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Palladium/2,2′-bipyridyl/Ag_2CO_3 catalyst for C–H bond arylation of heteroarenes with haloarenes

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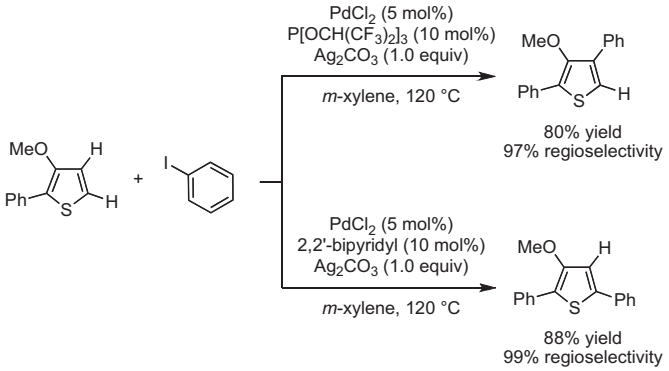
ABSTRACT

A Pd/bipy-based catalytic system for the C–H bond arylation of heteroarenes with haloarenes is described. The complex $PdBr_2$(bipy)·DMSO, whose structure was unambiguously determined by X-ray crystallography, turned out to be a general catalyst precursor for the process. The reaction is applicable to a range of electron-rich five-membered heteroarenes, such as thiophenes, thiazoles, benzofurans, and indoles.

1. Introduction

Heterobiaryls are one of the most important molecules that are frequently found in functional materials, pharmaceuticals, and natural products.[1] Consequently, the development of efficient methods to connect heteroarene and arene has been a topic of immense importance in chemical synthesis.[2] Although transition metal-catalyzed cross-coupling reactions have been a reliable and excellent method for constructing the biaryl structures,[3] there are common drawbacks, such as inevitable production of stoichiometric amount of metallic waste and necessity for preparing organometallic reagents from arenes prior to cross-coupling. Recently, transition metal-catalyzed direct C–H bond arylation of heteroarenes has received much attention as an alternative method for heterobiaryl synthesis by a number of research groups including our own (Pd, Rh, Cu, Ni, Ir, Ru, and Fe).[4–6]

During the study of programmed synthesis of tetraarylthiophenes, we discovered ligand-controlled regiodivergent C–H bond arylations of 3-methoxy-2-phenylthiophene with iodoarenes (Scheme 1).[6i] For example, the reaction of 3-methoxy-2-phenylthiophene and iodobenzene in the presence of $PdCl_2$, $P[OCH(CF_3)_2]_3$, and Ag_2CO_3 in *m*-xylene at 120 °C furnished C4-phenylated product in 80% yield with 97% regioselectivity. Interestingly, the C4 regioselectivity could be switched to C5 regioselectivity by simply changing the neutral ligand from $P[OCH(CF_3)_2]_3$ to 2,2′-bipyridyl (bipy), with which 3-methoxy-2,5-diphenylthiophene (C5-phenylated product) was obtained in 88% yield with 99% regioselectivity (Scheme 1). We further found that the unique C4-selective C–H arylation exerted by $PdCl_2/P[OCH(CF_3)_2]_3$ catalyst is applicable not only to 3-methoxy-2-phenylthiophene but also to a wide range of thiophene derivatives in general.[6j] We envisaged that the Pd/bipy/Ag_2CO_3 catalyst system might also have excellent potential for the C–H bond arylation of other heteroarenes.



Scheme 1. Discovery of ligand-controlled regiodivergent C–H bond arylation.

To date, a number of Pd-catalyzed direct C–H arylation reactions have been developed. However, most of the reported systems utilize phosphine-based supporting ligands and the example using nitrogen-based bidentate ligands, such as bipy is very rare.[4] Other

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than our catalytic system (Pd/bipy/Ag_2CO_3),[6i] there is only a few examples for the direct C–H bond arylation of heteroarenes catalyzed by a Pd complex having nitrogen-based bidentate ligand.[7,8] Very recently, Shibahara and Murai demonstrated that the cationic palladium complex bearing 1,10-phenanthroline (phen) ligand, $[Pd(phen)_2](PF_6)_2$, promotes the direct C–H bond arylation of various five-membered heteroarenes with haloarenes.[7] Cesium carbonate was used as a basic additive for the coupling.

Considering these backgrounds, we decided to investigate our Pd/bipy catalyst system in detail. The focal points of this study has been (i) to identify catalyst components necessary for the coupling, (ii) to develop user-friendly and air-stable pre-catalyst, and (iii) to identify the scope of heteroarene/haloarene coupling partners.

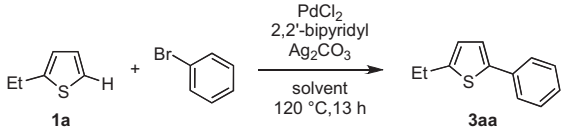
2. Results and discussion

2.1. Effect of catalyst components

Following the finding of Pd/bipy/Ag_2CO_3 catalysis, the effect of catalyst components was investigated in detail.

2.1.1. Effect of solvent. We began by examining the solvent effect in the coupling reaction between 2-ethylthiophene (**1a**) and bromobenzene. When bromobenzene was used as a substrate instead of iodobenzene (suitable phenylating agent established previously[6i]) in the presence of $PdCl_2$ (5 mol %), bipy (5 mol %), and Ag_2CO_3 (1.0 equiv) in *m*-xylene at 120 °C, 2-ethyl-5-phenylthiophene (**3aa**) was obtained only in 2% yield (Table 1, entry 1). To our surprise, DMAc and DMF, which are usually used in C–H bond arylation of (hetero)arenes, showed poor results (entries 2 and 3). As a result, it was found that 1,4-dioxane is the best solvent for the present system, which afforded the desired coupling product **3aa** in 32% yield (entry 4). On the other hand, DMSO, cyclopentyl methyl ether (CPME), ethanol, 1,2-dichloroethane, and *n*-octane were ineffective solvents (entries 5–9).

Table 1
Effect of solvent[a]

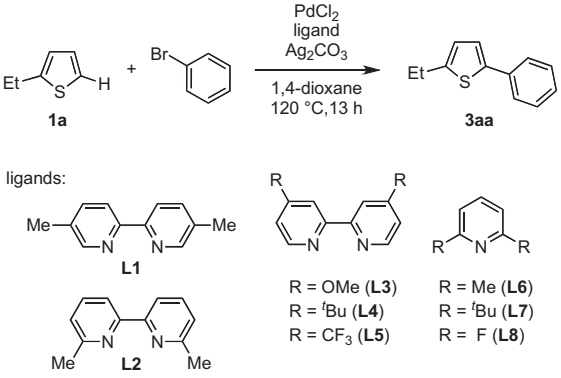


Entry	Solvent	Yield (%)[b]
1	*m*-Xylene	2
2	DMAc	14
3	DMF	7
4	1,4-Dioxane	32
5	DMSO	3
6	CPME	3
7	Ethanol	<2
8	1,2-Dichloroethane	<2
9	*n*-Octane	<2

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), $PdCl_2$ (5 mol %), 2,2′-bipyridyl (5 mol %), Ag_2CO_3 (1.0 equiv), solvent, 120 °C, 13 h.
[b] GC yield.

2.1.2. Effect of ligand. Subsequently, the ligand effect was examined focusing on nitrogen-based ligands (Table 2). First of all, the coupling reaction conducted without any ligand gave only trace amount of product (Table 2, entry 1). The sp^3 nitrogen ligand, such as TMEDA was ineffective for this reaction (entry 2). Since bipy gave relatively good result (entry 3), a variety of bipy-based ligands were investigated (entries 4–8). It was found that the reactivity is influenced by the steric environment around bipy core. While C5-substituted bipy ligand **L1** brought relatively good result (entry 4), ligands bearing substituents at C4 or C6 position (**L2**–**L5**) were ineffective (entries 5–8). Moreover, the use of 1,10-phenanthroline was found to be ineffective (entry 9). Monodentate pyridine-based ligands (pyridine and **L6**–**L8**) did not promote the reaction efficiently (entries 10–13).

Table 2
Effect of ligand[a]

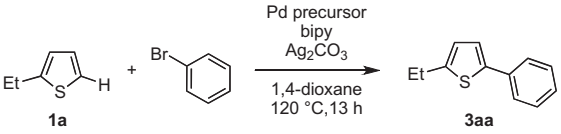


Entry	Ligand	Yield (%)[b]
1	None	<2
2	TMEDA	5
3	Bipy	32
4	**L1**	21
5[c]	**L2**	2
6	**L3**	3
7	**L4**	6
8[c]	**L5**	8
9	1,10-Phenanthroline	12
10[d]	Pyridine	8
11[d]	**L6**	<2
12[d]	**L7**	<2
13[d]	**L8**	<2

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), $PdCl_2$ (5 mol %), ligand (5 mol %), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h.
[b] GC yield.
[c] $PdBr_2$ was used instead of $PdCl_2$.
[d] Ligand (10 mol %) was employed.

2.1.3. Effect of Pd precursor. The effect of Pd precursor was also investigated and the results are summarized in Table 3. Pd(II) salts with two halogen ligands, such as $PdCl_2$, $PdBr_2$, and PdI_2, worked well (entries 1–3). On the other hand, $Pd(OAc)_2$ and $Pd(OCOCF_3)_2$ were not effective for this transformation (entries 4 and 5). The cationic palladium complex, $[Pd(CH_3CN)_4](BF_4)_2$, displayed almost no catalytic activity with bipy ligand (entry 6). Based on the inefficiency with 1,10-phenanthroline ligand and the fact that

Table 3
Effect of Pd precursor[a]



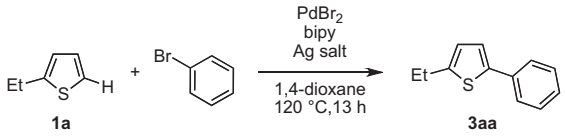
Entry	Pd precursor	Yield (%)[b]
1	$PdCl_2$	32
2	$PdBr_2$	59
3	PdI_2	39
4	$Pd(OAc)_2$	12
5	$Pd(OCOCF_3)_2$	3
6	$[Pd(CH_3CN)_4](BF_4)_2$	<2
7	$Pd_2(dba)_3 \cdot CHCl_3$	3

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), Pd precursor (5 mol %), bipy (5 mol %), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h.
[b] GC yield.

cationic palladium complex possesses poor reactivity, the present Pd system is likely to be different from the Pd catalysis developed by Shibahara and Murai.[7] When $Pd_2(dba)_3 \cdot CHCl_3$ was used as a precursor, the desired biaryl **3aa** was obtained only in 3% yield (entry 7). This result implies that Pd(0) species might not be included in the catalytic cycle under the present conditions.

2.1.4. Effect of silver salt. The investigation of silver salt was also conducted with $PdBr_2$/bipy system in 1,4-dioxane. The results are shown in Table 4. The reaction in the absence of silver salt under the standard catalytic conditions did not give the arylated product **3aa** (entry 1). Silver salts that are generally used for the generation of cationic transition metal species, such as $AgBF_4$, $AgPF_6$, $AgSbF_6$, and AgOTf, did not work well (entries 2–5). Silver acetate and silver fluoride also did not promote the reaction (entries 6 and 7). Though AgO promoted the reaction, the efficiency was low (21% yield, entry 8). Finally, Ag_2CO_3 was found to be the best silver-based additive giving rise to **3aa** in 59% yield (entry 9). It is clear from these results that the counter anion of silver salts play key role in catalysis.

Table 4
Effect of silver salt[a]

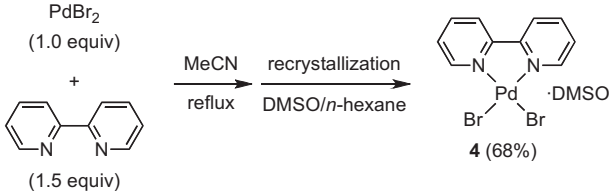


Entry	Silver salt	Yield (%)[b]
1	None	<2
2	$AgBF_4$	<2
3	$AgPF_6$	<2
4	$AgSbF_6$	<2
5	AgOTf	<2
6	AgOAc	2
7	AgF	<2
8	AgO	21
9	Ag_2CO_3	59

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), $PdBr_2$ (5 mol %), bipy (5 mol %), silver salt (1.0 equiv), 1,4-dioxane, 120 °C, 13 h.
[b] GC yield.

2.2. Synthesis, structure, and catalytic activity of $PdBr_2$(bipy) complex

Considering the results obtained during the optimization of catalyst components, $PdBr_2$/bipy seems to be the best combination for the coupling. To simplify the reaction system, we prepared $PdBr_2$(bipy) complex. Although the preparation and crystal structure of $PdBr_2$(bipy) complex was already reported,[10] we developed a new simple synthetic route to $PdBr_2$(bipy). Treatment of $PdBr_2$ (1.0 equiv) with bipy (1.5 equiv) in refluxing MeCN, followed by recrystallization from DMSO/*n*-hexane gave $PdBr_2$(bipy)·DMSO (**4**) in 68% yield as orange crystal (Scheme 2). The molecular structure of **4** was confirmed by X-ray crystal structure analysis (Fig. 1).[9] The crystal packing of **4** was found to be different from that of the previously reported $PdBr_2$(bipy) complex.[10]



Scheme 2. Synthesis of $PdBr_2$(bipy)·DMSO (**4**).

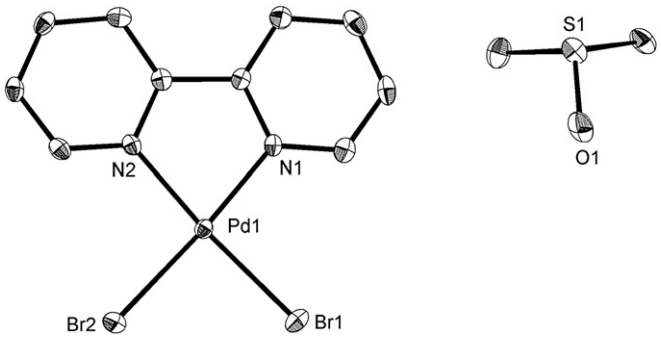


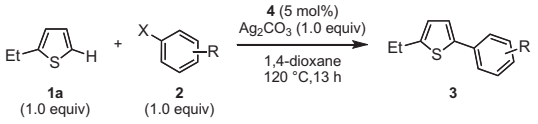
Fig. 1. X-ray crystal structure of **4** (50% thermal ellipsoids). All hydrogen atoms are omitted for clarity.

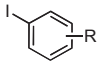
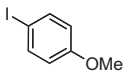
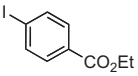
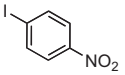
Subsequently, the reaction of 2-ethylthiophene (**1a**: 1.0 equiv) and bromobenzene (1.0 equiv) was carried out in the presence of 5 mol % of $PdBr_2$(bipy)·DMSO (**4**) and Ag_2CO_3 (1.0 equiv) in 1,4-dioxane at 120 °C for 13 h, and the C–H arylation product **3aa** was obtained in 52% isolated yield. Based on these results, we decided to use the complex $PdBr_2$(bipy)·DMSO (**4**) as a catalyst precursor for further investigation.

2.3. Substrate scope in C–H bond arylation of heteroarenes with haloarenes catalyzed by $PdBr_2$(bipy)·DMSO (4)

With the optimized conditions and the air-stable pre-catalyst **4** in hand, we investigated the substrate scope with respect to haloarenes **2** (Table 5). Although the present system was not applicable to chlorobenzene and phenyl triflate, the coupling reactions using

Table 5
Scope of haloarenes[a]



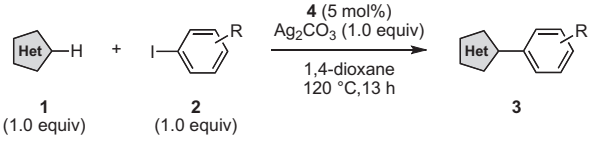
Entry	2		3 (Yield, %)[b]
1		X=I (**2a**)	**3aa** (70)
2		X=Br	**3aa** (52)
3		X=OTf	**3aa** (2)
4		X=Cl	**3aa** (<2)
5		R=2-Me (**2b**)	**3 ab** (80)
6		R=3-Me (**2c**)	**3ac** (82)
7		R=4-Me (**2d**)	**3ad** (78)
8		**2e**	**3ae** (77)
9		**2f**	**3af** (52)
10		**2g**	**3ag** (43)

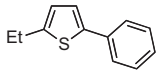
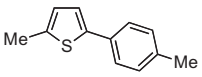
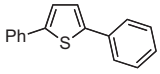
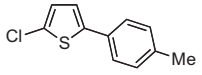
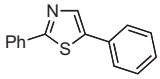
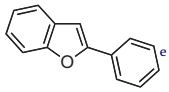
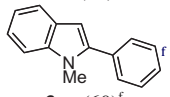
[a] Conditions: **1a** (1.0 equiv), **2** (1.0 equiv), **4** (5 mol %), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h.
[b] Isolated yield.

bromo- and iodobenzene (**2a**) took place efficiently (entries 1–4). To our delight, various electronically and structurally diverse iodoarenes were applicable to this coupling (entries 5–10). Noteworthy, the utilization of sterically hindered 2-iodotoluene (**2b**) also afforded the desired coupling product **3ab** in excellent yield (entry 5). Moreover, a range of functional groups, such as methoxy, ester, and nitro groups were tolerated in this coupling (entries 8–10). Haloarenes possessing electron-donating groups tend to show higher reactivity compared with those with electron-withdrawing groups.

By using the optimized conditions, we also surveyed heteroarenes that could be applied to this system. It was found that a variety of electron-rich five-membered heteroarenes, such as thiophenes, thiazoles, benzofurans, and indoles, were arylated with iodoarenes (Table 6). For example, 2-methylthiophene (**1b**), 2-phenylthiophene (**1c**), and 2-chlorothiophene (**1d**) were arylated in good to high yields (entries 2–4). 2-Phenylthiazole (**1e**), which could potentially be arylated at the phenyl ring through thiazole-directed arylation, was selectively arylated at the C5 position on thiazole ring with iodobenzene (**2a**) in 63% yield (entry 5). The arylation of benzofuran (**1f**) and *N*-methylindole (**1g**) took place, albeit as a mixture of regioisomers (entries 6 and 7). Unfortunately the electron-deficient aromatics, such as pyridine and pyrazine could not be arylated with haloarenes under the present system.

Table 6
Scope of heteroarenes[a]



Entry	1	2	3 (Yield, %)[b]
1	2-Ethylthiophene (**1a**)	**2a**	 **3aa** (70)
2	2-Methylthiophene (**1b**)	**2d**	 **3bd** (80)
3	2-Phenylthiophene (**1c**)	**2a**	 **3ca** (59)
4	2-Chlorothiophene (**1d**)	**2d**	 **3dd** (41)
5[c]	2-Phenylthiazole (**1e**)	**2a**	 **3ea** (63)
6[d]	Benzofuran (**1f**)	**2a**	 **3fa** (48)[e]
7[d]	*N*-Methylindole (**1g**)	**2a**	 **3ga** (60)[f]

[a] Conditions: **1** (1.0 equiv), **2** (1.0 equiv), **4** (5 mol %), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h.
[b] Isolated yield.
[c] Compound **1e** (1.5 equiv) was employed.
[d] Conditions: **1** (1.5 equiv), **2** (1.0 equiv), **4** (10 mol %), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 150 °C, 13 h.
[e] C3-isomer was also obtained. Isomer ratio: C2/C3=90:10.
[f] C3-isomer was also obtained. Isomer ratio: C2/C3=93:7.

3. Conclusion

In summary, we describe the effect of catalyst components and the scope of Pd/bipy/Ag_2CO_3 catalyzed C–H bond arylation of heteroarenes with haloarenes. The complex $PdBr_2$(bipy)·DMSO, whose structure was unambiguously determined by X-ray crystallography, turned out to be a general catalyst precursor for the process. The reaction is applicable to a range of electron-rich five-membered heteroarenes, such as thiophenes, thiazoles, benzofurans, and indoles.

4. Experimental section

4.1. General

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used without further purification. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware, using standard vacuum-line techniques. All arylation reactions were carried out in glass vessels equipped with J. Young® *O*-ring tap, heated in oil bath (heater+magnetic stirrer). All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid/sulfuric acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative recycling gel permeation chromatography (GPC) was performed with a JAI LC-9204 instrument equipped with JAIGEL-1H/JAIGEL-2H columns using chloroform as an eluent. Preparative thin-layer chromatography (PTLC) was performed using Wako-gel® B5-F silica coated plates (0.75 mm) prepared in our laboratory. Gas chromatography (GC) analysis was conducted on a Shimadzu GC-2010 instrument equipped with an HP-5 column (30 m×0.25 mm, Hewlett–Packard). GC/MS analysis was conducted on a Shimadzu GCMS-QP2010 instrument equipped with an HP-5 column (30 m×0.25 mm, Hewlett–Packard). High-resolution mass spectra (HRMS) were obtained from a JMS-T100TD (direct analysis in real time mass spectrometry, DARTMS) or a JEOL JMS-700 (fast atom bombardment mass spectrometry, FABMS) instrument. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet, br s=broad signal), coupling constant (Hz), and integration.

4.2. Synthesis and X-ray crystal structure analysis of Pd complex 4

A solution of $PdBr_2$ (79.9 mg, 0.3 mmol) in dry acetonitrile (1.5 mL) was refluxed for 0.5 h under argon. After cooling the reaction mixture to room temperature, bipy (70.3 mg, 0.45 mmol) was added, and the resultant mixture was stirred at room temperature for 1 h. Recrystallization from DMSO/*n*-hexane followed by filtration and washing with MeOH and ether afforded $PdBr_2$(bipy)·DMSO (**4**: 102 mg, 68%) as orange crystal. ^{1}H NMR

(600 MHz, DMSO-d_6) δ 7.79–7.81 (m, 2H), 8.36 (dd, J=7.9, 7.6 Hz, 2H), 8.59 (d, J=7.6 Hz, 2H), 9.39 (d, J=5.5 Hz, 2H).

Intensity data were collected at 123 K on a Rigaku Single Crystal CCD X-ray Diffractometer (Saturn 70 with MicroMax-007) with graphite-monochromated Mo Kα radiation (λ=0.7107 Å). A total 9953 reflections were corrected, of which 2704 were independent reflections (R_{int}=0.0290). The structure was solved by direct methods (SIR-97) and refined by the full-matrix least-squares techniques against F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions. The crystal data are as follows: $C_{12}H_{14}Br_2N_2OPdS$, FW=500.53, crystal size 0.10×0.10×0.05 mm^3, monoclinic, space group $C2/c$ (No.15). a=29.710(8) Å, b=7.9377(14) Å, c=22.102(6) Å, β=143.908(7)°, V=3070.4(12) Å^3, Z=8, D_{calcd}=2.166 g/cm^3. The refinement converged to R_1=0.0232, wR_2=0.0469 ($I>2\sigma(I)$), R_1=0.0270, wR_2=0.0484 (for all data), GOF=1.047. Selected bond lengths (Å): Pd(1)–N(1)=2.035(2), Pd(1)–N(2)=2.040(2), Pd(1)–Br(1)=2.4118(6), Pd(1)–Br(2)=2.4179(7). Selected angles (deg): N(1)–Pd(1)–N(2)=80.66(10), N(2)–Pd(1)–Br(2)=95.49(7), Br(2)–Pd(1)–Br(1)=88.96(3), Br(1)–Pd(1)–N(1)=94.93(7), N(1)–Pd(1)–Br(2)=175.15(6), N(2)–Pd(1)–Br(1)=175.48(7).

4.3. Typical procedure for C–H bond arylation of heteroarenes 1 with haloarenes 2 catalyzed by 4

A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added Pd complex **4** (8.1 mg, 16 μmol), Ag_2CO_3 (82.4 mg, 0.3 mmol), and dry 1,4-dioxane (0.75 mL) under a stream of argon. The vessel was heated at 60 °C for 0.5 h. To this vessel were added 2-ethylthiophene (**1a**: 33.7 mg, 0.30 mmol), iodobenzene (57 mg, 0.28 mmol), and dry 1,4-dioxane (0.75 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 13 h in oil bath with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford 2-ethyl-5-phenylthiophene (**3aa**: 36.9 mg, 70%) as colorless oil.

4.4. Compound data of representative coupling products 3

*4.4.1. 2-Ethyl-5-(2-methylphenyl)thiophene (**3ab**).* Yield (80%) from 2-ethylthiophene (**1a**) and 2-iodotoluene (**2b**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, J=7.6 Hz, 3H), 2.43 (s, 3H), 2.87 (q, J=7.6 Hz, 2H), 6.75 (d, J=3.4 Hz, 1H), 6.86 (d, J=3.4 Hz, 1H), 7.18–7.24 (m, 3H), 7.38 (d, J=7.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8, 21.2, 23.4, 123.3, 125.8, 126.0, 127.4, 130.2, 130.7, 134.6, 135.9, 140.4, 147.3. HRMS (DART) m/z calcd for $C_{13}H_{15}S$ $[MH]^+$: 203.0895, found 203.0892.

*4.4.2. 2-Ethyl-5-(3-methylphenyl)thiophene (**3ac**).* Yield (82%) from 2-ethylthiophene (**1a**) and 3-iodotoluene (**2c**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (t, J=7.6 Hz, 3H), 2.36 (s, 3H), 2.84 (q, J=7.6 Hz, 2H), 6.73 (d, J=3.4 Hz, 1H), 7.04 (d, J=7.6 Hz, 1H), 7.09 (d, J=3.4 Hz, 1H), 7.22 (t, J=7.6 Hz, 1H), 7.35–7.37 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 21.4, 23.6, 122.5, 122.6, 124.2, 126.2, 127.8, 128.6, 134.6, 138.3, 141.7, 147.0. HRMS (DART) m/z calcd for $C_{13}H_{15}S$ $[MH]^+$: 203.0895, found 203.0899.

*4.4.3. 2-Ethyl-5-(4-methoxylphenyl)thiophene (**3ae**).* Yield (77%) from 2-ethylthiophene (**1a**) and 4-iodoanisole (**2e**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (t, J=7.6 Hz, 3H), 2.84 (q, J=7.6 Hz, 2H), 3.80 (s, 3H), 6.71 (d, J=3.4 Hz, 1H), 6.88 (d, J=8.9 Hz, 2H), 6.99 (d, J=3.4 Hz, 1H), 7.47 (d, J=8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 23.5, 55.3, 114.2, 121.6, 124.1, 126.7, 127.7, 141.5, 146.2, 158.8. HRMS (DART) m/z calcd for $C_{13}H_{15}OS$ $[MH]^+$: 219.0844, found 219.0847.

*4.4.4. Ethyl 4-(5-ethylthiophen-2-yl)benzoate (**3af**).* Yield (52%) from 2-ethylthiophene (**1a**) and ethyl 4-iodobenzoate (**2f**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, J=7.6 Hz, 3H), 1.40 (t, J=7.6 Hz, 3H), 2.87 (q, J=7.6 Hz, 2H), 4.38 (q, J=7.6 Hz, 2H), 6.78 (d, J=3.5 Hz, 1H), 7.23 (d, J=3.5 Hz, 1H), 7.60 (d, J=8.9 Hz, 2H), 8.01 (d, J=8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 15.8, 23.6, 60.9, 124.2, 124.7, 124.9, 128.5, 130.1, 138.9, 140.2, 148.9, 166.3. HRMS (DART) m/z calcd for $C_{15}H_{16}O_2S$ $[MH]^+$: 261.0949, found 261.0957.

*4.4.5. 2-Ethyl-5-(4-nitrophenyl)thiophene (**3ag**).* Yield (43%) from 2-ethylthiophene (**1a**) and 4-iodonitrobenzene (**2g**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (t, J=7.6 Hz, 3H), 2.89 (q, J=7.6 Hz, 2H), 6.83 (d, J=3.5 Hz, 1H), 7.30 (d, J=3.5 Hz, 1H), 7.66 (d, J=8.9 Hz, 2H), 8.20 (d, J=8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8, 23.7, 124.3, 125.2, 125.3, 125.6, 138.7, 140.9, 146.1, 150.7. HRMS (DART) m/z calcd for $C_{12}H_{12}NO_2S$ $[MH]^+$: 234.0589, found 234.0587.

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