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Pd-Catalyzed β-Selective Direct C–H Bond Arylation of Thiophenes with Aryltrimethylsilanes

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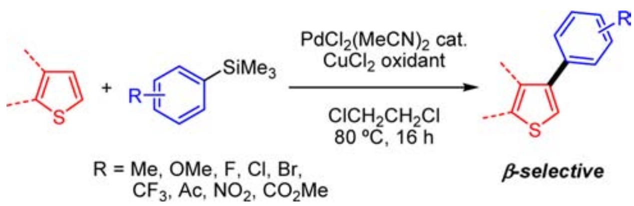
ABSTRACT



Direct arylation of thiophenes and benzothiophenes with aryltrimethylsilanes was effectively catalyzed by $PdCl_2(MeCN)_2$ in the presence of $CuCl_2$ as an oxidant. The reaction preferentially occurred at the β-position of both thiophenes and benzothiophenes.

The transition metal catalyzed cross-coupling reaction of aromatic compounds has emerged as a promising strategy for the construction of various fine chemicals, such as organic electronic materials, pharmaceuticals, and agrochemicals.[1] Most recently, the direct arylation of aromatic C–H bonds has attracted considerable attention because of the synthetic and atom efficient nature of the reaction. In particular, many different catalyst systems have been reported for direct C–H arylation of five-membered heteroarenes.[2–6] However, it is difficult to achieve the direct C–H bond arylation at a desired position of the five-membered heteroarene rings because several C–H bonds with different reactivities exist in these rings. An example of a switch in regioselectivity was reported for azoles, in which the regioselectivity of Pd- catalyzed arylation of imidazole and thiazole was switched from C-2 to C-5 when a Cu salt was added to the catalytic systems.[3] In contrast to this, it has been a challenge to achieve the β-selective arylation of thiophenes. The reaction of thiophenes and benzothiophenes with aryl halides or arylmetal reagents produces α-arylated products under a majority of the reaction conditions previously reported (eq 1).[4] Fagnou et al. reported a sequential method for the synthesis of β-arylbenzothiophenes by using α-chlorobenzothiophene as a substrate, which forced arylation at the β-position followed by reductive dechlorination to afford β-arylbenzothiophenes (eq 2).[5] Bach et al. reported the β-selective oxidative coupling

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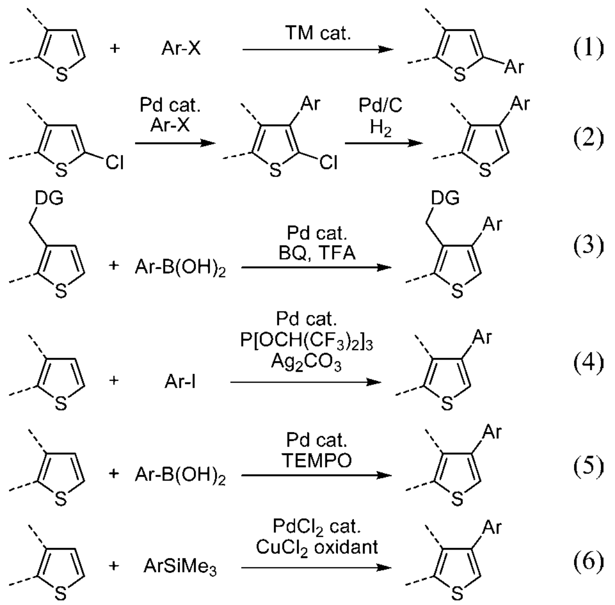
of arylboronic acid with thiophenes by using coordinative directing groups (DGs) such as ethoxycarbonyl and diethoxyphosphoryl groups (eq 3).[6a] Itami et al. reported the Pd-catalyzed β-selective direct arylation of thiophenes with the electron-deficient phosphorus ligand P[OCH-$(CF_3)_2]_3$ (eq 4).[6b,c] Moreover, Itami and Studer et al. reported the β-selective direct arylation with arylboronic acid by using TEMPO as an oxidant (eq 5).[6d]

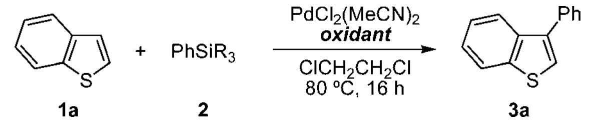
We previously reported the direct C−H bond arylation of simple arenes with arylmetal reagents by using a $PdCl_2$/$CuCl_2$ catalytic system.[7] These reactions were proposed to proceed via an aromatic electrophilic substitution in the C−H bond metalation process.



Following this, we focused our research on the direct arylation of heteroarenes with arylsilicon reagents and investigated both regioselectivity and reactivity. Herein, we report the effective direct arylation of thiophenes with aryltrimethylsilanes in the presence of $PdCl_2(MeCN)_2$ as a catalyst and $CuCl_2$ as an oxidant (eq 6). Very recently, gold-catalyzed direct arylation of aromatic compounds with aryltrimethylsilanes has been reported by Lloyd-Jones and Russell et al., which involves α-arylation of the thiophene ring.[8] In contrast to this, our catalytic system shows β-selectivity for both benzothiophenes and thiophenes.

At the onset of our studies, reaction conditions for the direct C−H bond arylation of benzothiophene (**1a**) with the phenylsilicon reagents (**2**) were optimized (Table 1). The reaction of **1a** (0.50 mmol) with trimethylphenylsilane (**2a**, 0.55 mmol) in the presence of 5 mol % $PdCl_2$ and 1.0 mmol $CuCl_2$ in 0.5 mL of 1,2-dichloroethane at 80 °C under N_2 provided 3-phenylbenzothiophene (**3a**) as a major product in 68% yield (87% β-selectivity, entry 1). The use of $PdCl_2(MeCN)_2$ instead of $PdCl_2$ increased the yield to 76% (entry 2), and the use of 1.0 mmol of **2a** further

Table 1. Optimization of Reaction Conditions for Direct C−H Bond Arylation of Benzothiophene[a]



entry	phenylsilicon reagent **2**	oxidant	GC yield (%)[b]
1[c]	$PhSiMe_3$ (**2a**)[d]	$CuCl_2$	68 (87%β)[e]
2	**2a**[d]	$CuCl_2$	76 (90%β)[e]
3	**2a**	$CuCl_2$	87 (93%β)[e]
4[f]	**2a**	$CuCl_2$	63 (90%β)[e]
5	**2a**	CuF_2	6
6	**2a**	$CuBr_2$	27
7	**2a**	$Cu(OAc)_2$	3
8	**2a**	CuO	5
9	**2a**	AgOAc	0
10	**2a**	$AgNO_3$	5
11	**2a**	Ag_2O	0
12	**2a**	Oxone	7
13	**2a**	*p*-benzoquinone	0
14	$PhSiEt_3$	$CuCl_2$	71
15	$PhSi^iPr_3$	$CuCl_2$	0
16	Ph_4Si	$CuCl_2$	0
17	$PhSi(OMe)_3$	$CuCl_2$	0
18	$PhSi(OEt)_3$	$CuCl_2$	0

[a] Conditions: **1a** (0.50 mmol), **2** (1.0 mmol), $PdCl_2(MeCN)_2$ (5.0 mol %), oxidant (2.0 equiv), $ClCH_2CH_2Cl$ (0.5 mL), 80 °C, 16 h under N_2. [b] Total yield including 2-phenylbenzothiophene. [c] $PdCl_2$ (5.0 mol %) was used as catalyst. [d] 0.55 mmol of **2a** was used. [e] Regioselectivity was determined by GC analysis. [f] The reaction was carried out in air.

increased the yield to 87% with better β-selectivity (93%, entry 3). The reaction in air also gave the coupling product in a slightly lower yield (entry 4). The use of palladium complexes with electron-donating ligands, such as $PdCl_2(PPh_3)_2$ and $PdCl_2$(bpy), or absence of a palladium catalyst did not give the coupling product. The use of other Cu and Ag salts, Oxone, or *p*-benzoquinone as the oxidant was not effective (entries 5−13). As the phenylsilicon reagent, $PhSiEt_3$ showed lower performance in obtaining the cross-coupling product **3a**; $PhSi^iPr_3$ and Ph_4Si did not provide the desired products (entries 14−16). This could be attributed to steric hindrance around the Si atom. The use of trialkoxyphenylsilanes, which are known to be good reagents for Hiyama coupling reactions,[9] resulted in no formation of the coupling product (entries 17 and 18).

With the optimized reaction conditions (entry 1 in Table 1), we attempted the direct arylation of **1a** with various aryltrimethylsilanes **2b**−**j** (Table 2). The reaction proceeded smoothly for *p*-tolyl- (**2b**) and *p*-anisyltrimethylsilane (**2d**) producing the arylated products **3b** and **3d** in 67% and 64% yields, respectively (entries 1 and 3). However, a

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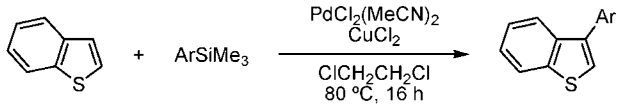
Table 2. *β*-Selective Direct C−H Bond Arylation of Benzothiophene with Various Aryltrimethylsilanes[a]



1a **2b-l** **3b-l**

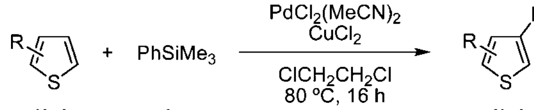
entry	Ar in **2**		major product **3**	isolated yield (%)[b,c]
1	4-MeC_6H_4	**2b**	**3b**	67 (90%*β*)
2	2-MeC_6H_4	**2c**	**3c**	19 (81%*β*)
3	4-$MeOC_6H_4$	**2d**	**3d**	64 (94%*β*)
4	4-FC_6H_4	**2e**	**3e**	78 (88%*β*)
5	4-ClC_6H_4	**2f**	**3f**	78 (88%*β*)
6	4-BrC_6H_4	**2g**	**3g**	81 (89%*β*)
7	4-$CF_3C_6H_4$	**2h**	**3h**	45 (88%*β*)
8[d]	4-$CF_3C_6H_4$	**2h**	**3h**	66 (86%*β*)
9[d]	4-MeC(O)C_6H_4	**2i**	**3i**	30 (93%*β*)
10[d]	3-MeC(O)C_6H_4	**2j**	**3j**	50 (91%*β*)
11[d]	3-$NO_2C_6H_4$	**2k**	**3k**	64 (86%*β*)
12[d]	3-$MeO_2CC_6H_4$	**2l**	**3l**	63 (82%*β*)

[a] Conditions: **1a** (0.50 mmol), **2** (1.0 mmol), $PdCl_2(MeCN)_2$ (5.0 mol %), $CuCl_2$ (1.0 mmol), $ClCH_2CH_2Cl$ (0.5 mL), 80 °C, 16 h. [b] Total yield including 2-arylbenzothiophene. [c] Regioselectivity was determined by GC analysis. [d] The reaction was performed in toluene at 100 °C.

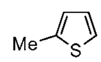
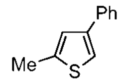
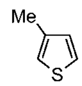
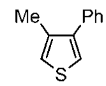
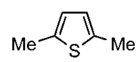
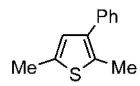
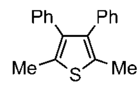
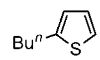
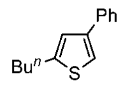
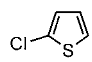
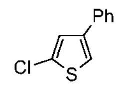
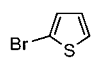
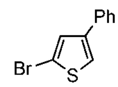
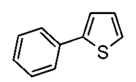
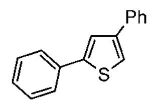
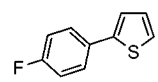
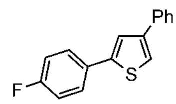
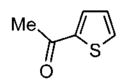
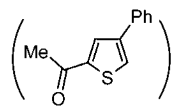
decreased yield was observed when *o*-tolyltrimethylsilane (**2c**) was employed (entry 2); this was probably due to increased steric hindrance. It is noted that halogen groups on the aromatic ring of Si reagents (**2e**−**2g**) were tolerated in the present catalytic reactions (entries 4−6). These findings offer the opportunity for further coupling to afford more complicated molecules. Though the reaction of arylsilanes bearing an electron-withdrawing trifluoromethyl group (**2h**) was slightly sluggish (45%, entry 7), a higher reaction temperature in toluene improved the yield to 66% with minimal loss of *β*-selectivity (entry 8). Other reactions of arylsilanes bearing electron-withdrawing groups (**2i**−**2l**) were also conducted at higher reaction temperatures in toluene, affording the corresponding arylated products **3i**−**3l** in moderate yields (entries 9−12).

The reactions of various substituted thiophenes with **2a** were then examined (Table 3). Alkyl-substituted thiophenes (**1b**−**1e**) gave moderate to good yields of the corresponding products under the optimized conditions (entries 1−4), while the 2-or 3-substituted thiophenes (**1b**, **1c**, and **1e**) were preferentially phenylated at the 4-positions. 2,5-Dimethylthiophene (**1d**) also reacted successfully, affording the 3-phenylated product **4d** together with a small amount of the diphenylated product **5d**. Halogen-substituted thiophenes could also be used as substrates without loss of the halogen substituent, affording 2-halo-4-phenylthiophenes **4f** and **4g** with high *β*-selectivity (entries 5 and 6). Moreover, 2-arylthiophenes **1h** and **1i** gave 2,4-diarylthiophenes in good yields (entries 7 and 8). Unfortunately, electron-poor thiophenes such as **1j** did not afford the coupling product (entry 9).

Table 3. *β*-Selective Direct C−H Bond Arylation of Substituted Thiophenes with Phenyltrimethylsilane[a]



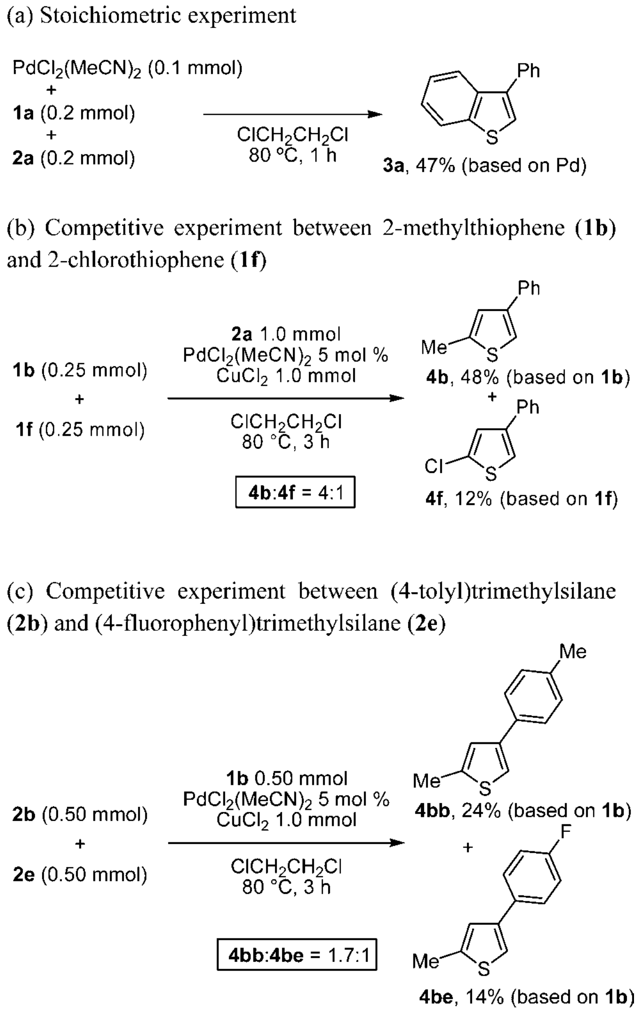
1b-j **2a** **4b-j**

entry	substrate **1**		major product **4**, **5**		yield (%)[b,c]
1		**1b**		**4b**	80 (93%*β*)
2		**1c**		**4c**	75 (98%*β*)
3		**1d**		**4d**	55
				**5d**	8
4		**1e**		**4e**	76 (91%*β*)
5		**1f**		**4f**	50 (>99%*β*)
6		**1g**		**4g**	43 (>99%*β*)
7[d]		**1h**		**4h**	73 (79%*β*)
8[d]		**1i**		**4i**	66 (86%*β*)
9		**1j**		(**4j**)	trace

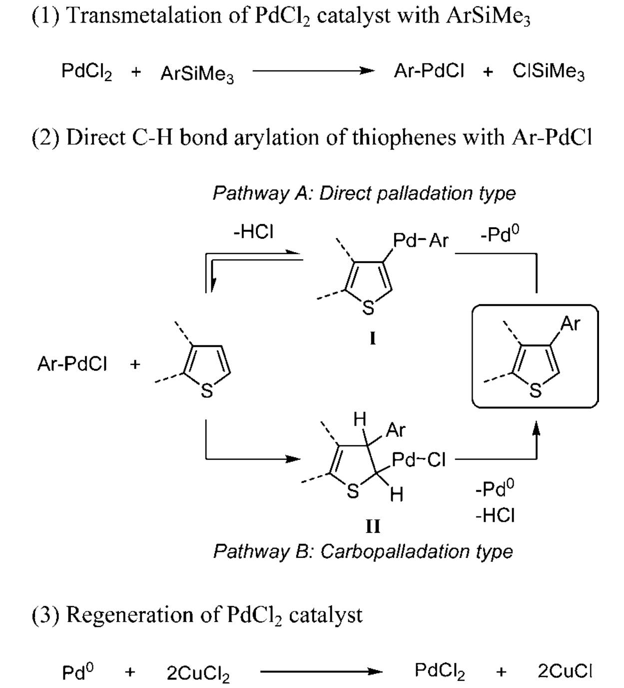
[a] Conditions: **1** (0.50 mmol), **2a** (1.0 mmol), $PdCl_2(MeCN)_2$ (5.0 mol %), $CuCl_2$ (1.0 mmol), $ClCH_2CH_2Cl$ (2.0 mL), 80 °C, 16 h. [b] Total yield including 2-arylbenzothiophene. [c] Regioselectivity was determined by GC analysis or ^1H NMR analysis. [d] The reaction was performed in 0.5 mL of $ClCH_2CH_2Cl$.

Next, we tried to gain some insight into the mechanism for the catalytic direct arylation by conducting some control experiments. First, the reaction of **1a** and **2a** using 0.5 equiv of $PdCl_2(MeCN)_2$ in the absence of $CuCl_2$ afforded the product **3a** in 47% yield based on Pd (Scheme 1a). In this reaction, a Pd metal deposit was observed. These results suggest that the reaction proceeds through a Pd(0)/Pd(II) catalytic cycle, and reduced Pd(0) is reoxidized to Pd(II) by $CuCl_2$ in the catalytic reaction. Second, a competitive reaction between the electron-rich thiophene **1b** and the electron-deficient one **1f** with **2a** showed preferential formation of the product from the electron-rich thiophene **1b** in a ratio of 4:1 (Scheme 1b). This result suggests that the Pd intermediate exhibits an

Scheme 1. Control Experiments



Scheme 2. Possible Reaction Mechanism



electrophilic character.[10] Third, a competitive reaction of **2b** and **2e** with **1b** showed a similar tendency for the above experimental result (Scheme 1c). Therefore, the transmetalation of aryltrimethylsilane with the Pd catalyst would generate an arylpalladium intermediate in an electrophilic way.[11]

A possible reaction pathway for the Pd-catalyzed β-selective direct C−H bond arylation is shown in Scheme 2. (1) Transmetalation between $PdCl_2$ and $ArSiMe_3$ generates ArPdCl and $ClSiMe_3$. (2) The reaction of thiophenes with ArPdCl gives the corresponding β-arylthiophene product. In this step, there are two possible pathways. One is the direct C−H bond palladation of the thiophene ring with ArPdCl at the β-position to generate a diarylpalladium intermediate (**I**), followed by reductive elimination to give the product and a Pd(0) species (Pathway A). The other route involves insertion of the thiophene C=C bond into the Ar−Pd bond to generate an intermediate (**II**), followed by deprotonation and elimination of the Pd(0) species to give the product (Pathway B), as was proposed by Itami and Studer et al.[12] (3) $PdCl_2$ regenerates by reoxidization of Pd(0) with $CuCl_2$.

In conclusion, we have demonstrated that the $PdCl_2$/$CuCl_2$ system is an effective catalyst for the β-selective direct C−H bond arylation of thiophenes and benzothiophenes with aryltrimethylsilanes. The reaction is operationally simple and easy, as it can be performed under aerobic conditions, no base or additional ligand is required, and only an inexpensive oxidant, $CuCl_2$, is required. Further studies to expand the substrate scope and applications are now in progress.

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Supporting Information Available. Experimental procedures and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) The competitive reaction between 2-methylthiophene and 2-chlorothiophene was also performed in refs 5 and 6c. In comparison with these results, our observation was similar to that in ref 6c.

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