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Palladium-Catalyzed Direct C-4 Arylation of 2,5-Disubstituted Furans with Aryl Bromides

Aditya L. Gottumukkala[a] and Henri Doucet[a,*]

[a] Institut Sciences Chimiques de Rennes,UMR 6226 CNRS-Université de Rennes "Catalyse et Organometalliques", Campus de Beaulieu, 35042 Rennes, France
Fax: (+33)-(0)2-2323-6939; phone: (+33)-(0)2-23-23-63-84; e-mail: henri.doucet@univ-rennes1.fr

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Abstract: A simple and atom-economic procedure for the selective C-4 arylation of 2,5-disubstituted furans *via* C–H bond activation using electron-deficient aryl bromides is reported. Only 0.5 mol% of the commercially available dimeric (allene)palladium chloride, $[Pd(C_3H_5)Cl]_2$, was employed as catalyst. This environmentally attractive procedure has been found to be tolerant to a variety of functional groups on the aryl bromide such as carbonyl, nitrile, nitro, fluoro, ester or trifluoromethyl.

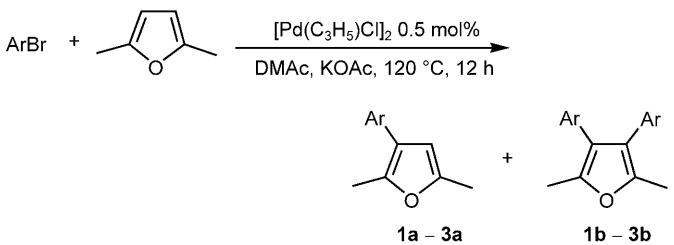
Keywords: aryl bromides; atom-economy; C–H bond activation; furans; palladium

Substituted furans continue to attract the attention of synthetic organic chemists, due to their inherent biological activity as evidenced by a number of recent reviews and communications.[1–3] Conventional methods for the synthesis of arylfurans include metal-catalyzed cross-coupling reactions such as Suzuki,[4] Stille[5] or Negishi[6] type reactions, which permit the coupling or aryl halides with organometallic derivatives of furans. Nevertheless, these procedures require the appropriate functionalization of one or both the coupling partners. Moreover, they produce stoichiometric amounts of metallic salts as by-products.

Among the various arylfurans, C-4 arylated carbonylfurans are of particular interest as they form a key structural unit of several natural products. Classical methods for their synthesis are based on regioselective Vilsmeier formylation, of pre-arylated furans.[7] Alternatively, metal-mediated cyclizations of pre-grafted propargyl alcohols to form the substituted arylfurans have also been reported.[8] Other methods include the bromination of 2,5-disubstituted furans, followed by bromide-lithium exchange and arylation.[2b] However, these protocols are multi-step approaches, resulting in relatively low overall yields, with the formation of considerably large amount of waste products.

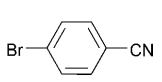
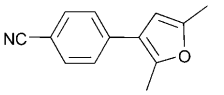
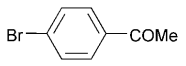
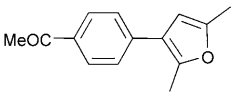
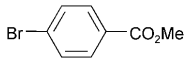
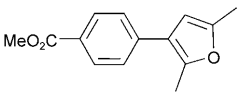
The direct coupling of furans with aryl halides *via* C–H activation/functionalization would provide a cost-effective and environmentally attractive procedure for the preparation of arylfurans. The C-2 or C-5 selective arylation of heteroaromatics including furans *via* a palladium-catalyzed C–H bond activation has been largely described in recent years.[9] On the other hand, the selective C-3 or C-4 arylation of furans using such a reaction has attracted less attention. Some examples of regioselective intramolecular cyclization of furan derivatives have been reported.[10] The perarylation of furans or diarylation of benzofuran has also been described.[11] However, to the best of our knowledge, the selective C-3 or C-4 arylation of furans *via* a palladium-catalyzed bimolecular C–H bond activation reaction has not been reported. Thus, it would be useful to develop a simple procedure allowing the direct arylation of furans to obtain 3- or 4-arylated furans in a regioselective manner.

We initially directed our efforts towards palladium-catalyzed direct arylation of the symmetrically substituted 2,5-dimethylfuran with aryl bromides (Scheme 1, Table 1). The reaction was found to produce **1a**–**3a**, with moderate yields using only 0.5



Scheme 1.

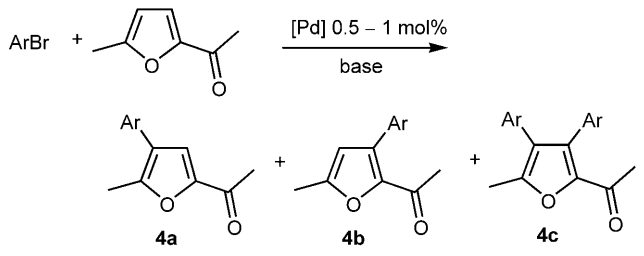
Table 1. Pd-catalyzed direct arylation of 2,5-dimethylfuran (Scheme 1).[a]

Entry	Aryl bromide	Major product	Yield [%]
1		**1a** 	52
2		**2a** 	36
3		**3a** 	46

[a] *Reaction conditions:* $[Pd(C_3H_5)Cl]_2$ (0.5 mol%), aryl bromide (0.5 mmol), 2,5-dimethylfuran (1.5 mmol), KOAc (1 mmol), DMAc (3 mL), 120 °C, 12 h, isolated yields.

mol% of $[Pd(C_3H_5)Cl]_2$ as catalyst, in the presence of KOAc as base, DMAc as solvent, at 120 °C for 12 h. Despite the use of an excess of 2,5-dimethylfuran (3 equiv.), the formation of relatively large quantities of diarylated products **1b**–**3b**, was also observed. In addition, the formation of homocoupling products of the aryl bromides was inevitable, lowering the yields. The highest yield (52%) was observed using 4-bromobenzonitrile (Table 1, entry 1). 4-Bromoacetophenone and methyl 4-bromobenzoate resulted in moderate yields of 36 and 46% of **2a** and **3a**, respectively (Table 1, entries 2 and 3).

Then, we studied the regioselectivity of this arylation reaction using non-symmetrically 2,5-disubstituted furans. When using 2-acetyl-5-methylfuran and KOAc as base, we generally observed a regioselective coupling in favour of the 4-arylated compound **4a** (Scheme 2). This regioselectivity suggests that the coordination of the metal species to the carbonyl group of the furan is not an essential step of the catalytic cycle. In the course of this reaction, the formation of products **4b** and **4c** was also observed. We observed that the ratio of products **4a**/**4b**/**4c** strongly depends on the reaction conditions and catalyst (Scheme 2, Table 2). In order to control the regioselectivity of this coupling, we performed a series of experiments using various solvents, bases and catalysts. We chose



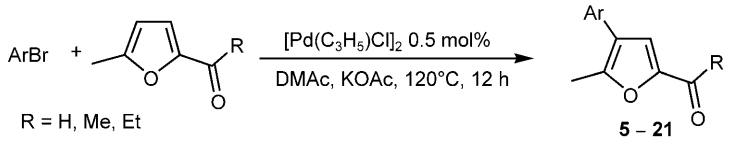
Scheme 2.

Table 2. Arylation of 2-acetyl-5-methylfuran, optimization of the reaction conditions (Scheme 2).[a]

Entry	Solvent	Base	Catalyst	Conv. [%]	Ratio [%] **4a**/**4b**/**4c**
1	DMAc	KOAc	$Pd(OAc)_2$	82	67/33/0
2	DMAc	KF	$Pd(OAc)_2$	55	39/39/12
3	DMAc	Cs_2CO_3	$Pd(OAc)_2$	54	0/42/58
4	DMAc	Na_2CO_3	$Pd(OAc)_2$	75	21/27/52
5	DMAc	K_2CO_3	$Pd(OAc)_2$	11	0/14/86
6	DMAc	K_3PO_4	$Pd(OAc)_2$	61	0/20/80
7	Xylene	KOAc	$Pd(OAc)_2$	18	nd
8	DMF	KOAc	$Pd(OAc)_2$	5	nd
9	DME	KOAc	$Pd(OAc)_2$	25	71/29/0
10	NMP	KOAc	$Pd(OAc)_2$	88	59/32/9
11	DMAc	KOAc	$Pd(OAc)_2$/DPPB	100	51/40/9[b]
12	DMAc	KOAc	$Pd(OAc)_2$/DPPE	100	54/35/11[b]
13	DMAc	KOAc	$Pd(OAc)_2$/PPh_3	100	57/38/5[c]
14	DMAc	KOAc	$[Pd(C_3H_5)Cl]_2$	93	87/13/0[d]
15	DMAc	KOAc	$[Pd(C_3H_5)Cl]_2$/DPPB	100	71/26/3[b]
16	DMAc	KOAc	$[Pd(C_3H_5)Cl]_2$/PPh_3	100	49/40/11[c]

[a] *Reaction conditions:* $Pd(OAc)_2$ (1 mol%) or $[Pd(C_3H_5)Cl]_2$ (0.5 mol%), 4-bromoacetophenone (0.5 mmol), 2-acetyl-5-methylfuran (1 mmol), base (1 mmol), solvent (3 mL), 12 h, conversions and ratios of **4a**/**4b**/**4c** determined by GC and NMR.
[b] 1 mol% of diphosphine ligand.
[c] 2 mol% of PPh_3.
[d] Isolated yield of **4a**: 63%.

the reaction of 2-acetyl-5-methylfuran with 4-bromoacetophenone, as the model reaction (Scheme 2). Initially, a series of bases was screened to determine their influence on the selectivity employing $Pd(OAc)_2$ (1 mol%) as catalyst, DMAc as the solvent, at 120 °C, for 12 h. Bases exhibit a considerable difference of efficiency and selectivity for this reaction (Table 2, entries 1–6). The best results for C-4 arylation were obtained using KOAc. In addition to the high conversion of the aryl bromide, a selectivity of 67% in favour of **4a** was observed (Table 2, entry 1). Bases such as KF or Na_2CO_3 led to almost equimolar mixtures of **4a** and **4b** together with diarylated product **4c**. On the other hand, Cs_2CO_3, K_2CO_3 or K_3PO_4 gave only C-3 arylation and diarylated products **4b** and **4c**. This dramatic switch in selectivity might come from different mechanisms. The presence of NaOAc should lead to the formation of ionic Pd^+ AcO^- complexes, whereas Cs_2CO_3, K_2CO_3 might stabilize neutral PdX species. The ionic Pd^+ AcO^- complexes should favour an electrophilic aromatic substitution mechanism and the PdX species a Heck-type reaction.[9a] Next, we examined the influence of the solvent. The non-polar



Scheme 3.

solvent xylene gave only traces of expected product (Table 2, entry 7). Among the polar solvents, the use of DME or DMF resulted in low conversion (Table 2, entries 8 and 9). DMAc and NMP showed nearly equal conversions of the starting material (Table 2, entries 1 and 10). However, DMAc gave a higher selectivity in **4a** and was employed for further optimization. The selectivity of the reaction was also largely dependent on the catalyst (Table 2, entries 11–16). We observed that $[Pd(C_3H_5)Cl]_2$, in the absence of phosphine, exhibit the highest selectivity (87%) towards the desired product **4a** (Table 2, entry 14). Lower selectivities were obtained in the presence of phosphine ligands (Table 2, entries 11–13 and 15, 16).

Then, we explored the scope and limitations of this reaction using various aryl bromides and 2-carbonyl-5-methylfurans (Scheme 3), using these optimized coupling conditions, ($[Pd(C_3H_5)Cl]_2$, KOAc, DMAc at 120 °C for 12 h). The results are summarized in the Table 3. 2-Formyl-5-methylfuran was coupled selec-

Table 3. 4-Arylation of 2-carbonyl-5-methylfurans with aryl bromides (Scheme 3).[a]

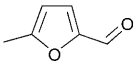
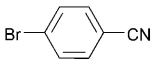
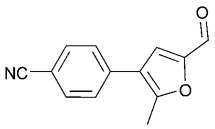
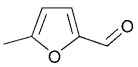
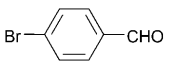
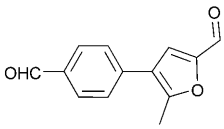
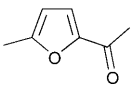
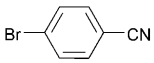
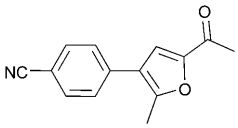
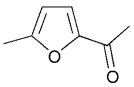
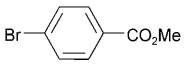
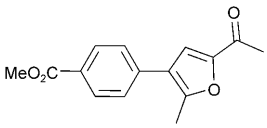
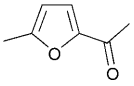
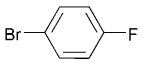
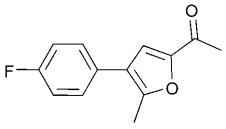
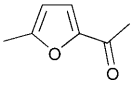
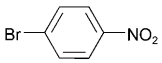
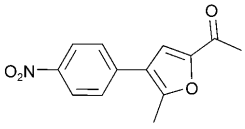
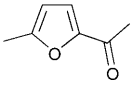
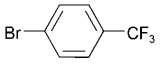
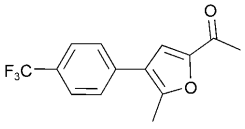
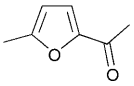
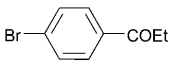
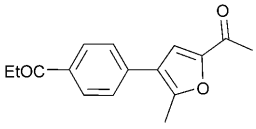
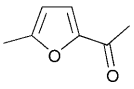
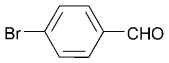
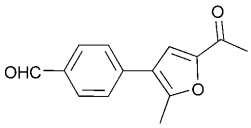
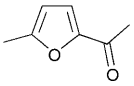
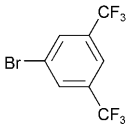
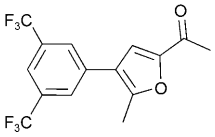
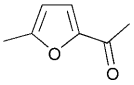
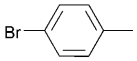
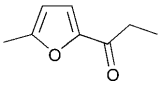
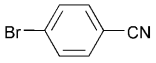
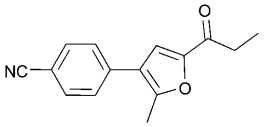
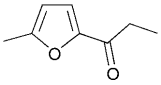
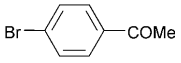
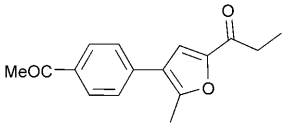
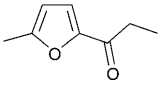
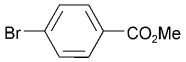
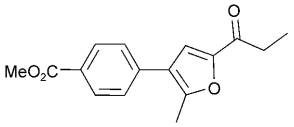
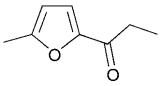
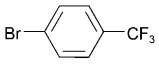
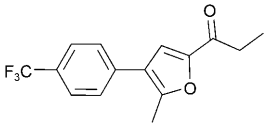
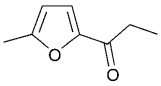
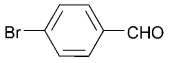
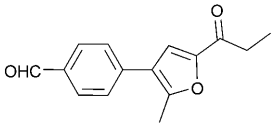
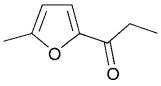
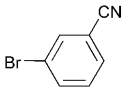
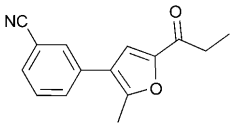
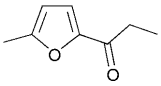
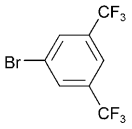
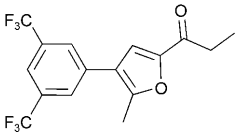
Entry	Furan derivative	Aryl bromide	Product		Yield [%]
1			**5**		48
2			**6**		54
3			**7**		76
4			**8**		36
5			**9**		72
6			**10**		52
7			**11**		56
8			**12**		53

Table 3. (Continued)

Entry	Furan derivative	Aryl bromide	Product		Yield [%]
9			**13**		65
10			**14**		46
11					traces
12			**15**		63
13			**16**		38
14			**17**		65
15			**18**		58
16			**19**		58
17			**20**		67
18			**21**		61

[a] *Reaction conditions:* $[Pd(C_3H_5)Cl]_2$ (0.5 mol%), aryl bromide (0.5 mmol), furan derivative (1 mmol), KOAc (1 mmol), DMAc (3 mL), 120 °C, 12 h, isolated yields.

tively to 4-bromobenzonitrile and 4-bromobenzaldehyde to form **5** and **6** in 48 and 54% yields, respectively (Table 3, entries 1 and 2). The reactions of 2-acetyl-5-methylfuran with electron-deficient aryl bromides also proceeded conveniently in most cases. Good regioselectivities and yields were observed using 4-bromobenzonitrile, 4-bromofluorobenzene or 4-bromobenzaldehyde, resulting in 76, 72 and 65% yields of **7**, **9** and **13**, respectively (Table 3, entries 3, 5 and 9). With these substrates, the reaction proceeded cleanly. Using 4-bromonitrobenzene, 4-(trifluoromethyl)bromobenzene, 4-bromopropiophenone or 3,5-bis(trifluoromethyl)bromobenzene, **10**–**12** and **14** were obtained in 46-56% yields (Table 3, entries 6–8 and 10). On the other hand, the use of 4-bromotoluene resulted in only traces of the expected product (Table 3,

entry 11). This demonstrates that the electron density on the aryl bromide drastically affects the reaction.

1-(5-Methylfuran-2-yl)propan-1-one was also found to be a suitable reactant (Table 3, entries 12–18). A relatively high yield of 63% was observed in the presence 4-bromobenzonitrile (Table 3, entry 12). Similar yields (58–67%) were observed in the presence of methyl 4-bromobenzoate, 4-(trifluoromethyl)bromobenzene, 4-bromobenzaldehyde, 3-bromobenzonitrile or 3,5-bis(trifluoromethyl)bromobenzene (Table 3, entries 14–18). A relatively lower yield of the 38% was obtained using 4-bromoacetophenone due to the formation of unidentified side-products (Table 3, entry 13).

In summary, we report herein an atom-economic method for the selective C-4 arylation of 2,5-disubstituted furans. No prior preparation of an organometallic derivative is required, reducing the number of required steps to obtain these compounds. An electron-withdrawing substituent on the furan seems to favour the reaction. This procedure has proved to be tolerant to a variety of functional groups on the aryl bromide such as ester, formyl, acetyl, nitrile, nitro, fluoro or trifluoromethyl. Moreover, it is economically and environmentally attractive as the only by-products are AcOH/KBr instead of metallic salts using classical coupling procedures.

Experimental Section

General Remarks

All chemical reactants and metal complexes were obtained from commerical sources and used without further purification. DMAc analytical grade (99%) was not distilled before use. KOAc (99+%) was employed. All reactions were run under argon using vacuum lines in Schlenk tubes and oven-dried glassware. ^{1}H (200 MHz) and ^{13}C (50 MHz, unless specifically mentioned) NMR spectra were recorded in $CDCl_3$ solutions. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$. Flash chromatographies were performed on silica gel (230–400 mesh).

General Procedure

In a typical experiment, the aryl bromide (0.5 mmol), furan derivative (1 mmol) and KOAc (1 mmol) were introduced in an oven-dried Schlenk tube, equipped with a magnetic stirring bar. The $[Pd(C_3H_5)Cl]_2$ (0.5 mol%) and DMAc (3 mL) were added, and the Schlenk tube was purged several times with argon. The Schlenk tube was placed in a pre-heated oil bath and reactants were allowed to stir for 12 h. Then, the reaction mixture was analyzed by gas chromatography to determine the conversion. The solvent was removed by heating the reaction vessel under vacuum and the residue was charged directly onto a silica gel column. The products were eluted, using appropriate mixtures of diethyl ether and pentane.

4-(2,5-Dimethylfuran-3-yl)benzonitrile (1a): The reaction of 4-bromobenzonitrile (0.091 g, 0.5 mmol), 2,5-dimethylfuran (0.144 g, 1.5 mmol) and KOAc (0.098 g, 1 mmol) with $[Pd(C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) affords the corresponding product **3a**; yield: 0.051 g (52%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3H), 2.45 (s, 3H), 6.15 (s, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 13.4, 106.3, 109.3, 119.2, 120.2, 127.6, 132.4, 139.4, 147.4, 150.6; anal. calcd. for $C_{13}H_{11}NO$: C 79.16, H 5.62; found: C 78.97, H 5.82.

Compound **1b** was also isolated in low yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.37 (s, 6H), 7.13 (d, J = 8.4 Hz, 4H), 7.59 (d, J = 8.4 Hz, 4H).

1-[4-(5-Acetyl-2-methylfuran-3-yl)phenyl]ethanone (4a): The reaction of 4-bromoacetophenone (0.100 g, 0.5 mmol), 2-acetyl-5-methylfuran (0.124 g, 1 mmol) and KOAc (0.098 g, 1 mmol) with $[Pd(C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) affords the corresponding product **4a**; yield: 0.076 g (63%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3H), 2.59 (s, 3H), 2.66 (s, 3H), 7.35 (s, 1H), 7.51 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 25.8, 26.6, 118.5, 123.2, 127.5, 128.9, 135.7, 137.2, 150.8, 154.0, 186.2, 197.4; anal. calcd. for $C_{15}H_{14}O_3$: C 74.36, H 5.82; found: C 74.21, H 5.68.

Compounds **4b** and **4c** were also isolated in low yields. ^{1}H NMR (**4b**, 200 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 2.48 (s, 3H), 2.65 (s, 3H), 6.35 (s, 1H), 7.74 (d, J = 8.1 Hz, 2H), 8.00 (d, J = 8.1 Hz, 2H); ^{1}H NMR (**4c**, 200 MHz, $CDCl_3$): δ = 2.44–2.65 (m, 12H), 7.35–7.55 (m, 4H), 7.90–8.10 (m, 4H).

Supporting Information

Additional experimental procedures and spectral data are available as Supporting Information.

Acknowledgements

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