C-H and C-Si Functionalizations of Furan Derivatives. Palladium-catalyzed Homocoupling and Arylation Reactions

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C–H and C–Si Functionalizations of Furan Derivatives. Palladium-catalyzed Homocoupling and Arylation Reactions

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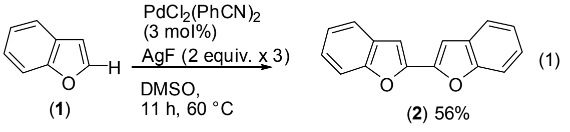
Abstract: Palladium-catalyzed arylation reactions of benzofuran derivatives were shown to take place at the carbon–hydrogen bond or carbon–silicon bond adjacent to the oxygen atom. The variety of furan derivatives are obtained in good yields.

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

We have recently shown that 5-memberd 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 to the reaction 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.

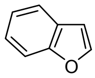
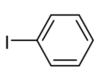
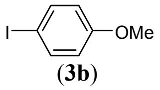
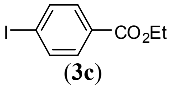
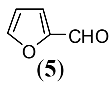
We first examined the homocoupling of benzofuran **1**. The reaction was carried out in the presence of $PdCl_2(PhCN)_2$ (3 mol%) in anhydrous DMSO at 60 ºC. The addition of AgF as an activator was carried out 3 times (2+2+2 equiv.) with stirring for 3 h, 3 h and 5 h, respectively, to afford the corresponding homocoupling product **2** in 56% yield. In sharp contract 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**.

equation 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 to afford the coupling product **4** at the C–H bond adjacent to the oxygen atom. 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.

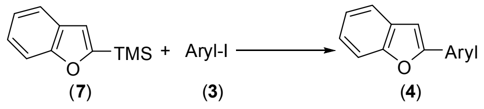
Table 1 CH arylation of furan derivatives[a]

Furan derivative	Aryl–I	Yield (%)[b]
 (**1**)	 (**3a**)	41[c]
1	 (**3b**)	41
1	 (**3c**)	53
 (**5**)	**3b**	33
5	**3c**	40[c,d]

[a] The reaction was carried out with **1** (0.5 mmol) with 3 mol% of $PdCl_2(PPh_3)_2$, aryl iodide **3** (0.6 mmol), and AgF (0.5 mmol x 3) in DMSO (2 mL) at 100 °C for 6 h (2 h x 3).
[b] Unless noted, isolated yield was shown. [c] The yield was estimated by ^{1}H NMR using trichloroethene as an internal standard. [d] The reaction was carried out with $AgNO_3$/KF (0.5 equiv. x 4)

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.[3,7] When the trimethylsilylated benzofuran (**7**) was treated with **3a** in the presence of 3 mol% of $PdCl_2(PPh_3)_2$ and AgF (1 equiv x 2) at 100 °C, the coupling product was obtained in 46% yield. 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-nitoro-iodobenzene (**3f**) and 4-cyano-iodobenzene (**3g**) underwent the arylation reaction in excellent yields. An activator AgF or $AgNO_3$/KF 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 promotor for Hiyama coupling[7a] resulted to afford only a trace amount of the coupling product **4c**.

Table 2 Arylation of TMS–benzofuran (**7**) with aryl iodide.[a]

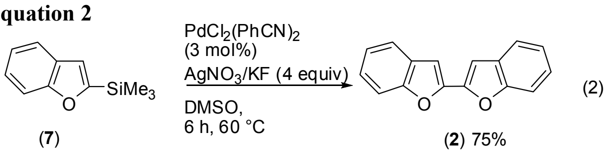


Aryl iodide (**3**)	Additive (equiv)	Time	Yield[b] (%)
C_6H_5I **(3a)**	AgF (1+1)	2 h x 2	46
	$AgNO_3$/KF (0.25 x 6)	1 h x 6	52
4-$MeOC_6H_4I$ **(3b)**	AgF (1+1)	1 h + 2 h	53
	$AgNO_3$/KF (0.25 x 6)	1 h x 6	47
4-$EtOCOC_6H_4I$ **(3c)**	$AgNO_3$/KF (0.25 x 6)	1 h x 6	75
4-$CF_3C_6H_4I$ **(3d)**	$AgNO_3$/KF (0.25 x 6)	1 h x 6	43
C_6F_5I **(3e)**	$AgNO_3$/KF (0.25 x 6)	1 h x 6	54
4-$O_2NC_6H_4I$ **(3f)**	$AgNO_3$/KF (0.25 x 6)	1 h x 6	86
4-NCC_6H_4I **(3g)**	$AgNO_3$/KF (0.25 x 6)	1 h x 6	85

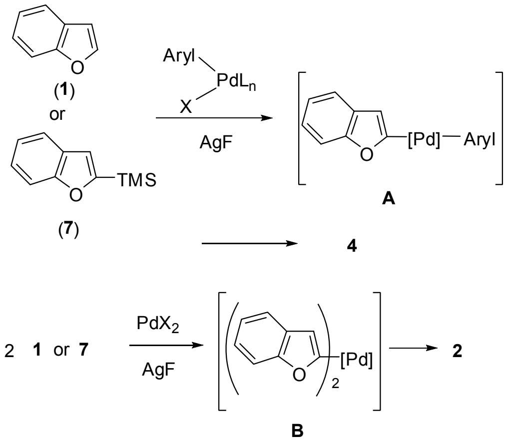
[a] The reaction was carried out with **7** (0.5 mmol), aryl iodide **3** (0.6 mmol), 3 mol% of $PdCl_2(PPh_3)_2$, AgF or $AgNO_3$/KF in DMSO (1 mL) at 100 ºC. [b] Isolated yield.

Homocoupling of trimethylasilyl 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 ºC for 4 h in DMSO afforded the homocoupling product **2** in 75% yield after stirring at 60 ºC for 6 h. The yield of **2** was also superior to the case of C–H homocoupling.

equation 2



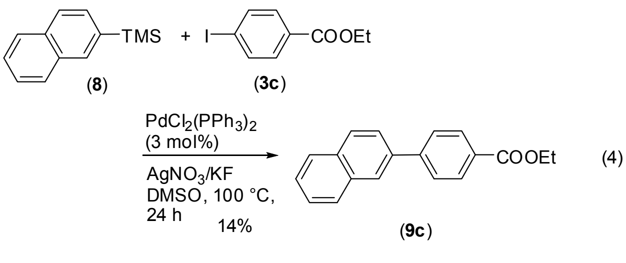
The plausible reaction mechanism of furan arylation at the C–H bond and the C–Si bond would be electrophilic substitution of the hydrogen or silicon atom with a palladium affording the corresponding organopalladium species **A**. Following reductive elimination would lead to the product **4**. The mechanism of homocoupling would be the double substitution reaction and the following reductive coupling through diaryl palladium intermediate **B** leading to **2**. These reactions would be similar to the case of thiophene and thiazole derivatives, which we have shown previously.[8]



Scheme 1 Plausible mechanism of C−H and C−Si homocoupling and arylation reactions.

Worthy of note is that the trialklated silyl group is 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,[3,7] 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-natphthyl(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 **9**.

equation 3



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 showing that arylation and homocoupling of trimethylsilylated furan are 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.

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(9) **Experimental Procedure for the Homocoupling Reaction of 1:** To a 50 mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PhCN)_2$ (5.8 mg, 0.015 mmol), DMSO (3 mL), 2-trimethylsilyl-benzofuran (**7**, 91 μL, 0.5 mmol), potassium fluoride (58 mg, 1.0 mmol), and $AgNO_3$ (170 mg, 1.0 mmol) in one portion and the resulting mixture was stirred at room temperature for 2 h. Additional potassium fluoride (58 mg, 1.0 mmol) and $AgNO_3$ (170 mg, 1.0 mmol) were then added and stirring was continued for further 4 h. The reaction mixture was passed through a Celite pad to remove a solid residue and the cake was washed repeatedly

with diethyl ether. The filtrate was washed with water twice (50 mL x 2) and brine (50 mL). Then, the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 44 mg of **2** (75%). **2,2'-Bibenzofuran (2):**[11] Mp 202-3; ^{1}H NMR δ 7.17 (s, 2H), 7.25-7.37 (m, 4H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR δ 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}.

(10)**Experimental Procedure for the C-H Cross-coupling 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 ^oC, potassium fluoride (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 ^oC were repeated for further 5 times. After cooling to room temperature, the mixture was passed through a Celite pad, which was washed with ethyl acetate repeatedly. The filtrate was washed with water twice. Then the organic layer was dried over anhydrous magnesium sulfate 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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Graphical abstract

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C–H arylation, benzofuran, palladium, homocoupling reaction, cross coupling reaction