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# Facile syntheses of substituted 2,3-dihydrofurans and benzofurans by palladium-catalyzed reactions of propargylic carbonates with nucleophiles

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**Abstract**—Substituted 2,3-dihydrofurans and benzofurans are synthesized by the palladium-catalyzed reaction of 5-methoxycarbonyloxy-3-pentyn-1-ols and 1-(2-hydroxyphenyl)-3-methoxycarbonyloxy-1-propyne with nucleophiles, respectively. Various substituted propargylic carbonates and nucleophiles are efficiently transformed to their corresponding products. Additionally, a reaction using substrates containing a nucleophilic phenoxy group within the same molecule also produces the corresponding dihydrofuran.
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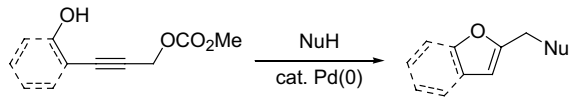
The chemistry of the reactions of propargylic compounds, via palladium catalysts, has received considerable attention due to their versatile and specific reactivity and extensive studies of these have now been undertaken.[1] Palladium-catalyzed reactions of propargylic carbonates with nucleophiles, first reported by Tsuji, are one of the most successful chemical processes that has been developed.[2,3] The reaction can be normally carried out under neutral conditions, and a number of various complex molecules can be prepared by specific substrate design. Based upon our current knowledge of these reactions, we have recently developed several cascade reactions of propargylic carbonates, containing a hydroxyl group at the propargylic position, with phenols. In these reactions, a rearrangement of a cyclobutane ring[4] and a $CO_2$-elimination–fixation process[5] have been shown to produce cyclopentanones and cyclic carbonates, respectively. To examine the scope of the reactivity of hydroxyl-substituted propargylic carbonates with phenols, we specifically investigated a propargylic carbonate, which has a hydroxyl group at the homopropargylic position. Herein, we describe a palladium-catalyzed reaction of propargylic carbonates, containing homopropargylic hydroxyl groups, with nucleophiles. These chemical processes selectively produce substituted 2,3-dihydrofurans and benzofurans in good yields (Scheme 1).

The initial reactions utilized 2,2-dimethyl-5-methoxycarbonyloxy-3-pentyn-1-ol **1a** and *p*-methoxyphenol (**2a**) (Table 1).[6] Reaction of **1a** with **2a** in the presence of 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol% dppe in dioxane at 60 °C, yields a dihydrofuran **3aa** at a yield of 45% (entry 1).[7] The structure of the product **3aa** was determined by its transformation into the known compound **4**.[8] Thus, catalytic hydrogenation of **3aa**, followed by the removal of a *p*-methoxyphenyl group with CAN produced compound **4** (Scheme 2). Dihydrofuran **3aa** is obtained in a 40% yield when dppp is used (entry 2) and it is clear that the reaction successfully proceeds in the presence of dppb and dppf to produce **3aa** in 74% and 84% yields, respectively (entries 3 and 4). In contrast, these reactions are significantly decreased when the monodentate ligands P(*o*-Tol)$_3$ and $PPh_3$ are utilized (entries 5 and 6).




**Scheme 1.**

*Keywords*: Palladium; Cyclization; Dihydrofurans; Phenols.
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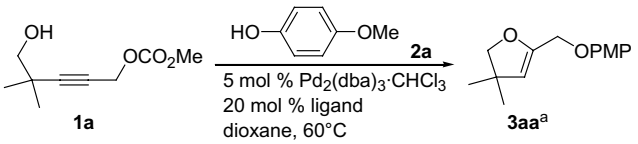
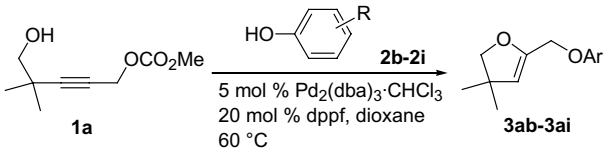
**Table 1.** Optimization of the palladium-catalyzed reaction of **1a** with **2a**




| Entry | Ligand | Yield (%)[b] |
|---|---|---|
| 1 | dppe | 45 (61) |
| 2 | dppp | 40 (45) |
| 3 | dppb | 74 |
| 4 | dppf | 84 |
| 5 | P(*o*-Tol)$_3$ | N.R. |
| 6[c] | PPh$_3$ | 15 (28) |

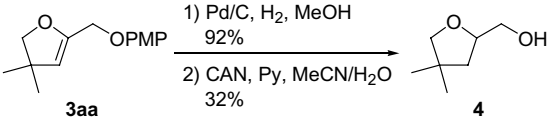
[a] PMP = *p*-methoxyphenyl.
[b] The yields shown in parentheses are based on the recovered starting material.
[c] Pd(PPh$_3$)$_4$ 10 mol % was used as a palladium catalyst.

**Table 2.** Reactions of propargylic carbonate **1a** with various phenols **2b–2i**



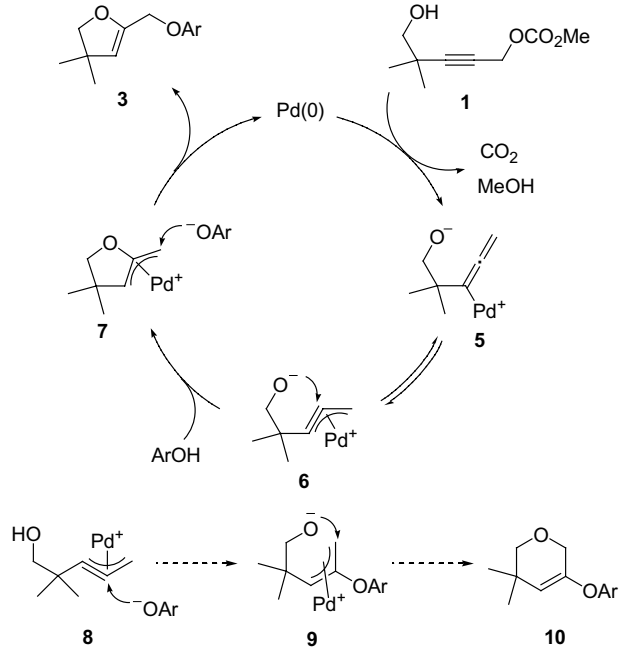

| Entry | ArOH | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | **2b**: R = 2-OMe | **3ab** | 83 |
| 2 | **2c**: R = 4-Me | **3ac** | 76 |
| 3 | **2d**: R = 2,4,6-trimethyl | **3ad** | 76 |
| 4 | **2e**: R = H | **3ae** | 82 |
| 5 | **2f**: 1-Naphthol | **3af** | 64 |
| 6 | **2g**: R = 4-Cl | **3ag** | 70 |
| 7 | **2h**: R = 4-F | **3ah** | 43 (55) |
| 8 | **2i**: R = 4-acetyl | **3ai** | 61 |

[a] The yields shown in parentheses are based on the recovered starting material.




**Scheme 2.**

A plausible mechanism for the formation of the dihydrofuran **3** is depicted in Scheme 3. In this process, a palladium catalyst initially promotes decarboxylation of a propargylic carbonate **1** to generate an allenylpalladium complex **5**. Species **5** is regarded as a π-propargylpalladium complex **6**,[9] which undergoes intramolecular nucleophilic attack by the resulting internal hydroxide to produce a π-allylpalladium intermediate **7**. Finally, regioselective addition of phenoxide to **7** at the less hindered site produces dihydrofuran **3**. In another possible pathway, the initial reactivity of a phenoxide group with the π-propargyl complex **8** followed by cyclization of the resulting π-allylcomplex **9** could yield dihydropyran **10**.[10] No formation of **10** was observed, however, which indicates that the hydroxide anion acts as a good nucleophile for the formation of five-membered rings, even in the presence of nucleophilic phenols.



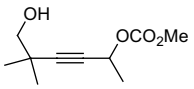
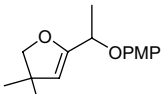
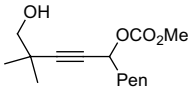
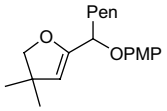
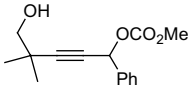
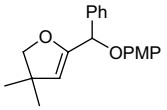

**Scheme 3.**

To more fully examine the scope of these reactions, various substituted phenols were introduced and tested as substrates (Table 2). The corresponding dihydrofurans **3ab**–**3ad** are formed in high yields when phenols bearing an electron donating group **2b**–**2d** are used (entries 1–3). Reactions of phenol (**2e**) and 1-naphthol (**2f**) also produce the corresponding products **3ae** and **3af** in good yields (entries 4 and 5). Dihydrofurans **3ag**–**3ai** are also obtained in acceptable yields by reactions employing the electron withdrawing group substituted phenols **2g**–**2i** (entries 6–8).

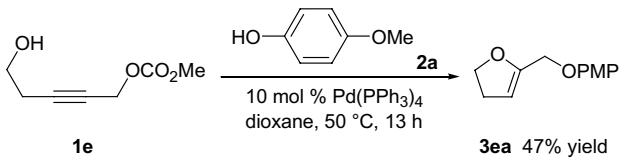
The results of the reactions of propargylic carbonates **1b**–**1d**, containing a substituent at the propargylic position, with *p*-methoxyphenol (**2a**) are summarized in Table 3. A methyl substituted compound **1b** undergoes a reaction that forms dihydrofuran **3ba** at a 64% yield (entry 1). Reactions of pentyl and phenyl substituted substrates **1c** and **1d** also synthesize the corresponding products **3ca** and **3da** at 70% and 66% yields, respectively (entries 2 and 3). These results show that the regioselective addition of phenol can proceed even in the presence of a bulky substituent at the propargylic position.

A reaction of propargylic carbonate **1e**, which has no substituent at the 2-position was then examined (Scheme 4). This reaction, in the presence of palladium, with dppf at 60 °C forms the corresponding product **3ea** at a 33% yield, as an unstable compound. After several attempts,

**Table 3.** Reactions of various propargylic carbonates **1b–1d** with *p*-methoxyphenol **2a**

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1[b] |  **1b** |  **3ba** | 64 |
| 2[b] |  **1c** |  **3ca** | 70 |
| 3[c] |  **1d** |  **3da** | 66 |

[a] Reactions were carried out in the presence of 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol% ligand, and 1.1 equiv of *p*-methoxyphenol **2a** in dioxane at 60 °C for 12–24 h.
[b] dppf was used as a ligand.
[c] dppb was used as a ligand.

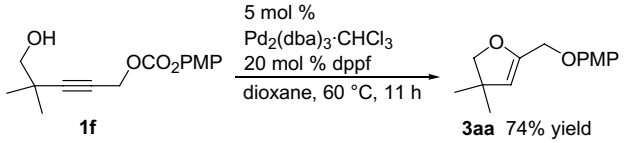



**Scheme 4.**

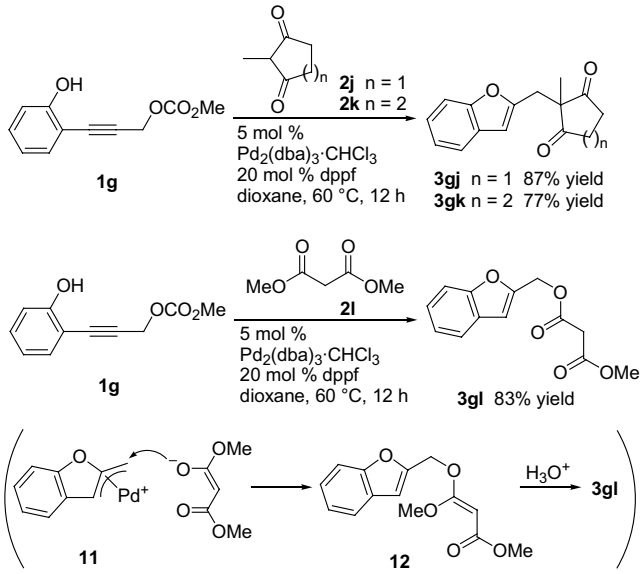
the yield was slightly increased to 47% by carrying out the reaction using $Pd(PPh_3)_4$ at 50 °C.[11]

The reaction of **1f**, containing a latent nucleophilic *p*-methoxyphenolic moiety as a part of the carbonate leaving group, was then examined (Scheme 5). When **1f** is subjected to a palladium–catalyzed reaction, the corresponding dihydrofuran **3aa** is formed at a 74% yield. In this reaction, the substrate initially releases the phenoxide, which then acts as a nucleophile for the resulting π-allyl complex **7** to efficiently produce the end product.

We further evaluated the reaction of **1g**, which has an introduced benzene ring within the molecule (Scheme 6). Our attempts to test the reaction of **1g** with various different phenols failed, because the reactive phenolic alcohol would also act as an additional nucleophile,




**Scheme 5.**




**Scheme 6.**

resulting in the formation of polymerized products. However, we were delighted that a reaction that produced benzofuran **3gj** at an 87% yield proceeded successfully when 2-methyl-1,3-cyclopentanedione **2j** was used as a nucleophile. The corresponding product **3gk** was obtained by reaction with 2-methyl-1,3-cyclohexanedione **2k** at a 77% yield. Interestingly, when dimethyl malonate **2l** is subjected to these reactions with **1g**, O-alkylated benzofuran **3gl** is produced at an 83% yield.[12] It was expected that in this case the reaction would proceed via a regioselective addition from the oxygen site to the π-allyl complex **11** followed by hydrolysis of the resulting enol ether **12** during the workup. It is not clear why the unusual O-alkylation occurs prior to the C-alkylation, and few examples have been previously reported concerning the regioselective O-alkylation of malonates to π-allylpalladium complexes.[13]

In conclusion, we have developed a methodology for the synthesis of substituted 2,3-dihydrofurans and benzofurans using a palladium catalyst. This process can produce a variety of dihydrofurans and benzofurans by reaction of propargylic carbonates, having a hydroxyl group at the homopropargylic position, with nucleophiles. Much attention has been paid to the synthesis of natural products containing these furan rings, which exhibit potentially very interesting biological activities.[14] Our process could therefore provide an efficient protocol for production of these molecules. Efforts to extend the scope of these reactions and their consequent application to the syntheses of natural products are currently in progress.

## Acknowledgements

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M.Y.) and Scientific Research on Priority Areas (A) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Prof. Masahiko Yamaguchi for his generosity and helpful discussions.

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3. (a) For recent examples of palladium-catalyzed reactions of propargylic carbonates with nucleophiles, see: Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Synlett.* **1996**, 553; (b) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025; (c) Labrosse, J.- R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527; (d) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869; (e) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499; (f) Damez, C.; Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2003**, *44*, 557; (g) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 8068.
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6. General procedure for palladium-catalyzed reactions of propargylic carbonates with phenols. Reaction of **1a** with **2a** (entry 5 in Table 1): To a stirred solution of propargylic carbonate **1a** (38.7 mg, 0.208 mmol) in dioxane (2 mL) we added *p*-methoxyphenol (**2a**) (28.4 mg, 0.229 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10.8 mg, 10.4 μmol) and dppf (23 mg, 41.6 μmol) in a sealed tube at room temperature. The reaction mixture was allowed to warm to 60 °C, and stirring was continued for 17 h. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane (2:98 v/v) as an eluent to produce 5-phenoxymethyl-2,3-dihydrofuran **3aa** (41 mg, 0.175 mmol, 84%) as colorless needles; $R_f = 0.70$ (AcOEt–hexane = 3:7 v/v); mp 28–29 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (s, 6H), 3.76 (s, 3H), 4.07 (s, 2H), 4.46 (s, 2H), 4.91 (s, 1H), 6.82 (dt, $J = 9.3$ and 2.8 Hz, 2H), 6.89 (dt, $J = 9.3$ and 2.8 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.6, 43.0, 55.6, 64.2, 83.1, 110.5, 114.6, 116.1, 152.3, 152.9, 154.3; IR (neat) 2866, 1506, 1229 cm$^{-1}$; MS (EI) *m*/*z* (relative intensity) 234 [M$^+$, 75], 219 (4), 111 (46), 96 (4), 81 (9), 65 (3), 51 (2); HRMS (EI) calcd for $C_{14}H_{18}O_3$ [M$^+$] 234.1256, was found to be 234.1275.
7. Recently, Mori reported a similar type of palladium-catalyzed reaction of propargylic carbonates with benzoate leading to formation of substituted carbapenams. In these reactions, nucleophilic benzoate reacts strongly with the π-allylpalladium complex from a more hindered site and produces a corresponding product having an *exo*-olefin, and hence exhibiting different regioselectivity from our result; see Ref. 3g.
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10. We previously observed the formation of phenoxy substituted dihydrofuran as a byproduct by the reaction of 4-methoxycarbonyloxy-2-butyn-1-ol with phenol, see Refs. 5a and 5b.
11. It is generally believed that a monodentate ligand is not suitable for the reaction of propargylic compounds with soft nucleophiles (see Refs. 2c,3g and 9c). The obtained result using monodentate $PPh_3$ is therefore interesting in view of this hypothesis, although the precise details of this reaction mechanism are still unclear.
12. The structure of **3gl** has been confirmed by the hydrolysis of this product to form a known benzofuran-2-yl methanol.
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