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DIRECT β-ARYLATION OF FURANS WITH ARYL IODIDES CATALYZED BY DINUCLEAR PALLADIUM COMPLEXES

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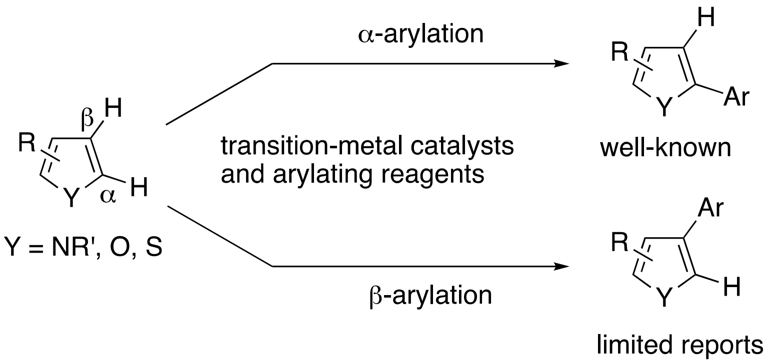
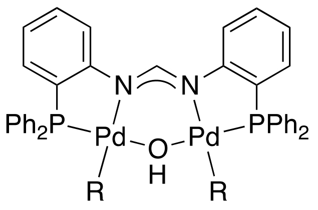
Abstract – Dinuclear palladium complexes formed by a chelate-bridging ligand showed β-selectivity in the direct arylation of furans with iodoarenes. In contrast, the arylation using PPh_3 or bpy as ligands gave α-arylfurans as major products. The arylation can be applied to several furans bearing functional groups except electron-withdrawing groups.

Direct arylation of aryl C-H bonds catalyzed by transition-metal complexes has attracted considerable attention as an alternative to the conventional palladium-catalyzed cross-coupling reactions.[1] The direct arylation has the advantage of enabling a more straightforward access to target molecules without prefunctionalization, and thus minimizing side products in fewer steps. However, difficulty in controlling of site-selectivity is a considerable problem for the direct arylation because there are several aryl C-H bonds in starting materials in most cases. While this issue is difficult to be solved for the reaction of benzene rings, the reaction of heteroarenes such as pyrroles, furans and thiophenes often proceeds with high site-selectivity due to an electronic effect of hetero atoms. Actually, there have been a lot of reports for α-selective direct arylation of the heteroarenes (Scheme 1).[2] Although β-selective direct arylation is desired as a complementary reaction, the number of reports for the β-selective reaction has been still limited, especially for the reaction of furans.[3] The β-arylation of thiophenes has been reported by several groups in the last decade.[4-10] The efficient β-selective arylation of pyrroles was reported by Itami and Yamaguchi's group in 2014.[11] In contrast, there is no efficient method for the β-arylation of furans, except the arylation of furans bearing directing groups[12] or furans in which the α positions are already substituted.[13] In 1985, Itahara demonstrated an oxidative coupling between furans and arenes, giving a mixture of β-aryl- and α-arylfurans in a ratio of 2:1.[14] However, stoichiometric amounts of palladium and large excess amounts of arenes were necessary for this reaction. Herein, we report a palladium-catalyzed arylation of furans with iodoarenes, giving β-arylfurans as major products.

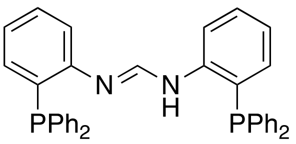


Scheme 1. Site-selectivity in transition metal-catalyzed arylation of pyrroles, furans and thiophenes

We previously reported that the reaction of thiophenes with iodoarenes in the presence of dinuclear palladium catalysts **1a** or **1b** gave β-arylthiophenes with high site-selectivity (Figure 1).[10,15] Thus, the application of the complexes **1a** and **1b** to the arylation of furans was investigated. The reaction of 2-*n*-pentylfuran with iodobenzene in the presence of acetoxy complex **1a** and Ag_2CO_3 showed good β-selectivity and gave 2-*n*-pentyl-4-phenylfuran **3a** and 2-*n*-propyl-5-phenylfuran **3b** in a ratio of 5.3:1 although the yield was moderate (Table1, entry 1). No unreacted furan and no multi-arylated furan were observed at all. The rest of 2-*n*-pentylfuran seems to be oligomerized or polymerized. While the reaction with trifluoroacetoxy complex **1b** gave a similar result, *p*-tolyl complex **1c** was ineffective as a catalyst (entries 2 and 3). Carboxyl ligands may be essential for the arylation. By addition of a half equivalent of chelate-bridging ligand dpfamH (**2**), the reaction using palladium acetate also afforded **3a** as a major product although the yield and selectivity are lower (entry 4). The dinuclear structure of the catalysts may be essential for the arylation. When equimolar amounts of **2** and palladium were used, the reaction did not proceed, not giving any products (entry 5). The reaction without **2** afforded the α-arylfuran **3b** as a major product in a lower yield (entry 6). The addition of ordinary phosphine and nitrogen ligands such as PPh_3, dppp and bpy did not switch the α-selectivity (entries 7-9).



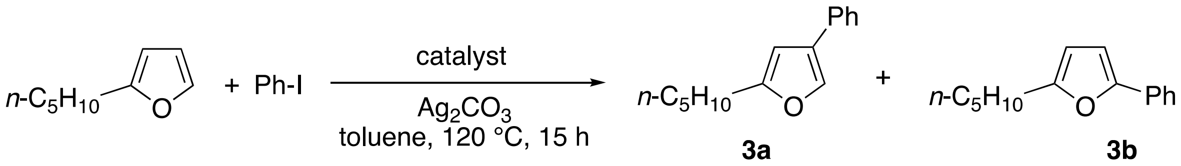
1a (R = AcO)
1b (R = CF_3CO_2)
1c (R = *p*-Tol)



dpfamH (**2**)

Figure 1. Dinuclear palladium complexes and chelate-bridging ligand dpfamH

Table 1. Palladium-catalyzed reactions of 2-*n*-pentylfuran with iodobenzene[a]

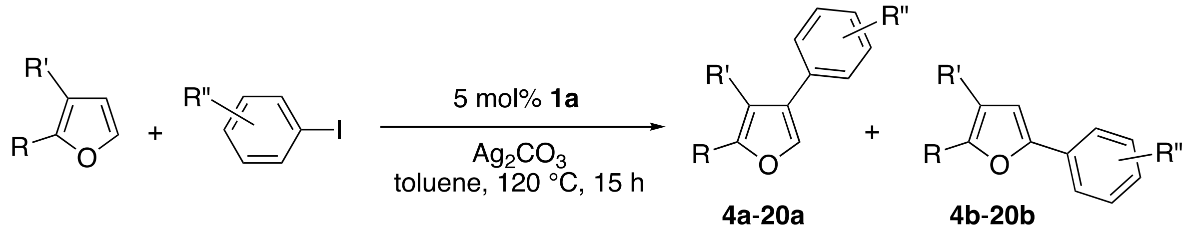


Entry	Catalyst (mol%)	Additive (mol%)	Yield[b] (%)	**3a**:**3b**[c]
1	**1a** (5)	–	41	5.3:1
2	**1b** (5)	–	32	4.9:1
3	**1c** (5)	–	2	1:2.3
4	$Pd(OAc)_2$ (10)	**2** (5)	33	4.0:1
5	$Pd(OAc)_2$ (10)	**2** (10)	trace	
6	$Pd(OAc)_2$ (10)	–	15	1:1.3
7	$Pd(OAc)_2$ (10)	PPh_3 (10)	12	1:1.7
8	$Pd(OAc)_2$ (10)	dppp (10)	10	1:3.0
9	$Pd(OAc)_2$ (10)	bpy (10)	20	1:>99

[a] A mixture of 2-*n*-pentylfuran (0.30 mmol), iodobenzene (0.30 mmol), and Ag_2CO_3 (0.30 mmol) in toluene (1.5 mL) was stirred at 120 °C for 15 h in the presence of the catalyst and the additive. [b] GC yields. [c] Determined by GC.

Table 2 summarizes the results of the reaction of various furans with various iodoarenes in the presence of **1a**.[16,17] The reaction of 2-benzylfuran afforded 2-benzyl-4-phenylfuran **4a** selectively (entries 1 and 2). 2-Benzyl-3-phenylfuran was not observed at all. This result shows that the benzylic position is not reactive and the benzyl group does not affect the site-selectivity in the reaction with **1a**.[12h] The reaction tolerates benzyl ether, silyl ether and acetal, giving β-phenylfurans **6a**-**8a** selectively (entries 3-5). Although formyl and methoxycarbonyl groups are also tolerated, the reaction of furfural and methyl 2-furoate afforded only α-phenylfurans **9b** and **10b** with high site-selectivity (entries 6 and 7). Both the yield and the site-selectivity were decreased in the reaction of 2,3-dimethylfuran, probably due to steric repulsion of the methyl group at the C3 position (entry 8). In the reaction of 3-silyloxymethylfuran, the β-selectivity was improved although the yield was low (entry 9). Coordination of palladium to the substituent would affect the site-selectivity. The reaction of iodoarenes substituted with electron-donating groups at the para and meta positions gave β-arylfurans **13a**, **14a** and **16a** with good site-selectivity (entries 10, 11 and 13). A substituent at the ortho position decreased the product yield (entry 12). The reaction of iodoarenes substituted with electron-withdrawing groups also proceeded to give arylfurans **17**-**20** (entries 14-17). However, the β-selectivity is lower than that in the reaction with iodobenzene. The reaction of *p*-iodonitrobenzene afforded α-arylfuran **20b** as a major product (entry 17).

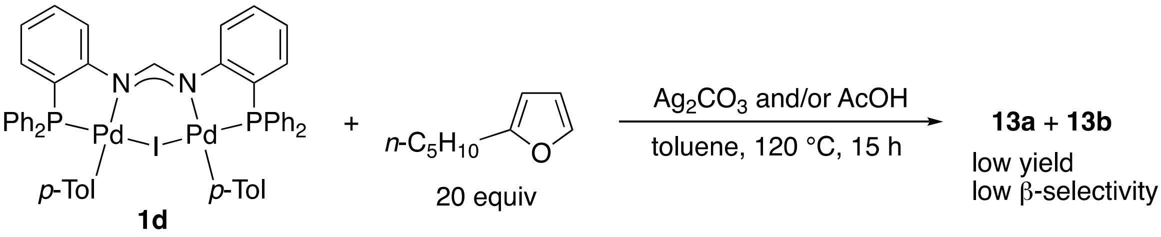
Table 2. Palladium-catalyzed reactions of furans with iodoarenes[a]



Entry	R	R'	R''	Product	Yield[b] (%)	**a**:**b**[c]
1	Bn	H	H	**4**	41	4.9:1
2	CH_2-*p*-Tol	H	H	**5**	40	5.3:1
3	CH_2OBn	H	H	**6**	54	2.7:1
4	CH_2OTBS	H	H	**7**	52	4.3:1
5	CH_2OTHP	H	H	**8**	50	2.7/1
6	CHO	H	H	**9**	23	1:>99
7	CO_2Me	H	H	**10**	70	1:>99
8	Me	Me	H	**11**	10	1.6:1
9	H	CH_2OTBS	H	**12**	28	6.1:1
10	*n*-C_5H_{10}	H	*p*-Me	**13**	44	5.3:1
11	*n*-C_5H_{10}	H	*m*-Me	**14**	50	4.0:1
12	*n*-C_5H_{10}	H	*o*-Me	**15**	19	3.0:1
13	*n*-C_5H_{10}	H	*m*-MeO	**16**	40	2.8:1
14	*n*-C_5H_{10}	H	*p*-MeCO	**17**	38	2.7:1
15	*n*-C_5H_{10}	H	*p*-MeOCO	**18**	47	3.0:1
16	*n*-C_5H_{10}	H	*p*-CF_3	**19**	25	1.6:1
17	*n*-C_5H_{10}	H	*p*-NO_2	**20**	35	1:1.4

[a] A mixture of a furan (0.30 mmol), a iodoarene (0.30 mmol), and Ag_2CO_3 (0.30 mmol) in toluene (1.5 mL) was stirred at 120 °C for 15 h in the presence **1a** (0.015 mmol). [b] Isolated yields. [c] Determined by GC.

To gain insight into the mechanism of the arylation, some reactions of the dinuclear palladium complexes with reagents used in the arylation were investigated. The reaction of the acetoxy complex **1a** with 2-*n*-pentylfuran or iodobenzene gave mixtures of many unidentified complexes. Next, the reaction of iodo-bridged palladium complex **1d** was performed (Scheme 2). The complex **1d** is one of plausible intermediates in the arylation using *p*-iodotoluene. The reaction of **1d** with 2-*n*-pentylfuran gave only a trace amount of arylated furan **13**. Addition of Ag_2CO_3 increased the yield of **13** to 6%. However, only α-isomer **13b** was obtained. The reaction in the presence of Ag_2CO_3 and AcOH afforded a 1:1 mixture of **13a** and **13b** in low yield. Since high β-selectivity was not observed in the reaction of **1d** with 2-*n*-pentylfuran, the complex **1d** may not be an intermediate of the catalysis. Details of the reaction mechanism are unclear at the present time.



Scheme 2. Reaction of iodo-bridged *p*-tolylpalladium **1d** with 2-*n*-pentylfuran

In summary, we found that the direct arylation of furans with iodoarenes proceeds with good β-selectivity by using dinuclear palladium complexes formed by the chelate-bridging ligand **2** as catalysts. The arylation can be applied to several furans bearing functional groups except electron-withdrawing groups. Mechanistic studies and applications of the catalysts to other site-selective coupling reactions are in progress.

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16. Typical procedure for direct arylation of furans with iodoarenes: To a mixture of **1a** (0.015 mmol, 14 mg) and Ag_2CO_3 (0.30 mmol, 83 mg) were added toluene (1.5 mL) and then benzylfuran (0.30 mmol, 45 μL) and iodobenzene (0.30 mmol, 33 μL) in a pressure vial. After stirring at 120 °C for 15 h, the mixture was cooled to room temperature and filtered through a short plug of silica gel using EtOAc as an eluent. Evaporation of the filtrate and silica gel column chromatography (hexane) of the residue gave a mixture of **4a** and **4b** in 41% yield (29 mg). Analytical pure **4a** was obtained by flash column chromatography. **4a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.62 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.36-7.21 (m, 8H), 6.32 (s, 1H), 4.00 (s, 2H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 155.74, 137.80, 137.28, 132.62, 128.75, 128.70, 128.56, 127.08, 126.80, 126.60, 125.66, 105.58, 34.62; HRMS (EI): calcd for $C_{17}H_{14}O$: 234.1045. Found; 234.1016.
17. Spectral data for representative products. **6a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.71 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.40-7.23 (m, 8H), 6.64 (s, 1H), 4.59 (s, 2H), 4.51 (s, 2H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 152.82, 138.56, 137.78, 132.31, 128.79, 128.44, 127.93, 127.77, 127.12, 127.03, 125.77, 108.55, 72.02, 63.96; HRMS (EI): calcd for $C_{18}H_{16}O_2$: 264.1150. Found; 264.1135. **15a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37 (s, 1H), 7.32 (m, 1H), 7.24-7.17 (m, 3H), 6.18 (s, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.68 (m, 2H), 1.39-1.33 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 156.47, 138.02, 135.62, 132.71, 130.58, 129.00, 126.86, 126.08, 125.84, 106.55, 31.42, 28.01, 27.65, 22.42, 21.25, 14.02; HRMS (EI): calcd for $C_{16}H_{20}O$: 228.1514. Found; 228.1465. **18a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.02 (d, *J* = 8.9 Hz, 2H), 7.68 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 2H), 6.33 (s, 1H), 3.92 (s, 3H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.68 (m, 2H), 1.39-1.31 (m, 4H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 166.93, 158.26, 137.68, 137.52, 130.11, 128.16, 126.08, 125.31, 103.72, 52.03, 31.32, 28.01, 27.57, 22.40, 13.98; HRMS (EI): calcd for $C_{17}H_{20}O_3$: 272.1412. Found; 272.1379.