# Cationic Palladium(II)-Catalyzed Synthesis of 2-Substituted 3-Hydroxymethylbenzo[*b*]furans

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**Abstract:** A tandem reaction involving an intramolecular oxypalladation of an alkyne and an addition to the carbonyl group to quench the carbon–palladium bond to complete the catalytic cycle was developed. The reaction was catalyzed with the cationic palladium(II) species without the necessity of a redox system.

**Key words:** aldehyde, alkyne, cationic palladium(II) complex, 3-hydroxymethylbenzofuran, oxypalladation

The benzofuran moiety is popular in many biologically active natural and therapeutic products.[1] Some benzofuran-containing products may serve as targets or precursors for pharmaceutical researches and even as promising units in material science.[2] Many efforts have been made to achieve an efficient synthesis of this skeleton.[3] Among the various approaches to benzofurans, the transition-metal-catalyzed intramolecular cyclization would be straightforward and versatile.[4] It is worth noting that palladium-catalyzed heteroannulation reactions are now emerging as a unique, powerful, and versatile synthetic approach toward a variety of structural cores of heterocycles, especially for indoles and benzofurans.[4a,b,e] Palladium(0)-catalyzed annulation reactions of *o*-alkynyl-allyloxybenzenes or *o*-alkynylphenols with allyl carbonates were reported.[5] There were also some reports for the palladium(II)-catalyzed synthesis of multiply substituted benzofurans from 2-alkynylphenols because of their availability. Some groups reported the carboxylative annulation to synthesize benzofuran-3-carboxylic esters or acids.[6] Papers related to the synthesis of 3-alkenylbenzofurans by an oxypalladation–Heck-type coupling reaction were also reported.[7] In all of these tandem reactions, a redox system is necessary for the regeneration of the catalytic palladium(II) species.

In our previous work, we developed some tandem reactions initiated by nucleopalladation of alkynes and quenched by 1,2-addition to carbon–heteroatom multiple bonds.[8] The use of $Pd(OAc)_2$/bpy or cationic palladium complexes as catalysts is the key for the success of these reactions. In all of these reactions, palladium(II) species were regenerated in the final protonolysis step to complete the catalytic cycle without the necessity of a redox system.

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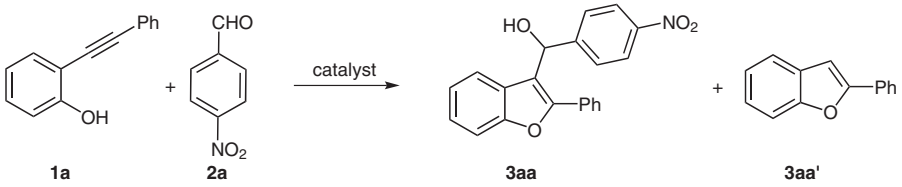
In an effort to expand the synthetic scope of previously reported palladium(II)-catalyzed annulation reactions, we explored here the reaction of 2-alkynylphenols with aldehydes to prepare substituted 3-hydroxymethylbenzofurans in one pot. In the literature, such compounds usually can be obtained by the reaction of 3-metalated benzofuran with aldehydes or ketones,[9] or from benzofurans and aldehydes by a Friedel–Crafts reaction.[10]

Initially, 2-phenylethynylphenol (**1a**) and *p*-nitrobenzaldehyde (**2a**) were chosen as the substrates to study the annulation reaction. Different palladium catalysts were firstly surveyed. When cationic palladium catalysts $[Pd(dppp)(H_2O)_2](BF_4)_2$ and $[Pd(dppp)(H_2O)_2](OTf)_2$ were used, the annulation product **3aa** could be obtained in moderate yield (Table 1, entries 1 and 2) together with the byproduct 2-phenylbenzofuran (**3aa′**). However, when the catalyst such as $[Pd(bpy)(H_2O)_2](OTf)_2$, $Pd(OAc)_2$/bpy or $Pd(CO_2CF_3)_2$/dppp was used, no product could be detected (Table 1, entries 3, 7, and 8). The cationic palladium(II) complexes took advantage in this reaction, which maybe due to their stronger Lewis acidity and vacant coordination.[11] Then a binuclear cationic palladium catalyst $[Pd(dppp)(\mu\text{-}OH)]_2(BF_4)_2$ was used, the desired product **3aa** could be obtained in 85% yield (Table 1, entry 4). THF was the best solvent (Table 1, entries 4–6). When 4 Å molecular sieve was added to the reaction system catalyzed by $[Pd(dppp)(H_2O)_2](BF_4)_2$, the yield of **3aa** increased to 90% (Table 1, entry 9).[12] Subsequently, the effect of temperature on the reaction was studied. Higher temperature was not good for the reaction, and lower temperature slowed the reaction progress (36 h, Table 1, entries 10–12). Finally, $[Pd(dppp)(H_2O)_2](BF_4)_2$ and 4 Å MS in THF at 45 °C were used as the optimal conditions. In the screening process above, the 2-phenylbenzofuran was found to be the main byproduct.

Under the optimized reaction conditions as shown in Table 1 (entry 9) a series of substituted 2-alkynylphenol and aromatic aldehydes were chosen to test this annulation reaction as shown in Table 2. Aldehydes with a strong electron-withdrawing group such as $NO_2$, CN, or $CF_3$ on the benzene ring provided good results (Table 2, entries 1–4, 10, and 11). When there are one or more halogen atoms on the benzene ring of the aldehydes, the reactions could proceed smoothly to provide the corresponding products in moderate to excellent yields (Table 2, entries 5–9 and 12). 4-Acetylbenzaldehyde could also react with **1a** in a yield of 52% (Table 2, entry

**Table 1** Optimization of the Reaction Conditions[a]

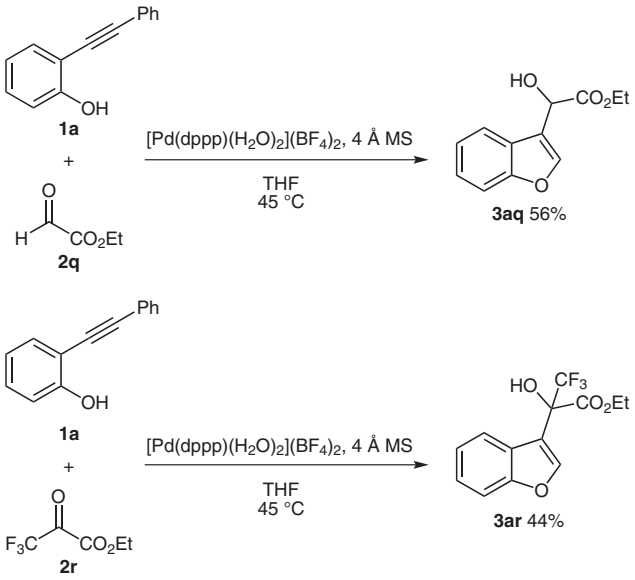



**1a** **2a** **3aa** **3aa'**

| Entry | Catalyst | Solvent | Time (h) | Yield of **3aa** (%)[b] |
|---|---|---|---|---|
| 1[c] | $[Pd(dppp)(H_2O)_2](BF_4)_2$ | THF | 1.7 | 66 |
| 2 | $[Pd(dppp)(H_2O)_2](OTf)_2$ | THF | 13 | 54 |
| 3 | $[Pd(bpy)(H_2O)_2](OTf)_2$ | THF | 48 | n.r. |
| 4 | $[Pd(dppp)(\mu\text{-}OH)]_2(BF_4)_2$ | THF | 3 | 85 |
| 5 | $[Pd(dppp)(\mu\text{-}OH)]_2(BF_4)_2$ | DME | 8 | trace |
| 6 | $[Pd(dppp)(\mu\text{-}OH)]_2(BF_4)_2$ | dioxane | 7 | 59 |
| 7 | $Pd(OAc)_2$/bpy | THF | 48 | n.r. |
| 8 | $Pd(CO_2CF_3)_2$/dppp | THF | 48 | n.r. |
| 9[d] | $[Pd(dppp)(H_2O)_2](BF_4)_2$ | THF | 2.5 | 90 |
| 10[c,d] | $[Pd(dppp)(H_2O)_2](BF_4)_2$ | THF | 2 | 66 |
| 11[d,e] | $[Pd(dppp)(H_2O)_2](BF_4)_2$ | THF | 2.8 | 85 |
| 12[d,f] | $[Pd(dppp)(H_2O)_2](BF_4)_2$ | THF | 36 | 94 |

[a] A mixture of **1a** (0.1 mmol), **2a** (0.2 mmol, 2.0 equiv), and the catalyst (5 mol%) were stirred at 45 °C in solvent.
[b] Isolated yields.
[c] Reflux.
[d] 4 Å MS was used.
[e] 60 °C.
[f] At r.t.

13). It is worth noting that benzaldehyde or 1-naphthylaldehyde could also be used to react with **1a**, even the yields were low (Table 2, entries 15 and 24).

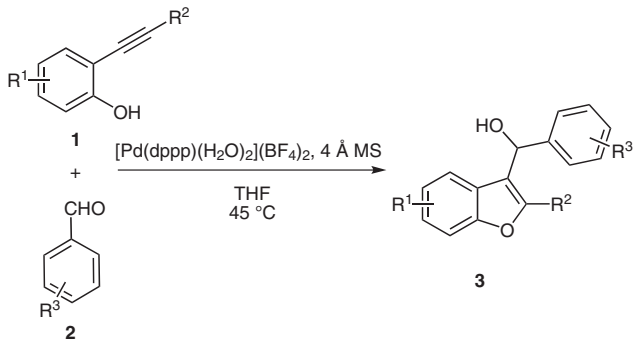



**Scheme 1** Tandem annulation reaction of 2-phenylethynylphenol with activated aldehyde or ketone

Furthermore, the reaction hardly occurred for 2-methylbenzaldehyde. For the substrates 2-alkynylphenols, alkynes bearing aryl groups substituted with F, Br, Me, or MeO reacted well with *p*-nitrobenzaldehyde to give the desired products (Table 2, entries 16, 17, and 19–22). However, when the phenyl ($R^2$) group was replaced by *n*-Bu or $CH_2OMe$, no reactions occurred at all. Then, some other activated aldehyde or ketone was used to examine the annulation reaction. Both ethyl glyoxylate and 3,3,3-trifluoropyruvate could react with substrate **1a** in moderate yields (Scheme 1). From the above-mentioned results, it could be seen that strong electron-withdrawing groups on the aldehydes were very important for this tandem reaction, which might be due to the change of the electrophilicity of the carbon atom of the aldehydes.

Some control experiments were also run to gain further insight into the mechanistic details of this sequential process. From the literature, it is known that 2-alkynylphenol derivatives could be easily transformed to benzofuran through intramolecular cyclization reaction under transition-metal catalysts,[13] and 3-unsubstituted benzofurans were also the main byproducts in our reactions. So the question aroused whether the intramolecular cyclization of 2-alkynylphenol occurred first and the generated ben-

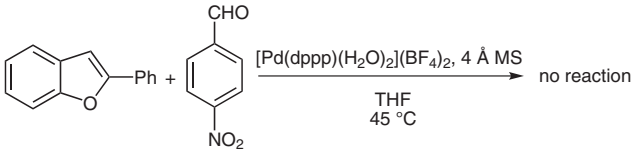
**Table 2** Tandem Annulation Reaction of 2-Arylethynylphenols with Substituted Aldehydes[a]




| Entry | 1 | | 2 | Yield (%)[b] |
|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | |
| 1 | H | **1a** Ph | **2a** 4-$O_2N$ | **3aa** 90 |
| 2 | H | **1a** Ph | **2b** 2-$O_2N$ | **3ab** 98 |
| 3 | H | **1a** Ph | **2c** 3-$O_2N$ | **3ac** 83 |
| 4 | H | **1a** Ph | **2d** 4-CN | **3ad** 93 |
| 5 | H | **1a** Ph | **2e** 2,4,5-$F_3$ | **3ae** 85 |
| 6 | H | **1a** Ph | **2f** 4-Cl | **3af** 53 |
| 7 | H | **1a** Ph | **2g** 2,6-$Cl_2$ | **3ag** 52 |
| 8 | H | **1a** Ph | **2h** 2,4-$Cl_2$ | **3ah** 45 |
| 9 | H | **1a** Ph | **2i** 2,3-$Cl_2$ | **3ai** 100 |
| 10 | H | **1a** Ph | **2j** 2-Cl-3-$F_3C$ | **3aj** 100 |
| 11 | H | **1a** Ph | **2k** 2-Cl-5-$O_2N$ | **3ak** 100 |
| 12 | H | **1a** Ph | **2l** 2-Br | **3al** 82 |
| 13 | H | **1a** Ph | **2m** 4-Ac | **3am** 52 |
| 14 | H | **1a** Ph | **2n** 2-Me | trace |
| 15 | H | **1a** Ph | **2o** H | **3ao** 37 |
| 16 | H | **1b** 4-$MeC_6H_4$ | **2a** 4-$O_2N$ | **3ba** 81 |
| 17 | H | **1c** 4-$BrC_6H_4$ | **2a** 4-$O_2N$ | **3ca** 68 |
| 18 | H | **1d** *n*-Bu | **2a** 4-$O_2N$ | n.r. |
| 19 | 4-Me | **1e** Ph | **2a** 4-$O_2N$ | **3ea** 64 |
| 20 | 4-F | **1f** Ph | **2a** 4-$O_2N$ | **3fa** 58 |
| 21 | 4-Br | **1g** Ph | **2a** 4-$O_2N$ | **3ga** 44 |
| 22 | 5-OMe | **1h** Ph | **2a** 4-$O_2N$ | **3ha** 66 |
| 23 | H | **1i** $CH_2OMe$ | **2a** 4-$O_2N$ | n.r. |
| 24 | H | **1a** Ph | **2p**[c] | **3ap** 51 |

[a] A mixture of **1** (0.1 mmol), **2** (0.2 mmol, 2.0 equiv), 4 Å MS (20 mg), and $[Pd(dppp)(H_2O)_2](BF_4)_2$ (5 mol%) were stirred in THF at 45 °C for 2–5 h.
[b] Isolated yields.
[c] Compound **2p** is 1-naphthylaldehyde.

zofuran subsequently transferred to the final products through palladium(II)-catalyzed Friedel–Crafts-type reaction. However, when 2-phenylbenzofuran was employed to react with *p*-nitrobenzaldehyde under standard reaction conditions, no reaction occurred at all (Scheme 2). This result indicated that our reaction was a tandem reaction, not a one-pot, two-step process.




**Scheme 2** Reaction of 2-phenylbenzo[*b*]furan with *p*-nitrobenzaldehyde

A possible mechanism of this annulation reaction was proposed as shown in Scheme 3. Initially, the active palladium species **A**, which came from the dissociation of the cationic palladium complex, activated the triple bond of the substrate **1** through coordination to form intermediate **B**. Then intermediate **C** was generated by an intramolecular attack of hydroxyl group to the activated triple bond. The carbon–palladium bond in intermediate **C** added to the carbonyl group of the aldehyde through intermediate **D** to produce intermediate **E**. The final product **3** was formed via protonolysis of intermediate **E** with regeneration of the palladium(II) species to make the catalytic cycle possible. Concerning the generation of the byproduct as shown in Scheme 3, the shift of the lone-pair electron of the oxygen atom may promote the protonolysis of the vinyl–Pd bond in the intermediate **C**.

In conclusion, we developed a new process for the synthesis of 2,3-disubstituted benzo[*b*]furans from readily accessible 2-alkynylphenols and aldehydes through cationic palladium(II) complex catalyzed annulation reaction.[14] This is a tandem reaction involving an oxypalladation of the alkyne followed by an addition to the carbonyl group of the aldehyde to quench the carbon–palladium bond by protonolysis. This tandem reaction is catalyzed by cationic Pd(II) species under relatively mild conditions and has a good tolerance of substituents without the necessity of a redox system. The asymmetric version of this reaction is under way in our group.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

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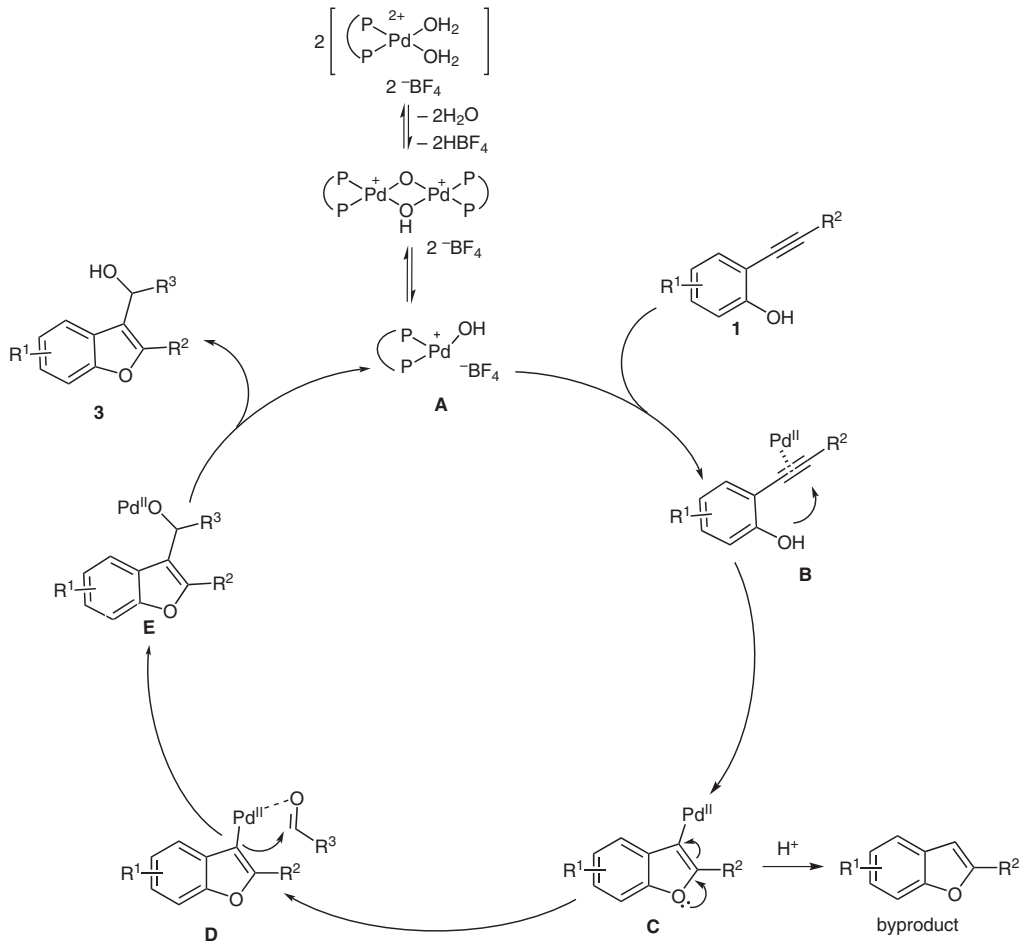


**Scheme 3** Possible mechanism for the annulation reaction of 2-alkynylphenols and aldehydes

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(14) **General Procedure for the Synthesis of 2-Substituted 3-Hydroxymethylbenzofuran Catalyzed by $[Pd(dppp)(H_2O)_2](BF_4)_2$**
A dried small tube with screw-cap was charged with

$[Pd(dppp)(H_2O)_2](BF_4)_2$ (1.2 mg, 0.002 mmol), 4 Å MS (20 mg), THF (0.5 mL), then substrates **1** (0.1 mmol) and aldehydes **2** (0.2 mmol, 2 equiv) were added to the mixture, and the solution was stirred at 45 °C until complete consumption of substrates **1** (monitored by TLC). Then, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel using EtOAc and PE as the eluent to afford the product.

**Compound 3aa:** solid; mp 87–89 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.8 Hz, 2 H), 7.77 (d, *J* = 6.8 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.52–7.45 (m, 4 H), 7.28–7.23 (m, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 6.39 (s, 1 H), 2.61 (d, *J* = 3.6 Hz, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 154.3, 153.5, 149.1, 147.1, 129.7, 129.5, 129.0, 127.7, 126.9, 124.9, 123.0, 121.0, 116.2, 111.4, 67.7. IR (KBr): ν = 3349, 3065, 1600, 1518, 1453, 1344, 1027, 834, 746 cm$^{-1}$. MS (EI): *m/z* (%) = 345 (100) [M$^+$], 328, 223, 165, 105, 77, 57. HRMS (EI): *m/z* calcd for $C_{21}H_{15}NO_4$: 345.1001; found: 345.1005.