Palladium-Catalyzed Direct Arylation Reaction of 2,3,5-Trisubstituted Furans with Aryl Iodides or Aryl Bromides

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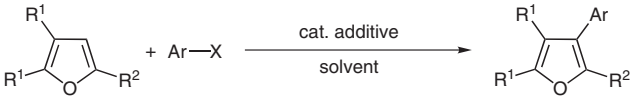
Abstract: Pd-catalyzed direct arylation of 2,3,5-trisubstituted furans with a variety of aryl iodides or aryl bromides that showed high activity with reasonably broad scope was developed. Under optimal conditions, all reactions gave the desired products in moderate to good yields.

Key words: palladium, arylation reaction, 2,3,5-trisubstituted furans, aryl iodides, aryl bromides

The transition-metal-catalyzed direct arylation reaction to form C–C bonds is one of the most powerful tools for the preparation of complex biaryl compounds under mild conditions.[1] Development of new transition-metal-catalyzed approaches to construct biaryl compounds for their syntheses is currently a popular research area. Recently, the vast majority of direct arylation reactions were carried out to construct biaryl compounds by Pd,[2] Rh,[3] Ru[4] triad. And there were also several reviews on the subject of C–H direct arylation,[5] many focusing on areas such as catalyzed arylation toward direct arylation of heterocycles,[6] intermolecular direct arylation reactions,[7] and synthesis of polyarenes.[8] Among these new approaches and methodologies, palladium was probably the most versatile and widely used metal for diect arylation to synthesize diaryl compounds. Over the past decades, palladium-catalyzed direct C–H bond functionalization became a highly attractive strategy to form C–C bonds in organic synthesis[9] and represented a highly desirable goal.[10] This was mainly due to palladium's relatively lower cost and better performance in autocatalysts. In this paper, we describe an efficient Pd-catalyzed direct arylation process to construct biaryl compounds.

Biaryl compounds were always one of the most important class of organic molecules[11] because of the abundance of the biaryl structural motif in natural products, in biologically active molecules,[12] and in materials chemistry. As a pharmacophore, those compounds exhibited a wide range of biological activities such as antibiotic, anti-inflammatory, anticancer, and antifungal.[13] Due to their wide range of practical applications, the development of new efficient and convenient methods for the arylation of heterocycles still remains a challenging goal. Therefore, more and more synthetic organic chemists have focused much of their attention on the transition-metal-catalyzed reactions to develop novel and convenient direct arylation of heteroarenes for the synthesis of biaryl compounds. Although several methodologies have been developed to synthesize biaryl compouds during the last decades, there is still an intrinsic need to develop new arylation of heteroarenes for the synthesis of more diverse biaryl compounds under mild conditions and simple catalytic systems.

In the current study, we report our new finding which was a facile direct arylation reaction for the synthesis of biaryl compounds from aryl halides(X = I, Br) with 2,3,5-trisubstituted furans (Scheme 1).



Scheme 1 Arylation of furans with aryl halides

Diethyl 5-formylfuran-2,3-dicarboxylate (**1a**) and iodobenzene (**2a**) were chosen as model substrates to optimize the reaction conditions for the formation of biaryl compounds in our initial study (Table 1). Various palladium catalysts were firstly examined for the direct arylation process. As demonstrated in Table 1, we were pleased to observe that the desired product **3a** was formed in 36% yield in the presence of $PdCl_2$ and Cs_2CO_3 (Table 1, entry 1) in *N*,*N*-dimethylformamide (DMF) for 20 hours at 100 °C. Undoubtedly, palladium was an efficient catalyst for this transformation. Thus, other palladium catalysts, such as $Pd(OAc)_2$ and $Pd(dba)_2$, were also employed in this reaction, and the arylation product **3a** was obtained in 59%, 33% yields, respectively(Table 1, entries 2 and 3). Stimulated by these results, a variety of ligands, such as DABCO, Ph_3P, and PBu_3, were also tested in the next step in the presence of $Pd(OAc)_2$ and Cs_2CO_3 at 100 °C for 20 hours (Table 1, entries 4–6). Interestingly, the reaction yield of **3a** was dramatically increased to 79% (Table 1, entry 4) by using Ph_3P as ligand. Solvent effects were also investigated in the following tests. It was found that arylation product **3a** could be isolated in very good yields in DMA (Table 1, entry 7), but when THF, benzene, toluene, and dimethyl sulfoxide (DMSO) were employed, the reaction was severely retarded (Table 1, entries 8–11). Finally, the effects of temperature were also detected (Table 1, entries 12–15), and it was evident that 120 °C was the most optimal temperature for this transformation.

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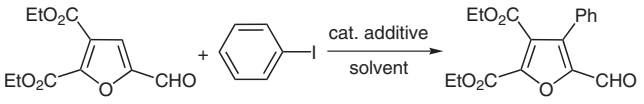
Table 1 Condition Screening for the Palladium-Catalyzed Direct Arylation Reaction of **1a** with **2a**[a]



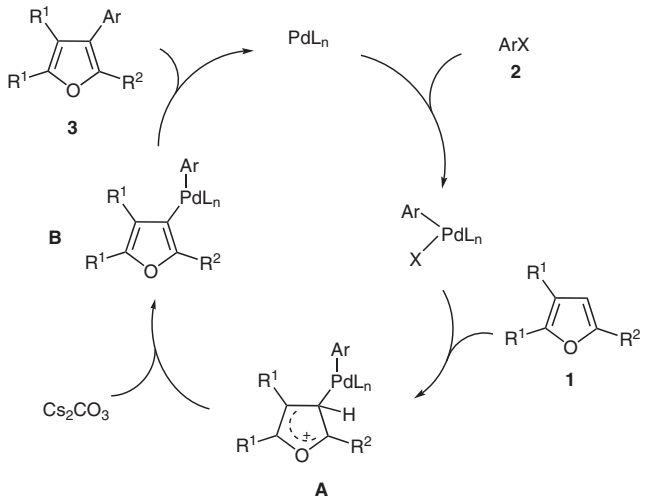
Entry	Catalyst	Additive	Solvent	Temp (°C)	Yield (%)[b]
1	$PdCl_2$	Cs_2CO_3	DMF	100	36
2	$Pd(OAc)_2$	Cs_2CO_3	DMF	100	59
3	$Pd(dba)_2$	Cs_2CO_3	DMF	100	33
4	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	DMF	100	79
5	$Pd(OAc)_2$	Bu_3P/Cs_2CO_3	DMF	100	65
6	$Pd(OAc)_2$	DABCO/Cs_2CO_3	DMF	100	67
7	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	DMA	100	83
8	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	THF	reflux	30
9	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	benzene	100	70
10	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	toluene	100	72
11	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	DMSO	100	79
12	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	DMA	110	84
13	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	DMA	120	89
14	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	DMA	150	80
15	$Pd(OAc)_2$	Ph_3P/Cs_2CO_3	DMA	r.t.	–

[a] Reactions conditions: **1a** (0.5 mmol), aryl iodide (0.7 mmol), Pd catalyst (5 mol%), Cs_2CO_3 (1.0 mmol), ligand (10 mol%), solvent (4 mL), 20 h.
[b] GC yields.

With the optimal reaction conditions in hand, we explored the scope of this arylation reaction (Table 2). By using **1a** as the substrate, we carried out the reactions with various types of aryl iodides and aryl bromides (X = I, Br; Table 2, entries 1–6). In general, all reactions were very clean, and the arylation products **3** were obtained in good yields especially those using aryl iodides under the optimized conditions. These results indicated that all aryl iodides, regardless of their electronic or steric properties, proceeded smoothly to afford the expected biaryls in good yields. Meanwhile, higher isolated yields were obtained when electron-withdrawing substituents were on the aromatic ring (Table 2, entry 5), and sterically demanding *ortho* substituents did not hamper the arylation reaction (Table 2, entry 3). It was especially noteworthy that this direct arylation reaction could take place and gave moderate yields by using **1a** and aryl bromides. Obviously, compared with the aryl iodides, arylation products using aryl bromides were obtained in lower yields. Similarly, **1b** was also employed, and the products were also obtained in good yield.

The catalytic system was also found to be useful for carrying out arylation reactions of diethyl 5-methylfuran-2,3-dicarboxylate (**1c**) with aryl iodides or aryl bromides. This indicated that most aryl iodides or aryl bromides with different substituent groups presented on the aromatic ring could react smoothly, and the corresponding products were obtained in moderate to good yields in the presence of $Pd(OAc)_2/Ph_3P$ catalytic system. However, in comparison to **1a** and **1b**, arylation products prepared from **1c** were obtained in lower yields.

A plausible mechanism for the direct arylation reaction is described in Scheme 2. A mechanism similar to those of previous studies on the arylation of heterocycles[2i] may be involved in the present reaction. First, intermediate **A** was formed from the reaction of **1** with the palladium species. Intermediate **A** then converted to intermediate via the abstraction of the acidic hydrogen in **B** with the help of Cs_2CO_3. Finally, reductive elimination of **B** gives the desired products **3** and releases the Pd catalyst.

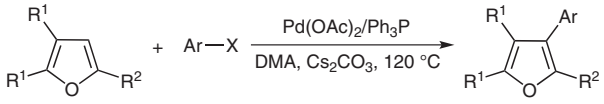


Scheme 2 Plausible mechanism for the arylation of **1** with **2**

In summary, an efficient palladium-based catalytic system for the direct arylation reaction of 2,3,5-trisubstituted furans and aryl halides that showed high activity with reasonably broad scope was developed. The direct arylation of 2,3,5-trisubstituted furans took place with aryl iodides or aryl bromides to afford a range of biaryl compounds in moderate to excellent yields in the presence of $Pd(OAc)_2/Ph_3P$ and Cs_2CO_3 in DMA for 20 hours.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 2 Pd-Catalyzed Direct Arylation Reaction of Furan with Aryl Halides[a]



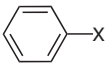
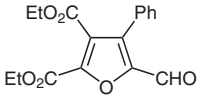
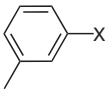
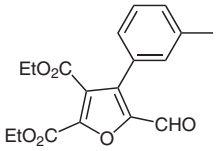
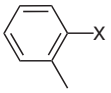
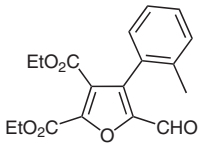
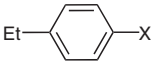
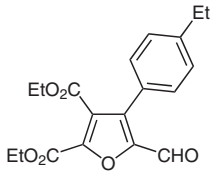
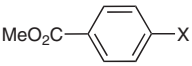
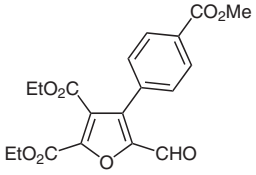
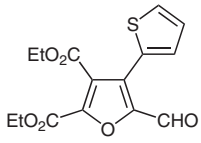
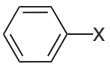
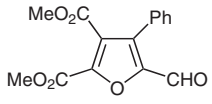
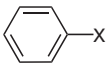
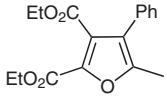
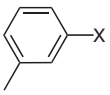
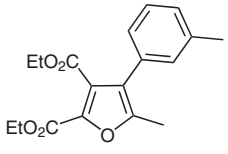
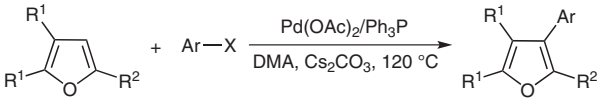
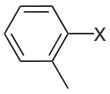
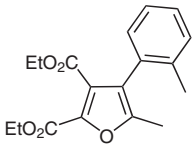
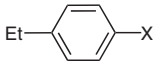
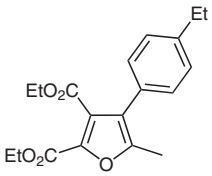
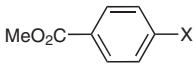
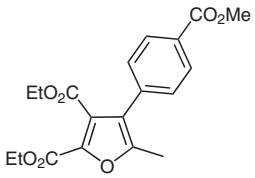
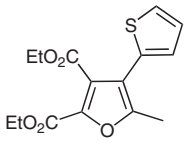
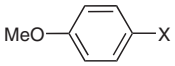
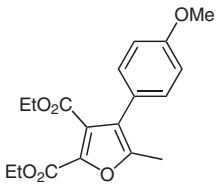
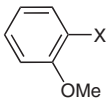
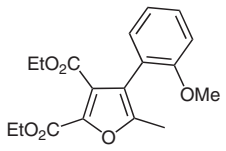
Entry	Furans[14,15]	Aryl halides(X = I, Br)	Products[16]	Yield (%)[b]
1	$R^1 = CO_2Et$ $R^2 = CHO$ **1a**		 **3a**	X = I, 85 X = Br, 76 X = Cl, trace
2	**1a**		 **3b**	X = I, 84 X = Br, 72
3	**1a**		 **3c**	X = I, 82 X = Br, 71
4	**1a**		 **3d**	X = I, 83 X = Br, 70
5	**1a**		 **3e**	X = I, 90 X = Br, 80
6	**1a**		 **3f**	X = I, 82 X = Br, 73
7	$R^1 = CO_2Me$ $R^2 = CHO$ **1b**		 **3g**	X = I, 81 X = Br, 71
8	$R^1 = CO_2Et$ $R^2 = Me$ **1c**		 **3h**	X = I, 74 X = Br, 65
9	**1c**		 **3i**	X = I, 73 X = Br,66

Table 2 Pd-Catalyzed Direct Arylation Reaction of Furan with Aryl Halides[a] (continued)



Entry	Furans[14,15]	Aryl halides(X = I, Br)	Products[16]	Yield (%)[b]
10	**1c**		 **3j**	X = I, 5 X = Br, 62
11	**1c**		 **3k**	X = I, 77 X = Br, 68
12	**1c**		 **3l**	X = I, 85 X = Br, 76
13	**1c**		 **3m**	X = I, 76 X = Br, 67
14	**1c**		 **3n**	X = I, 74 X = Br, 67
15	**1c**		 **3o**	X = I, 75 X = Br, 62

Acknowledgment

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(14) **General Procedure for the Synthesis of 1a**
Diethyl acetylenedicarboxylate (2 mmol), prop-2-yn-1-ol (2 mmol), DABCO (0.2 mmol) in CH_2Cl_2 were stirred for 10 min at r.t. And then the solution was evaporated to dryness under reduced pressure. Subsequently, CuI (10% mmol) and DMF were added at 80 °C. After completion of the reaction (monitored by TLC), the solution was evaporated to dryness under reduced pressure, and then H_2O (10 mL) was added. The aqueous solution was extracted with Et_2O (3 × 10 mL), and the combined extract was dried with anhyd $MgSO_4$. The solvent was removed, and the crude product was separated by column chromatography to give a pure sample of **1a**.

(15) **General Procedure for the Synthesis of 1c**
Diethyl acetylenedicarboxylate (2 mmol), prop-2-yn-1-ol (2 mmol), DABCO (0.2 mmol) in CH_2Cl_2 were stirred for 10 min at r.t. And then the solution was evaporated to dryness under reduced pressure. Subsequently, AgOAc/Ph_3P and toluene were added at 50 °C. After completion of the reaction (monitored by TLC), the solution was evaporated to dryness under reduced pressure, and then H_2O (10 mL) was added. The aqueous solution was extracted with Et_2O (3 × 10 mL), and the combined extract was dried with anhyd $MgSO_4$. The solvent was removed, and the crude product was separated by column chromatography to give a pure sample of **1c**.

(16) **General Procedure for the Synthesis of 3a**
To the mixture of $Pd(OAc)_2$ (5% mol), Ph_3P (10% mol), Cs_2CO_3 (1.0 mmol), **1a** (0.5 mmol), **2a** (0.7 mmol), and DMP (4 mL) were added successively. The mixture was stirred at 120 °C for 20 hours. The solution was extracted with EtOAc (3 × 15 mL), and the combined extract was dried with anhyd $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample **3a**.

Diethyl 5-Formyl-4-phenylfuran-2,3-dicarboxylate (3a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 7.47 (s, 5 H), 4.43 (q, *J* = 8.0 Hz, 2 H), 4.28 (q, *J* = 8.0 Hz, 2 H), 1.40 (t, *J* = 8.0 Hz, 3 H), 1.22 (q, *J* = 8.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 162.0, 157.1, 147.5, 144.3, 136.1, 129.7, 129.5, 128.7, 127.5, 126.3, 62.3, 62.1, 14.0, 13.7. MS (EI): *m/z* (%) = 316, 288, 225, 213, 170, 115, 77.