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Palladium-Catalyzed Synthesis of 2,3-Disubstituted Benzofurans: An Approach Towards the Synthesis of Deuterium Labeled Compounds

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Dedicated to Prof. Stephen L. Buchwald on the occasion of his 60th birthday.

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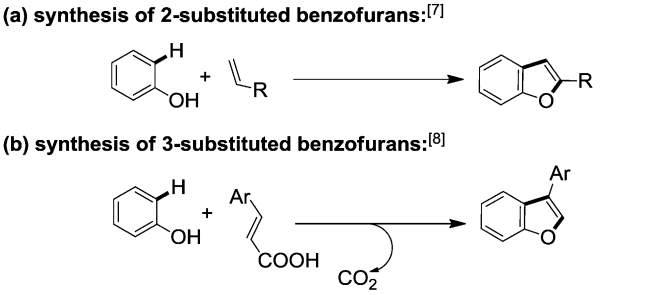
Abstract: Palladium-catalyzed oxidative annulations between phenols and alkenylcarboxylic acids produced a library of benzofuran compounds. Depending on the nature of the substitution of the phenol precursor, either 2,3-dialkylbenzofurans or 2-alkyl-3-methylene-2,3-dihydrobenzofurans can be synthesized with excellent regioselectivity. Reactions between conjugated 5-phenylpenta-2,4-dienoic acids and phenol gave 3-alkylidenedihydrobenzofuran alkaloid motifs while biologically active 7-arylbenzofuran derivatives were prepared by starting from 2-phenylphenols. More interestingly, selective incorporation of deuterium from D_2O has been discovered, which offers an attractive one-step method to access deuterated compounds.

Keywords: benzofurans; C–H activation; deuterium; palladium; synthetic methods

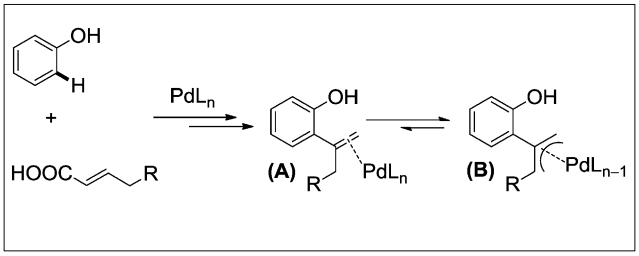
Benzofurans are an important class of heterocyclic compounds[1] with unique biological activities.[2] Notable instances include derivatives of benzofurans acting as antitumor agents,[3] angiotensin II inhibitors,[4] and 5-lipoxygenase inhibitors etc.[5] Therefore, synthesis of these organic motifs has drawn significant attention from the synthetic community.[6] Recently, we have contributed to this area by synthesizing a wide array of 2-substituted benzofurans through a unique Pd-catalyzed annulation of simple phenols and olefins.[7] Of more interest was an orthogonal approach with cinnamic acids, which gave rise to 3-substituted benzofurans with excellent selectivity.[8] In this context, we became interested in the prospect of synthesizing 2,3-disubstituted benzofuran derivatives starting from phenols. Although numerous approaches have been made to synthesize these scaffolds,[9] the widely adopted method is the transition metal-catalyzed annulation[10] by using pre-functionalized phenol,[6a,11] thus limiting the scope of the reaction to a considerable extent. Free phenols also have been employed in several cases but reactions with cinnamic acids remained exceedingly rare.[12]

In addition, we disclose a one-step method to synthesize deuterium-labeled benzofurans in the presence of D_2O (Scheme 1). Deuterated compounds are ubiquitous in the realms of metabolic studies, mechanistic experimentations and most importantly in mass spectrometry.[13] Furthermore, deuterium incorporated compounds are found to improve the therapeutic and metabolic profiles of a drug candidate.[14] To the best of our knowledge, the synthesis of deuterated benzofurans from unbiased phenol remains unsolved as yet.

At the beginning of our investigation, we hypothesized about an alteration of the reaction mode upon changing the coupling partner from cinnmic acids to α,β-unsaturated aliphatic acids (Scheme 2). This preliminary idea was based on the putative intermediate (**A**) which is less likely to undergo a direct oxopalldation due to the decreased stabilization of the incipient



Scheme 1. Our approaches to benzofuran synthesis.



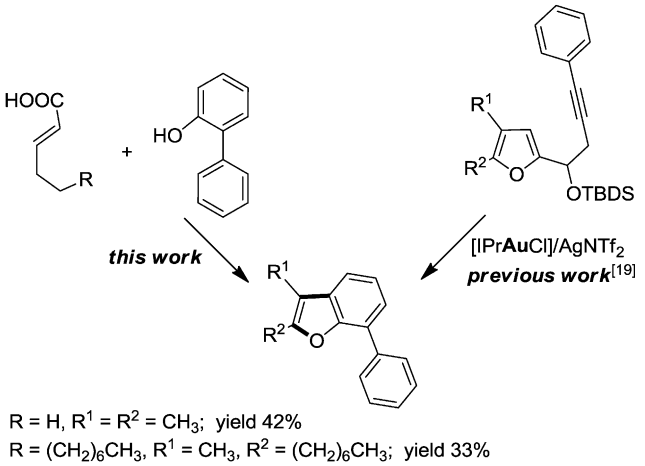
Scheme 2. Mechanistic outline.

negative charge (monobenzyl *vs.* dibenzyl center). In fact, in the next step an allylpalladium species **B** can be envisaged with the tentative migration of the double bond to the more substituted position, which can generate disubstituted benzofurans as opposed to the 3-substituted ones observed previously.[8] In accordance with this hypothesis, we commenced our initial studies with a reaction of 2-chloro-4-nitrophenol and 8-nonenoic acid with the catalyst Pd/1,10-phen in the presence of $Cu(OAc)_2 \cdot H_2O$ as the terminal oxidant. After several sets of optimization, we found that desired disubstituted benzofurans can be synthesized efficiently in dichloroethane (DCE) solvent at 130 °C.[15]

The scope of the phenol coupling partners was studied subsequently under the optimized reaction condition (**3a–4k**). Depending on the nature of substitution of the phenols, we observed formation of either 3-methylene-2,3-dihydrobenzofuran (**3**) or 2,3-dialkylbenzofuran (**4**) derivatives (Table 1). The 8-nonenoic acid reacted with 4-cyanophenol to produce 3-methylene-2,3-dihydrobenzofuran as the major product (**3b**) along with isomer **4b** in trace amount (**3b/4b**, 10:1). In a similar fashion, 4-nitrophenol reacted with the same olefin to produce **3c** in preparatively useful yields. Such compounds were previously synthesized by ruthenium-carbene promoted cycloisomerization of *O*-allyl-*o*-vinylphenols.[16] In the present case, formation of **3** likely involved a β-migratory insertion and β-hydride elimination pathway (*vide infra*).

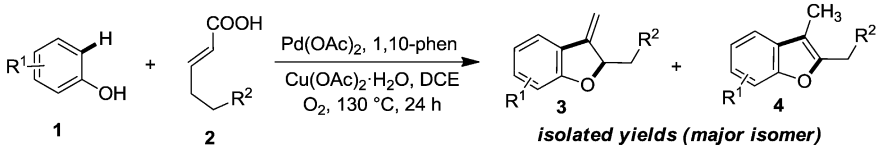
Relatively less electron-deficient phenols were also found to be suitable under the present system. A keto-substituted phenol could produce 3-methyl-substituted **4f** as the major product along with the exocyclic isomer in an negligible amount (**4f/3f**, 56:1). Similar products were also observed in **4g–4k**. Despite our best efforts, the preference for **3** *vs.* **4** (Table 1) cannot be rationalized at this point. We speculated that a subtle difference in electronic nature of phenols (e.g., strongly electron-deficient phenols gave **3**) is crucial for these product formations. Although **3** is known to isomerize to the corresponding 3-methyl-2,3-disubstituted benzofuran (**4**) under acidic conditions,[17] we failed to promote such a transformation in our laboratory (e.g., with **3a**). In addition to the synthesis of benzofurans, naphthofurans (e.g., **4e**; **4e/3e**, 26:1) can also be synthesized, which are integral components in natural products and pharmacologically relevant compounds.[18] Expectedly, electron-rich phenols reacted with 4-pentenoic acid to produce 2,3-dimethyl-substituted benzofuran compounds **4j** and **4k** with useful synthetic yields.

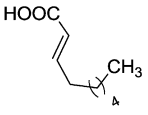
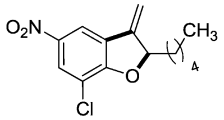
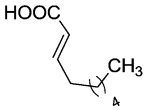
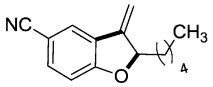
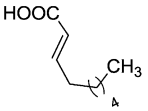
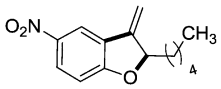
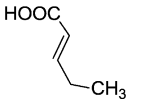
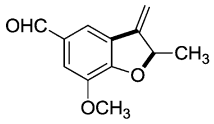
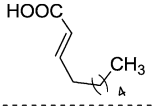
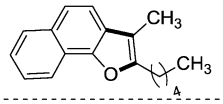
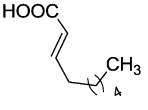
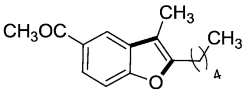
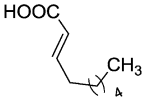
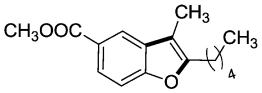
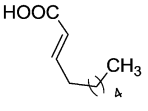
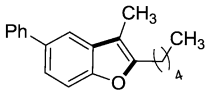
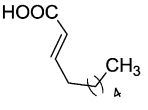
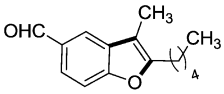
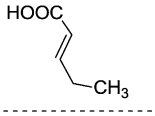
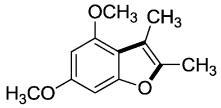
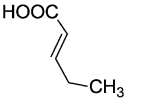
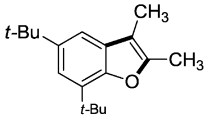
Subsequently, we planned to synthesize 7-arylbenzofuran derivatives which are present in a number of natural products.[19] Note that the synthesis of 7-arylbenzofuran from simple precursors remained problematic up to date (Scheme 3).



Scheme 3. Synthesis of 2,3-disubstituted-7-arylbenzofurans.

Table 1. Scope with different phenols and α,β-unsaturated carboxylic acids.[a]



Acrylic acid	Product
	 **3a**, 66% yield[b] (***43:1***)
	 **3b**, 69% yield (***10:1***)
	 **3c**, 47% yield (***30:1***)
	 **3d**, 59% yield (***3:1***)
	**4e**, 45% yield (***26:1***) 
	**4f**, 59% yield (***56:1***) 
	**4g**, 51% yield (***31:1***) 
	**4h**, 48% yield (***15:1***) 
	**4i**, 60% yield (***53:1***) 
	**4j**, 57% yield (***12:1***) 
	**4k**, 50% yield (***3:1***) 

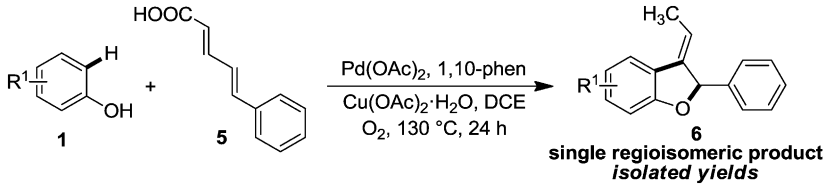
[a] *Reaction conditions:* **1** (0.75 mmol, 3 equiv.), **2** (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (0.025 mmol, 10 mol%), 1,10-phenanthroline (0.05 mmol, 20 mol%), $Cu(OAc)_2$ (0.25 mmol, 1 equiv.), $ClCH_2CH_2Cl$ (4 mL), 130 °C for 24 h in an O_2 atm. Yields are those of the isolated major products. Compound ratio was determined on the basis of GC-MS analysis of the reaction mixture. Compound **3:4** ratio was mentioned for entries **3a**–**3d** and compound **4:3** ratio was mentioned for entries **4e**–**4k**. The minor product could not be isolated in pure form.
[b] Compound was characterized by 1D and 2D NMR.

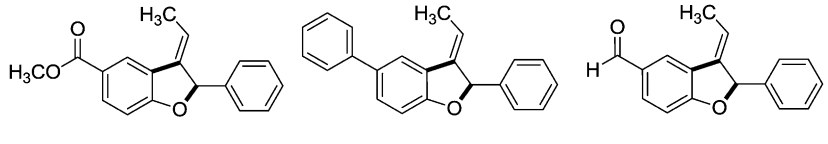
Next, the scope of the present method was expanded to 3-alkylidenedihydrobenzofuran derivatives, which are very relevant to alkaloid chemistry, by reacting conjugated 5-phenylpenta-2,4-dienoic acid with phenol.[1b,20] Ylide hydrolysis and intramolecular cyclization were previously explored to synthesize these 3-alkylidenedihydrobenzofuran compounds.[21] However, under the present conditions, an array of 3-alkylidenedihydrobenzofuran derivatives (**6**) could be synthesized in a much simpler way in good yields (Table 2).

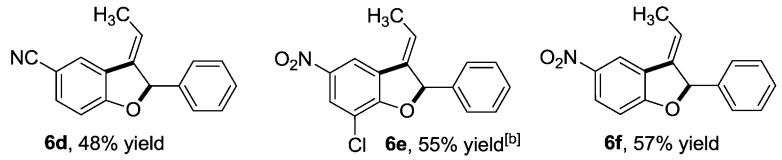
In view of the lability of the carboxylic proton, deuterium-exchange was planned with the addition of D_2O under standard reaction conditions. After a brief optimization effort we found that 500 μL D_2O are sufficient to obtain the maximum percentage of deuterium incorporation.[15] Employing the present approach, an array of deuterated benzofuran analogues were accessed in one step (Scheme 4). Furthermore, deuterated 3-methylene-2,3-dihydrobenzofuran derivatives were also synthesized in a similar fashion. The 8-nonenoic acid in the presence of the electron -withdrawing partner like 2-chloro-4-nitrophenol (**3′a**) and 4-cyanophenol (**3′b**) provided the desired benzofuran products in 65% and 47% yields, respectively. Substitution on the phenol coupling partner like *t*-Bu and Ph gave the expected 2,3-disubstituted benzofurans, where a $-CD_3$ group is present on the 3-position (**4′a** and **4′b**). Dimethoxy-substituted phenol resulted in non-selective over deuteration (**4′c**) due to the acidic nature of protons present in the *ortho*-position of the methoxy group. Next, we synthesized deuterated 3-alkylidenedihydrobenzofuran derivatives from conjugated 5-phenylpenta-2,4-dienoic acid and phenol with synthetically useful yields (**6′a**–**6′c**). Note that, by using PhOH-d_5 as coupling partner in the absence of D_2O, we did not observe any deuterium scrambling (Scheme 5).

Based on the experimental observations, a plausible mechanism of 3-methylene-2,3-dihydrobenzofuran and 2,3-disubstituted benzofuran synthesis is depicted in Scheme 6. Formation of a phenanthroline-palladi-

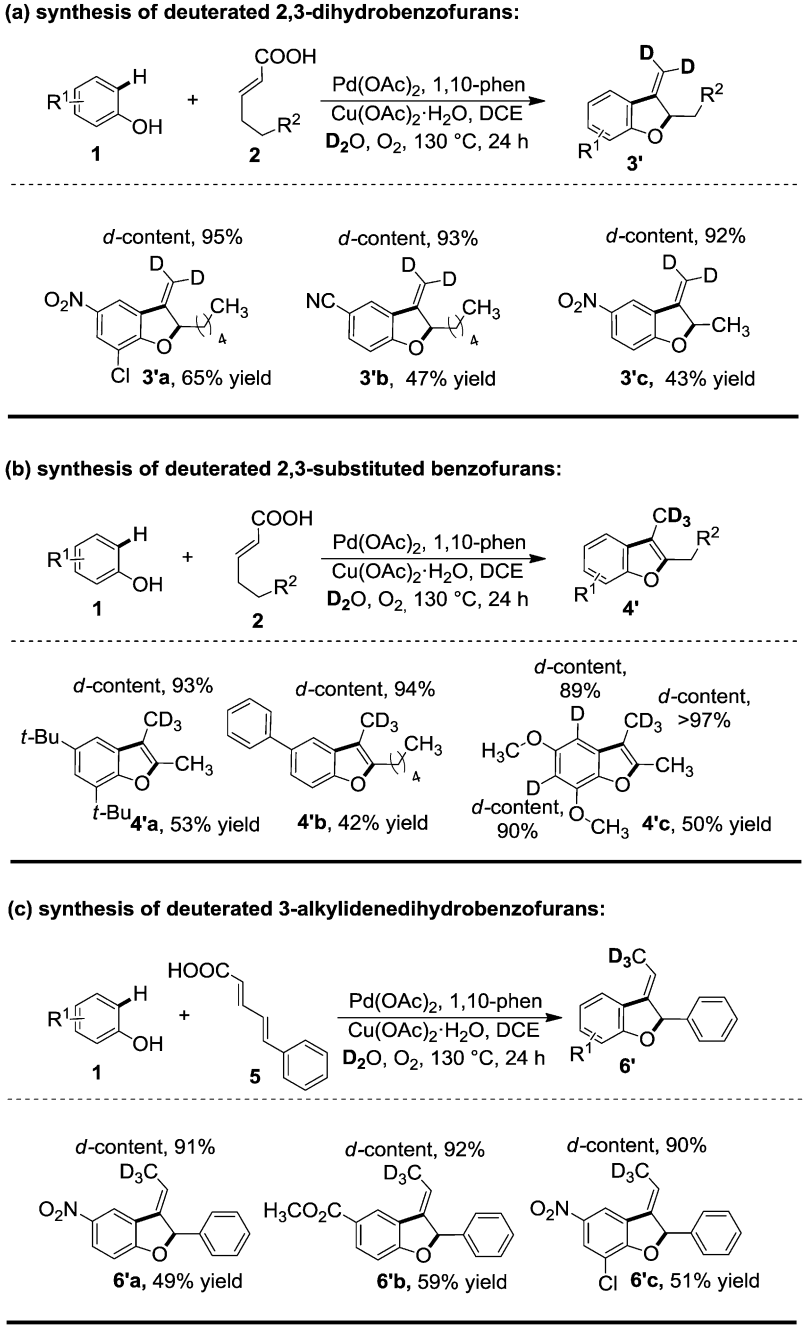
Table 2. Scope with conjugated α,β-unsaturated carboxylic acids.[a]







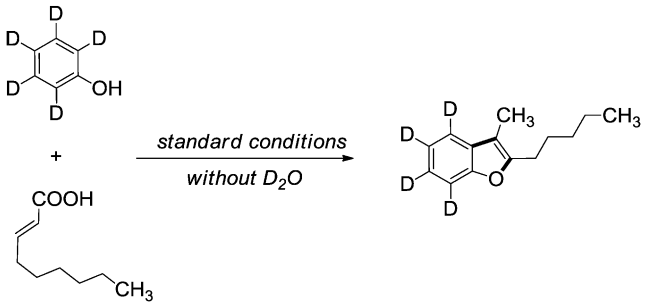
[a] *Reaction conditions:* **1** (0.75 mmol, 3 equiv.), **2** (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (0.025 mmol, 10 mol%), 1,10-phenanthroline (0.05 mmol, 20 mol%), $Cu(OAc)_2$ (0.25 mmol, 1 equiv.), $ClCH_2CH_2Cl$ (4 mL), 130 °C for 24 h in an O_2 atm. Yields are those of the isolated products. Compounds were characterized by 1D and 2D NMR.
[b] Bathophenanthroline as the ligand.



Scheme 4. D_2O addition under standard conditions. *Reaction conditions:* **1** (0.75 mmol, 3 equiv.), **2** (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (0.025 mmol, 10 mol%), 1,10-phenanthroline (0.05 mmol, 20 mol%), $Cu(OAc)_2$ (0.25 mmol, 1 equiv.), D_2O (500 μL), $ClCH_2CH_2Cl$ (4 mL), 130 °C for 24 h in an O_2 atm. Yields are those of the isolated products.

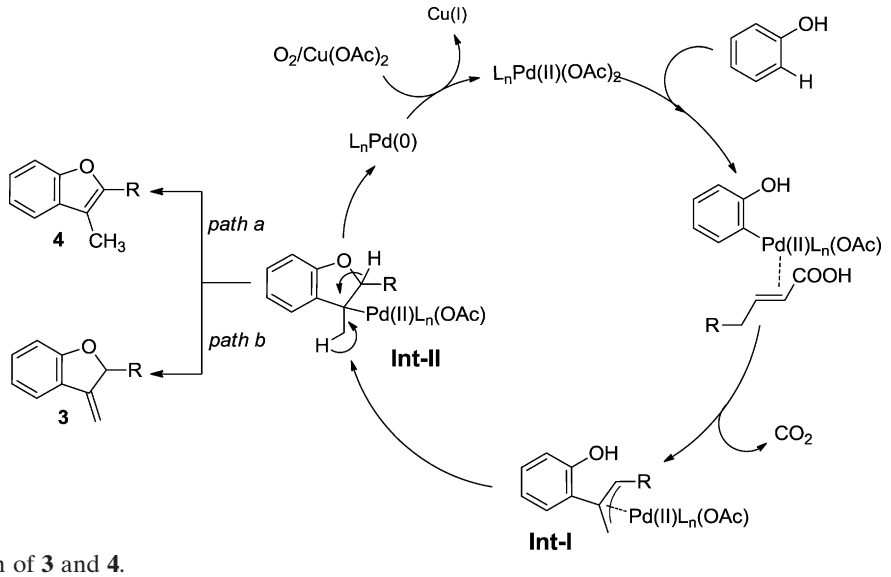
um(II) complex increases the solubility and electrophilicity of the resulting catalyst. We tentatively speculated that the electrophilic palladium center will coordinate to the *ortho*-position of the phenol to give a palladium-phenolic complex.[12e,22] Then α,β-unsaturated carboxylic acids will be inserted across the C–Pd bond and subsequent decarboxylation will give the Pd-allyl species (**Int-I**).[8,23] In the presence of palladium, intermediate **I** will cyclize to form **Int-II**, which is the key species for the formation of **3** and **4**.[1b,7,11c] Syn β-hydride elimination from intermediate **II** leads to the formation of the desired benzofuran products and regenerates the Pd(0) species.[7] This Pd(0) is readily oxidised to Pd(II) by $Cu(OAc)_2·H_2O$ under an oxygen atmosphere to maintain the catalytic process.

A reasonable pathway to obtain **3′** and **4′** (Scheme 4) *via* deuterium incorporation, β-migratory insertion and β-hydride elimination can also be envisaged (Scheme 7).

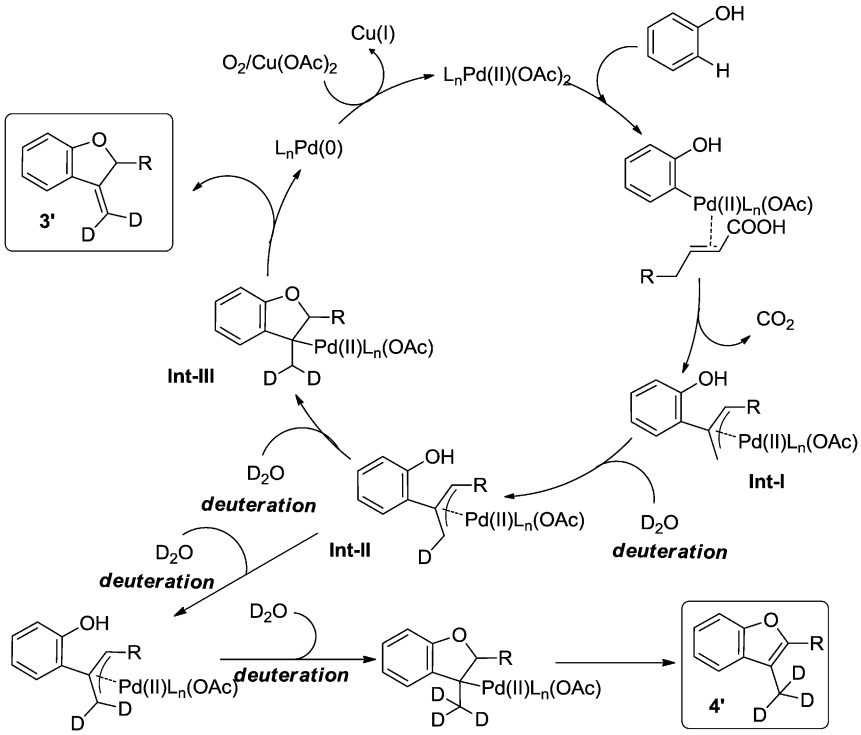


Scheme 5. Complementary isotope labeling study using deuterated phenol.

In summary, 2, 3-disubstituted benzofuran analogues are synthesized from readily available phenols and aliphatic α,β-unsaturated carboxylic acids. Excellent regioselectivity and use of inexpensive reagents make this method synthetically useful. An inverse insertion with α,β-unsaturated carboxylic acids compared to alkenes, was observed upon *ortho*-palladation of phenol. Additionally, this method can be utilized for the preparation of deuterated benzofuran compounds. Further mechanistic investigations and expansion of such strategies are currently underway in our laboratory.



Scheme 6. Formation of **3** and **4**.



Scheme 7. Formation of **3′** and **4′**.

Experimental Section

General Procedure

To an oven-dried screw cap reaction tube charged with a magnetic stir-bar, $Pd(OAc)_2$ (10 mol%, 0.025 mmol, 5.6 mg), 1,10-phenonthroline monohydrate (20 mol%, 0.05 mmol, 10 mg) or bathophenanthroline (20 mol%, 0.05 mmol, 16.62 mg), $Cu(OAc)_2{\cdot}H_2O$ (0.25 mmol, 50 mg) were added. Then phenol (0.75 mmol) and α,β-unsaturated carboxylic acid (0.25 mmol) were introduced into the reaction mixture. Solid compounds were weighed before the other reagents, whereas liquid phenols/α,β-unsaturated carboxylic acids were added by micro-liter syringe and laboratory syringe under an air atmosphere. In the reaction tube 4 mL $ClCH_2CH_2Cl$ were added and O_2 was purged in the reaction mixture for 15 min. For the deuterated compounds (**3′a**–**6′c**), 500 μL D_2O were added by micro-liter syringe under the positive pressure of oxygen. Then the reaction mixture was vigorously stirred in a preheated oil bath at 130 °C for 24 h. After completion, the reaction mixture was filtered through a celite pad with ethyl acetate as the washing solvent. The ethyl acetate layer was washed with brine solution and dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography.

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