroxyarylacetylenes with different substitution patterns were transformed into their corresponding benzo-[*b*]furan-3-carboxylic acids (**2a**−**2g**, Table 2), all in good yields, which proved the significance of this novel method.

Many oxidants, such as O_2, 1,4-benzoquinone, DDQ, $Fe(OTs)_3$, $CuCl_2$, $Cu(OAc)_2$, CBr_4, etc., were tried in order to turn over the Pd^0 back to Pd^{II}. Currently, the best result (40% yield) was achieved by using $Pd(CH_3CN)_4(BF_4)_2$ (5%) and 1,4-benzoquinone (2 equiv).

During our model study, two observations came to our attention: one was the acetylation of substrate **1a** (Table 1) as a major side reaction, and the other was that bases other than AcO^- hardly promoted any formation of the product

(5) Fenton, D. M.; Steinwand, P. J. *J. Org. Chem.* **1974**, *39*, 701.
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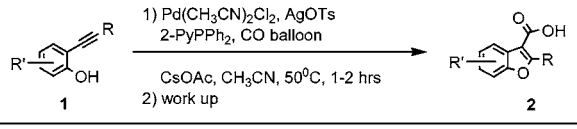
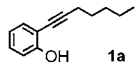
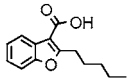
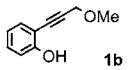
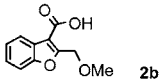
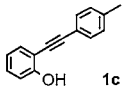
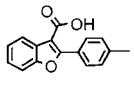
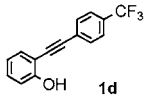
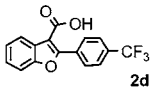
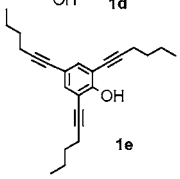
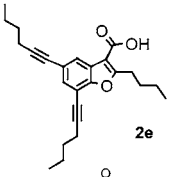
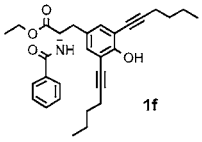
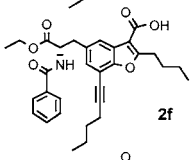
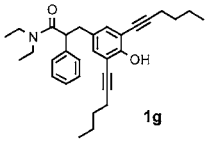
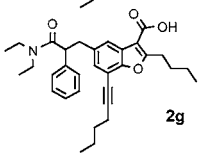
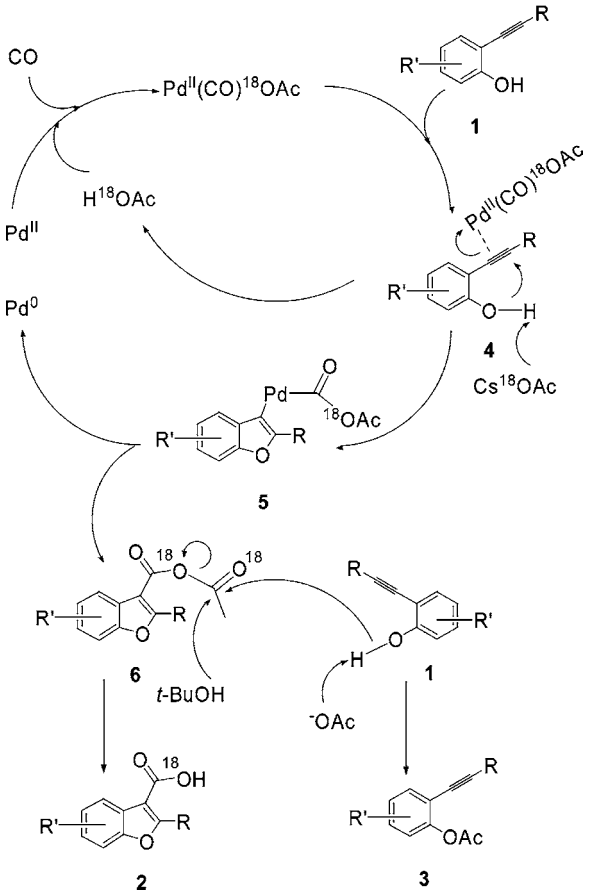
Table 2. Carboxylative Annulation on Diverse Substrates



Entry	Substrate	product	Yield (%)
1	 1a	 2a	80
2	 1b	 2b	68
3	 1c	 2c	70
4	 1d	 2d	78
5	 1e	 2e	81
6	 1f	 2f	66
7	 1g	 2g	72

2a (Table 1, entries 1, 6−8), which prompted us to propose that AcO^- does not simply serve as a base but is also involved in the formation of both **2a** and **3a**. This led to our newly proposed mechanism (Scheme 2). The $Pd^{II}(CO)^{18}OAc$ could be generated from association of the original Pd^{II} reagent with CO and $H^{18}OAc$ (generated from the deprotonation of the substrate **1** by $Cs^{18}OAc$), and its further association with **1** forms a triple-bond-activated Pd^{II} π-complex **4**. With the assistance of AcO^-, the annulation of **4** could then give a $Pd^{II}\sigma$-complex **5** and reductive elimination could then ensue to generate the Pd^0 and an acetic benzo[*b*]furan-3-carboxylic anhydride **6**, which could serve as an acetylating reagent for substrate **1** and lead to acetate **3** as a byproduct. The hydrolysis of **6** during the workup would afford the final product **2**. This mechanism was supported by an ^{18}O-labeling study utilizing $Cs^{18}OAc$ followed by quenching of the reaction with bulky *t*-BuOH in order to achieve regioselective alcoholysis of the possible anhydride intermediate **6** to obtain the ^{18}O-labeled product **2**, which was isolated in high yield and confirmed by both NMR and

Scheme 2. Plausible Mechanism



MS studies. On the basis of this mechanism, if the Pd^{II} species is not reactive enough to allow **1** to be consumed rapidly, the **1** that remains will be acetylated by the anhydride **6** to give the unreactive acetate **3**, which cannot be utilized for further carboxylative annulation. Thus, our endeavor to increase the reactivity of the cationic Pd^{II} fulfills the demands acquired by this mechanism.

In summary, we have described a novel and mild method for the rapid synthesis of benzo[*b*]furan-3-carboxylic acids directly from the substituted *o*-alkynyl- phenols in good yields by utilizing a Pd^{II}-mediated carboxylative annulation. This method may find further application in the future for rapidly constructing other useful heterocyclic carboxylic acids.

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Supporting Information Available: Experimental procedures and NMR and LC-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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