# C–H and C–Si Functionalization of Furan Derivatives: Palladium-Catalyzed Homocoupling and Arylation Reactions

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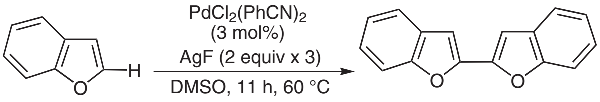
**Abstract:** Palladium-catalyzed arylation reactions of benzofuran derivatives are shown to take place at the carbon–hydrogen bond or carbon–silicon bond adjacent to the oxygen atom. A variety of furan derivatives are obtained in good yields.

**Key words:** C–H arylation, benzofuran, palladium, homocoupling reaction, cross-coupling reaction

We have recently shown that five-membered heteroaromatic compounds such as thiophene and thiazole undergo transition-metal-catalyzed homocoupling[1] and arylation reactions[2] at the C–H bond adjacent to the sulfur atom. The reactions have shown to proceed under mild conditions to form a carbon–carbon bond. Comparing with the related coupling with organometallic reagents such as boron, tin, Grignard, and zinc,[3] the direct coupling at the C–H bond is much straightforward and shows high atom efficiency.[4,5] Our concern is centered if the reaction occurs at the C–H bond of furan derivatives,[6] which possess oxygen atom in the five-membered aromatic ring, under the conditions for thiazoles and thiophenes. We herein describe that palladium-catalyzed homocoupling and arylation reactions takes place at the carbon–hydrogen bond adjacent to the oxygen atom.

We first examined the homocoupling of benzofuran (**1**). The reaction was carried out in the presence of $PdCl_2(PhCN)_2$ (3 mol%) in anhydrous DMSO at 60 °C. The addition of AgF as an activator was carried out three times (2 + 2 + 2 equiv) with stirring for 3 hours, 3 hours, and 5 hours, respectively, to afford the corresponding homocoupling product **2** in 56% yield.[7] In sharp contrast with the case of thiophene and thiazole derivatives,[1] it was found to be important to perform the reaction with carefully dehydrated DMSO, otherwise significant decrease of the yield occurred to result in giving a much lower yield despite complete consumption of **1** probably due to the hydrolytic decomposition leading to unidentified byproducts (Scheme 1).

The palladium-catalyzed C–H arylation of **1** with several aryl iodides were then carried out. The reaction conditions employed was also similar to the related arylation of thiophenes and thiazoles.[2,4] As summarized in Table 1, reactions proceeded in moderate to good yields. Iodobenzene (**3a**), 4-methoxy-iodobenzene (**3b**), and ethyl 4-iodobenzoate (**3c**) were found to react at the C–H bond adjacent to the oxygen atom to afford the coupling product **4**. The reaction with electron-deficient aryl iodide appears to result in a relatively superior yield. In addition to benzofuran (**1**), furfural (**5**) also reacted with **3b** and **3c** to give the arylated product **6b** and **6c**, respectively.

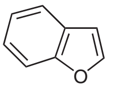
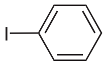
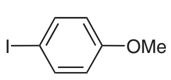
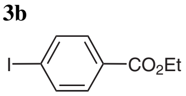
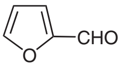


1

2 56%

**Scheme 1**

**Table 1** CH Arylation of Furan Derivatives[a]

| Furan derivative | Aryl iodide | Product | Yield (%)[b] |
|---|---|---|---|
| <br>**1** | <br>**3a** | **4a** | 41[c] |
| **1** | <br>**3b** | **4b** | 41 |
| **1** | <br>**3c** | **4c** | 53 |
| <br>**5** | **3b** | **6b** | 33 |
| **5** | **3c** | **6c** | 40[c,d] |

[a] The reaction was carried out with **1** (0.5 mmol), of $PdCl_2(PPh_3)_2$ (3 mol%), ArI **3** (0.6 mmol), and AgF (3 × 0.5 mmol) in DMSO (2 mL) at 100 °C for 6 h (3 × 2 h).

[b] Unless noted, isolated yield was shown.

[c] The yield was estimated by $^1H$ NMR using trichloroethene as an internal standard.

[d] The reaction was carried out with $AgNO_3$/KF (4 × 0.5 equiv)

With the reaction conditions to undergo C–H arylation reactions of furan derivatives with aryl iodide **3**, it was found that functionalization of the related C–Si bond of furans took place in a similar manner.[8] When the trimethylsilylated benzofuran (**7**) was treated with **3a** in the presence of 3 mol% of $PdCl_2(PPh_3)_2$ and AgF (2 × 1 equiv) at 100 °C, the coupling product was obtained in 46% yield.

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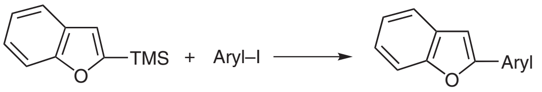
The reaction was found to take place with several aryl iodides as shown in Table 2. The reaction with the combination of $AgNO_3$ and KF, in which in situ formation of AgF would occur, also proceeded to afford **4a** in a comparable yield. Aryl iodides bearing an electron-withdrawing or -donating group were subjected to the reaction. In particular, the use of 4-nitro-iodobenzene (**3f**) and 4-cyano-iodobenzene (**3g**) underwent the arylation reaction in excellent yields. An activator, AgF or $AgNO_3$/KF, was appeared to be effective in the functionalization of silylated furan derivatives, while the attempted coupling reaction of **7** and **3c** with TBAF that was a well-known reaction promoter for Hiyama coupling[8] resulted to afford only a trace amount of the coupling product **4c**.

**Table 2** Arylation of TMS-benzofuran (**7**) with Aryl Iodide[a]

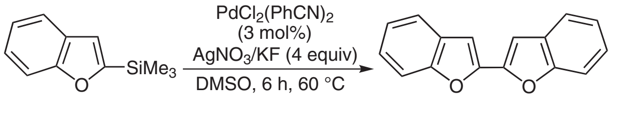


**7** + **3** → **4**

| Aryl iodide **3** | Additive (equiv) | Time | Yield (%)[b] |
|---|---|---|---|
| PhI (**3a**) | AgF (1 + 1) | 2 × 2 h | 46 |
| | $AgNO_3$/KF (6 × 0.25) | 6 × 1 h | 52 |
| 4-$MeOC_6H_4I$ (**3b**) | AgF (1 + 1) | 1 h + 2 h | 53 |
| | $AgNO_3$/KF (6 × 0.25) | 6 × 1 h | 47 |
| 4-$EtOCOC_6H_4I$ (**3c**) | $AgNO_3$/KF (6 × 0.25) | 6 × 1 h | 75 |
| 4-$F_3CC_6H_4I$ (**3d**) | $AgNO_3$/KF (6 × 0.25) | 6 × 1 h | 43 |
| $C_6F_5I$ (**3e**) | $AgNO_3$/KF (6 × 0.25) | 6 × 1 h | 54 |
| 4-$O_2NC_6H_4I$ (**3f**) | $AgNO_3$/KF (6 × 0.25) | 6 × 1 h | 86 |
| 4-$NCC_6H_4I$ (**3g**) | $AgNO_3$/KF (6 × 0.25) | 6 × 1 h | 85 |

[a] The reaction was carried out with **7** (0.5 mmol), ArI **3** (0.6 mmol), $PdCl_2(PPh_3)_2$ (3 mol%), AgF or $AgNO_3$/KF in DMSO (1 mL) at 100 °C.
[b] Isolated yield.

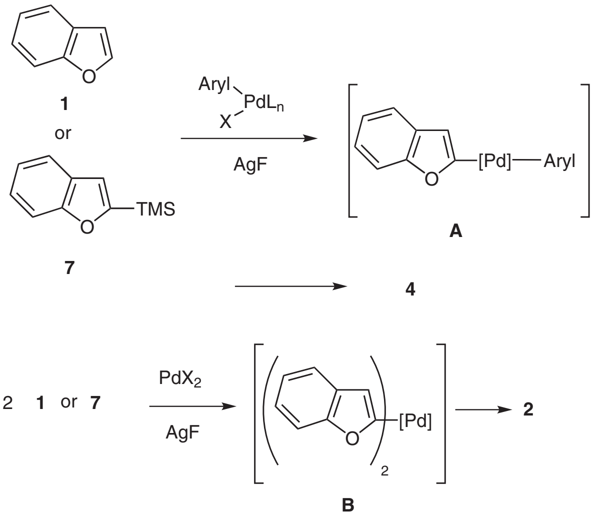
Homocoupling of trimethylsilyl benzofuran (**7**) also proceeded in a similar manner. Treatment of **7** with 3 mol% of $PdCl_2(PhCN)_2$ and $AgNO_3$/KF (2 equiv) at 60 °C for four hours in DMSO afforded the homocoupling product **2** in 75% yield after stirring at 60 °C for six hours. The yield of **2** was also superior to the case of C–H homocoupling (Scheme 2).



**7** **2** 75%

**Scheme 2**

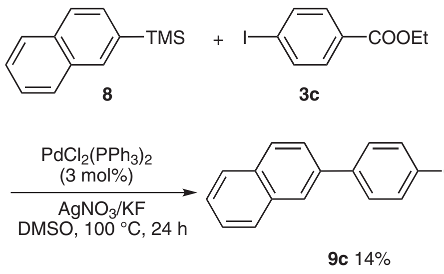
The plausible reaction mechanism of furan arylation at the C–H bond and the C–Si bond would be electrophilic substitution of the hydrogen or silicon atom with palladium affording the corresponding organopalladium species **A** (Scheme 3).[9] Following reductive elimination would lead to the product **4**. The mechanism of homocoupling would be the double substitution reaction and the reductive coupling leading to **2** through difuryl palladium intermediate **B**. These reactions would occur similarly to the case of thiophene and thiazole derivatives, which we have shown previously.[1,2] The silver species employed as an activator was confirmed in the reactions of thiophene and thiazole derivatives to be transformed into AgI, while Ag(0) was obtained in homocoupling.



**Scheme 3** Plausible mechanism of C–H and C–Si homocoupling and arylation reactions

Worthy of note is that the trialkylated silyl group can be employed for the coupling reaction by the activation of $AgNO_3$/KF system. Although coupling reactions of organosilanes with various electrophiles are shown to proceed by the catalysis of transition-metal complex, available silicon species have been limited to those bearing heteroatom substituents on silicon,[8] otherwise, transmetalation of the trialkylsilyl group with transition metal hardly occurs. Accordingly, the reaction of trimethylsilylated furan derivatives would be induced by the effect of the oxygen atom of furan. Indeed, the reaction of 2-naphthyl(trimethyl)silane (**8**) with **3c** in the presence of a palladium catalyst under similar conditions ($AgNO_3$/KF as an activator) resulted in considerably lower yield to afford **9c** (Scheme 4).

In summary, we showed that the palladium-catalyzed arylation and homocoupling reactions of furan derivatives using the $AgNO_3$/KF system as an activator take place at the carbon–hydrogen or the carbon–silicon bond adjacent to the oxygen atom to afford the corresponding coupling products in moderate to good yields. In the functionalization of furan derivatives at the carbon–silicon bond, the $AgNO_3$/KF system served as an effective activator show-



**Scheme 4**

ing that arylation and homocoupling of trimethylsilylated furan are a novel class of reactions. These methods are effective for the functionalization reactions of furan derivatives, which are potentially employed as several advanced organic materials showing light-emitting characteristics, etc.[10]

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(10) **Experimental Procedure for the Homocoupling Reaction of 1**

To a 50 mL Schlenk tube equipped with a magnetic stirring bar were added PdCl$_2$(PhCN)$_2$ (5.8 mg, 0.015 mmol), DMSO (3 mL), benzofuran (**1**, 55 μL, 0.5 mmol), and AgF (127 mg, 1.0 mmol) in one portion, and the resulting mixture was stirred at r.t. for 3 h. Additional AgF (2 × 1.0 mmol) were then added, and stirring was continued for further 3 h and 5 h, respectively. The reaction mixture was passed through a Celite pad to remove a solid residue, and the cake was washed repeatedly with Et$_2$O. The filtrate was washed with H$_2$O twice (2 × 50 mL) and brine (50 mL). Then, the organic layer was dried over anhyd MgSO$_4$ and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 33 mg of **2** (56%).

**2,2′-Bibenzofuran (2)**[11]

Mp 202–203 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.17$ (s, 2 H), 7.25–7.37 (m, 4 H), 7.55 (d, $J = 8.0$ Hz, 2 H), 7.63 (d, $J = 8.2$ Hz, 2 H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 103.7$,

111.3, 121.4, 123.3, 125.1, 128.5, 147.7, 155.1. IR (KBr): 1441, 1256, 1173, 1049, 876, 804, 750 $cm^{-1}$.

**Experimental Procedure for the C–Si Arylation Reaction of 7 and 3c**

To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added, $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol), DMSO (1 mL), 2-trimethylsilylbenzofuran (**7**, 95 mg, 0.5 mmol), and ethyl 4-iodobenzoate (**6c**, 165 mg, 0.6 mmol) under argon atmosphere. The mixture was heated in an oil bath at 100 °C, KF (7.3 mg, 0.125 mmol), and $AgNO_3$ (21.2 mg, 0.125 mmol) were added in one portion, and the resulting mixture was continued for 1 h. Addition of $AgNO_3$/KF (0.125 mmol) and stirring for 1 h at 100 °C were repeated for further 5 times. After cooling to r.t., the mixture was passed through a Celite pad, which was washed with EtOAc repeatedly. The filtrate was washed with $H_2O$ twice. Then the organic layer was dried over anhyd $MgSO_4$ and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 99 mg of **4** (75%).[12]

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