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Suzuki–Miyaura Coupling of Aryl Iodides, Bromides, and Chlorides Catalyzed by Bis(thiazole) Pincer Palladium Complexes

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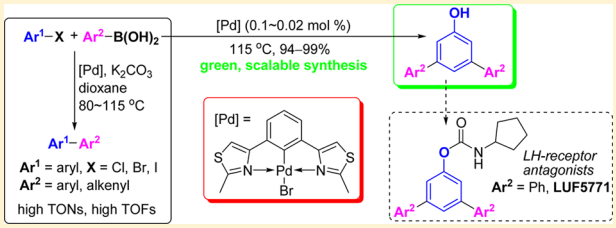
Supporting Information

ABSTRACT: Bis(thiazole) pincer palladium complexes showed efficient catalytic activity for the Suzuki–Miyaura coupling of aryl halides, allowing the synthesis of biaryls with very high turnover numbers and turnover frequencies. The complexes were successfully applied in the scalable and green synthesis of the key intermediates of bioactive LUF5771 and its analogues.



Palladium-catalyzed cross-coupling reactions are versatile tools in modern organic synthesis.[1] Among these transformations, Suzuki–Miyaura (SM) coupling undoubtedly belongs to the most powerful methods for C–C bond construction.[2,3] Palladacycles, a class of organopalladium derivatives containing at least one Pd–C bond, are able to efficiently catalyze SM coupling.[4,5] Pincer palladium complexes are well-defined palladacycles that contain a Pd–C bond stabilized by the intramolecular coordination of two neutral donor atoms (N, P, As, O, Se, or S).[6−8] The rich chemistry of pincer-Pd complexes has attracted considerable attention,[9−12] and a plethora of pincer-Pd compounds were available for catalyzing the SM coupling.[13] The catalytic activities of these complexes depended on the structure of their ligands. The most efficient pincer-Pd complexes were those containing phosphines or phosphine mimics (such as *N*-heterocyclic carbenes, NHCs) as ligands.[14,15] The NCN type of pincer-Pd complexes, containing two nitrogen atoms as donating sites in the coordination sphere, were developed as a variety of nonphosphine pincer catalytic system.[6] To date, most NCN pincer-Pd systems were only able to catalyze the couplings of relatively active substrates,[4] and those lacking phosphorus and NHCs in their ligands were rarely active toward the coupling of the less active substrates, such as *ortho*-disubstituted bromobenzenes and chloroarenes. There were no symmetrical examples and only one unsymmetrical example of NCN palladium complexes that allowed the use of aryl chlorides in SM coupling.[16]

As five-membered heterocyclic structures, thiazoles can be used as *N*-donor ligands. However, thiazole-derived tridentate ligands are underrepresented in the chemistry of coordination compounds.[17,18] Recently, Odinets and co-workers reported that an unsymmetrical SCN pincer complex, bearing a thiophosphoryl and a benzothiazole ring as donating sites, showed an ability to efficiently promote the SM coupling of chloroacetophenone.[19] Symmetrical pincer structures have many advantages over unsymmetrical ones, such as structural simplicity and synthetic conciseness and convenience. Following our interest in the development of bis(azoline) pincer complexes and their applications,[20−22] we herein report the synthesis, characterization, and catalysis study of symmetrical NCN pincer-Pd complexes containing bis(thiazole) motifs in the SM coupling of aryl halides (Figure 1, complexes **1** and **2**).

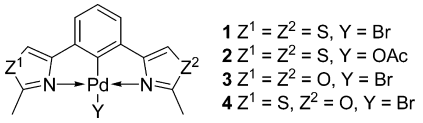


Figure 1. Bis(azoline) pincer complexes **1**–**4**.

These complexes were robust for catalyzing the SM coupling of less active aryl halides, such as bromophenols, *ortho*-disubstituted bromobenzenes, and chloroarenes.

The synthetic routes of complexes **1** and **2** are summarized in the Supporting Information (Scheme S1). The solid state structures were determined by single-crystal X-ray diffraction.[23] The synthesis of complexes **3** and **4** was reported previously.[21] The catalytic investigation began with an examination of the coupling of 4-methoxybromobenzene with $PhB(OH)_2$ to evaluate the catalytic activities of complexes **1**–**4** (Table 1, Entries 1–4). The results showed that the activity of the complexes was **1** > **2** > **3** > **4**. Complexes **1** and **2**, containing the same bis(thiazole) pincer structure, were of similar activity and greatly superior to complexes **3** and **4**, which indicated that the pincer scaffold of the Pd complexes [bis(thiazole) vs bis(oxazole) and thiazole-oxazole in complexes **1**, **3**, and **4**, respectively] had more impact on the catalytic activity than the ligand ion (bromine ion vs acetate ion in complexes **1** and **2**, respectively). Because the pincer scaffold in complexes **1** and **2** is same and their catalytic activities were close, the activity test was hereafter focused on complex **1**. In the SM coupling performed with bromoarenes (Table 1, Entries 5–17), the

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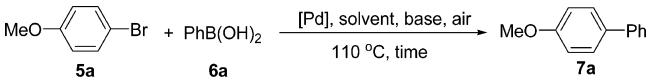
Table 1. Catalyst Screening and Reaction Condition Optimization for the SM Coupling Performed with 4-Methoxybromobenzene[a]



5a 6a 7a

entry	[Pd] (loading)	solvent	base	time (h)	isolated yield (%)
1	**1** (0.05 mol %)	dioxane	K_2CO_3	15	97
2	**2** (0.05 mol %)	dioxane	K_2CO_3	15	94
3	**3** (0.05 mol %)	dioxane	K_2CO_3	15	52
4	**4** (0.05 mol %)	dioxane	K_2CO_3	15	18
5	**1** (1 mol %)	dioxane	K_2CO_3	4	99
6	**1** (1 mol %)	DMSO	K_2CO_3	4	5
7	**1** (1 mol %)	DMF	K_2CO_3	4	63
8	**1** (1 mol %)	toluene	K_2CO_3	4	83
9	**1** (1 mol %)	*p*-xylene	K_2CO_3	4	97
10	**1** (1 mol %)	^{t}BuOH/H_2O (9:1)	K_2CO_3	4	trace
11	**1** (1 mol %)	dioxane	$K_3PO_4{\cdot}3H_2O$	4	95
12	**1** (1 mol %)	dioxane	NaOH	4	44
13	**1** (1 mol %)	dioxane	KOAc	4	19
14	**1** (1 mol %)	dioxane	KF	4	17
15	**1** (1 mol %)	dioxane	Cs_2CO_3	4	85
16	**1** (1 mol %)	dioxane	NEt_3	4	4
17	**1** (1 mol %)	dioxane	pyridine	4	trace

[a]Reaction conditions: **5a** (1 mmol), **6a** (1.5 mmol), pincer-Pd complex (indicated amount), base (3 mmol) and solvent (5 mL). The product was isolated by chromatographic purification on silica column.

change of solvent or base strongly influenced the isolated yields. The best results were obtained with 1,4-dioxane as solvent (Entry 5 vs Entries 6−10) and K_2CO_3 as base (Entry 5 vs Entries 11−17), whereas neither polar solvents (Entries 6 and 10) nor organic bases (Entries 16 and 17) yielded good results.

With the optimized reaction conditions, we further examined the catalytic activity of complex **1** in the SM coupling of various haloarenes with organoboronic acids. As shown in Table 2, complex **1** was a robust (pre)catalyst toward SM coupling. Iodoarenes (Table 2, Entries 1−7) underwent coupling with a turnover number (TON) of up to 1.9×10^8 and a turnover frequency (TOF) of up to 5×10^6 h^{-1} (Table 2, Entry 5). The catalytic efficiency is better than that of the NHC-type pincer-Pd complexes.[24−26] Remarkably, the couplings could afford the desired product in fair yield even with a ppm scale catalyst loading (Table 2, Entries 2−5, with 2×10^{-6} mol % Pd-loading, 61% of yield). Palladium-catalyzed reactions frequently present the problem that the products were contaminated by a high level of residual palladium (typically 300−2000 ppm). With a palladium loading as low as 2×10^{-6} mol %, the problem of Pd residue could be ignored if the coupling yield exceeded 40% because the total amount of palladium from the (pre)catalyst did not exceed the level of residual palladium in the active pharmaceutical ingredients required by government regulations (typically <5 ppm).[27] The coupling of iodoarenes worked well at a temperature of less than 90 °C (Table 2, Entries 1 and 6). For deactivated bromoarenes, excellent yields were obtained under aerobic conditions with 0.01−0.05 mol % of complex **1** (Table 2, Entries 8−17). Complex **1** also showed potent catalytic activities toward the sterically hindered substrates (e.g., 2-bromotoluene and 2,6-dimethylbromobenzene) (Table 2, Entries 14−16). The catalytic efficiency of complex **1** toward bromoarenes was close to that of the phosphorus-containing complex **8** {C_6H_3[NHP(piperidinyl)$_2$]$_2$Pd(Cl)},[28] and better than that of many NHC-type pincer-Pd complexes.[15,29] Notably, the reactions gave good results for activated aryl chlorides (Table 2, Entries 18−24), and TON was up to 4400 (Table 2, Entry 20), the same order of magnitude as PCP pincer complex **8**[30] for chloroarenes. Unactivated chloroarenes also worked using complex **1**, but with lower yields (Table 2, Entries 25 and 26). According to the literature,[16,19,30−35] the best results for coupling of aryl chlorides were achieved with phosphorus-containing pincer complexes or with palladacycles modified by carbenes. The pincer-Pd complexes that contained phosphorus-free ligands and were active toward aryl chlorides were extremely rare. A comparison of catalytic efficiency among the most active pincer-Pd complexes known to catalyze the SM coupling of chloroarenes with arylboronic acids is discussed in the Supporting Information. Complex **1** was the first example of a symmetrical NCN pincer-Pd complex that completely lacked phosphorus and NHCs in its ligand while allowing the use of chloroarenes in SM coupling. Overall, complex **1** ranks among the most active pincer complexes suggested for this reaction.

The catalytic efficiency of complex **1** was further exemplified in the synthesis of terphenyl-derived antagonists of the luteinizing hormone (LH) receptor (Scheme 1). The terphenylcarbamate derivatives **10**, especially **LUF5771** (**10a**), were recently identified as efficient LH-receptor antagonists by Heitman and co-workers.[36] However, because of the relatively low activity of bromophenol (**5n**), the key intermediates **9** were prepared in poor to moderate yields (34−71%) via SM couplings catalyzed by the classic Pd reagent $Pd(PPh_3)_4$. A good alternative for the preparation of **9**, newly reported by Stahl and co-workers, was to transform the substituted cyclohexanones into the targeted diarylphenol derivatives via palladium-catalyzed oxidative dehydrogenation (Scheme 1, reaction (iii)).[37] Nevertheless, the SM coupling-involved route is believed to be more concise. Subsequently, the catalytic behavior of complex **1** was examined in the synthesis of disubstituted phenols **9a** and **9b**. As shown in Scheme 1, the catalytic efficiency of complex **1** was distinguished by its practicality, and this protocol integrated several advantages compared with the results above. (1) The catalyst loading was as low as 0.1 mol % [Pd] or less (Scheme 1, Entries 1−6), much lower than those required above. (2) The couplings catalyzed by complex **1** underwent a greener reaction condition, in which no organic solvent or other additives were required except the catalyst, common inorganic base, and water. (3) This protocol permitted the operations to be managed in a very convenient way. The reactions did not need susceptible reagents or special equipment. Complex **1** is stable toward air and moisture, and the couplings could be carried out under aerobic conditions. Thus, the reaction installation did not require strictly air-free techniques. (4) The scale up (from milligram-scale to gram-scale) of the reaction hardly affected the catalytic efficiency. Comparatively, Stahl's method was also capable of scale-up, but it needed a prolonged reaction time of 48 h and an extra portion of catalyst.

In conclusion, two bis(thiazole) NCN-type pincer palladium(II) complexes were synthesized through a facile route in good yields. Their solid structures were confirmed by single-crystal X-ray diffraction. Complex **1** was proved to be highly robust

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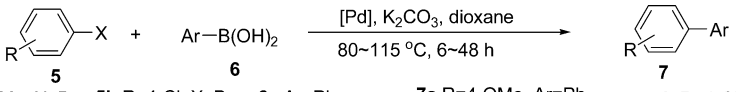
Table 2. Evaluation of the Catalytic Activity of Complex 1 in the SM Coupling of Aryl Halide[a]



5a R=4-OMe, X=Br; **5b** R=4-OMe, X=I; **5c** R=4-Me, X=I; **5d** R=4-Me, X=Br; **5e** R=H, X=Br; **5f** R=2-Me, X=Br; **5g** R=2,6-dimethyl, X=Br; **5h** R=4-Cl, X=Br; **5i** R=4-NO_2, X=Cl; **5j** R=4-CN, X=Cl; **5k** R=4-Ac, X=Cl; **5l** R=4-Ph, X=Cl; **5m** R=4-OMe, X=Cl

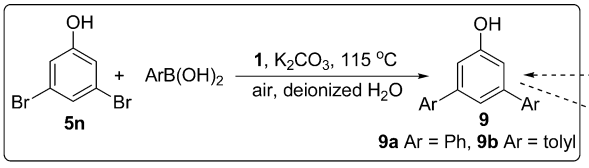
6a Ar=Ph; **6b** Ar=(*E*)-styryl; **6c** Ar=p-ClC_6H_4; **6d** Ar=*p*-$CH_3C_6H_4$

7a R=4-OMe, Ar=Ph; **7b** R=4-OMe, Ar=(*E*)-styryl; **7c** R=4-Me, Ar=Ph; **7d** R=4-Me, Ar=*p*-ClC_6H_4; **7e** R=H, Ar=Ph; **7f** R=2-Me, Ar=Ph; **7g** R=2,6-dimethyl, Ar=Ph; **7h** R=4-Cl, Ar=Ph; **7i** R=4-NO_2, Ar=Ph; **7j** R=4-NO_2, Ar=*p*-ClC_6H_4; **7k** R=4-NO_2, Ar=*p*-$CH_3C_6H_4$; **7l** R=4-CN, Ar=Ph; **7m** R=4-Ac, Ar=Ph; **7n** R=4-Ph, Ar=Ph

entry	5	X	6	7	[Pd] (loading)	*T* (°C)	*t* (h)	yield[b]	TON	TOF (h^{-1})
1	**5b**	I	**6a**	**7a**	**1** (0.1 mol %)	90	28	98	980	35
2	**5b**	I	**6a**	**7a**	**1** (2×10^{-4} mol %)	110	20	96	4.8×10^5	2.4×10^4
3	**5b**	I	**6a**	**7a**	**1** (2×10^{-5} mol %)	115	30	88	4.4×10^6	1.5×10^5
4	**5b**	I	**6a**	**7a**	**1** (2×10^{-6} mol %)	115	38	61	3.0×10^7	8.0×10^5
5	**5b**	I	**6a**	**7a**	**1** (2×10^{-7} mol %)	115	38	38	1.9×10^8	5.0×10^6
6	**5b**	I	**6b**	**7b**	**1** (1×10^{-3} mol %)	80	8	92	9.2×10^4	1.1×10^4
7	**5c**	I	**6a**	**7c**	**1** (1×10^{-4} mol %)	110	20	99	9.9×10^5	4.9×10^4
8	**5a**	Br	**6a**	**7a**	**1** (0.05 mol %)	110	15	97	1.9×10^3	129
9	**5a**	Br	**6a**	**7a**	**1** (5×10^{-3} mol %)	110	36	75	1.5×10^4	416
10	**5a**	Br	**6a**	**7a**	**1** (5×10^{-4} mol %)	110	48	22	5.5×10^4	1.1×10^3
11	**5d**	Br	**6a**	**7b**	**1** (0.05 mol %)	110	12	95	1.9×10^3	158
12	**5d**	Br	**6c**	**7d**	**1** (0.5 mol %)	110	6	98	196	32
13	**5e**	Br	**6a**	**7e**	**1** (0.05 mol %)	110	24	97	1.9×10^3	81
14	**5f**	Br	**6a**	**7f**	**1** (0.05 mol %)	110	24	83	1.6×10^3	69
15	**5g**	Br	**6a**	**7g**	**1** (0.05 mol %)	110	24	70	1.4×10^3	58
16	**5g**	Br	**6a**	**7g**	**1** (0.1 mol %)	110	24	98	980	41
17	**5h**	Br	**6a**	**7h**	**1** (0.01 mol %)	110	18	98	9.8×10^3	544
18	**5i**	Cl	**6a**	**7i**	**1** (1 mol %)	110	24	89	89	3.7
19[c]	**5i**	Cl	**6a**	**7i**	**1** (0.1 mol %)	110	24	76	760	31.7
20[c]	**5i**	Cl	**6a**	**7i**	**1** (0.01 mol %)	110	24	44	4.4×10^3	183
21[d]	**5i**	Cl	**6c**	**7j**	**1** (1 mol %)	110	24	61	61	2.5
22[d]	**5i**	Cl	**6d**	**7k**	**1** (1 mol %)	110	24	80	80	3.3
23[e]	**5j**	Cl	**6a**	**7l**	**1** (0.5 mol %)	110	24	85	170	7.1
24[f]	**5k**	Cl	**6a**	**7m**	**1** (1 mol %)	110	24	74	74	3.1
25[c]	**5l**	Cl	**6a**	**7n**	**1** (1 mol %)	110	40	21	21	0.5
26[d]	**5m**	Cl	**6a**	**7a**	**1** (1 mol %)	110	24	21	21	0.9

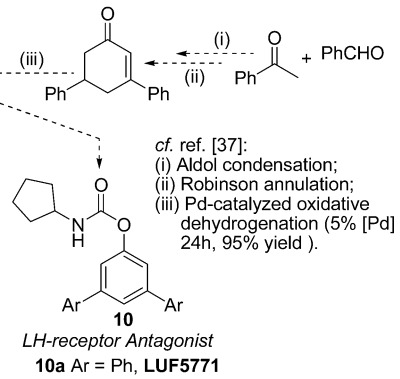
[a]Reaction conditions: **5** (1 mmol), **6** (1.5 mmol), **1** (indicated amount), K_2CO_3 (3 mmol), and 1,4-dioxane (5 mL), for entries 1–17, under the ambient atmosphere; for entries 18–26, under argon atmosphere. TON: turnover number, ratio of yield to catalyst amount. TOF: turn over frequency, ratio of TON to reaction time. [b]Isolated yields are given in all cases. [c]Added NaBr (1 equiv). [d]Added H_3BO_3 (50 mol %). [e]Added TBAB (1 equiv). [f]Added PPh_3 (3 mol %).

Scheme 1. Applications of 1 in the Catalytic Synthesis of Terphenyl-Derived Antagonists of the Luteinizing Hormone Receptor



Entry	Reaction scale[a]	**1** (loading)	Time	**9**	Isolated yield
1	0.1 mmol	0.02 mol %	4h	**9a**	95%
2	0.1 mmol	0.02 mol %	4h	**9b**	95%
3	0.5 mmol	0.1 mol %	3h	**9a**	98%
4	0.5 mmol	0.1 mol %	4h	**9b**	99%
5	5 mmol	0.1 mol %	8h	**9a**	94%
6	5 mmol	0.1 mol %	8h	**9b**	94%

vs ref. [36]: toluene, $Pd(PPh_3)_4$ (5 mol %), Na_2CO_3, 150 °C, microwave. Yield: **9a**, 71%; **9b**, 67%



[a]Reaction scales are based on **5n**.

(pre)catalyst for the SM couplings of less active aryl halides, such as bromophenols, *ortho*-disubstituted bromobenzenes, and chloroarenes. This was the first example of symmetrical NCN pincer-Pd complexes that lacked phosphorus and *N*-heterocyclic carbene in the ligands while being capable of catalyzing the Suzuki–Miyaura cross-coupling of chloroarenes. The

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applications of **1** in the scalable and green synthesis of the key intermediates of bioactive **LUF5771** and its analogues highlight the prospective utility in the synthesis of aryl-substituted arenes, and could have a positive impact on laboratory- and industrial-scale chemical synthesis.

EXPERIMENTAL SECTION

Synthesis of Complexes 1 and 2 (Scheme S1). *1-Bromo-2,6-bis(2-methylthiazol-4-yl)benzene.* 1-Bromo-2,6-bis(2-bromoacetyl)-benzene[38] (400 mg, 1 mmol) and thiacetamide (300 mg, 4 mmol) were dissolved in 5 mL of DMF. After being stirred for 24 h at room temperature, the resultant mixture was diluted with 15 mL of H_2O, and then extracted with EtOAc (three portions of 20 mL each). The combined organic phase was successively washed with water and brine, dried over anhydrous $MgSO_4$, and then purified by column chromatography (silica, hexanes/EtOAc 4:1 as eluent) to afford **1-bromo-2,6-bis(2-methylthiazol-4-yl)benzene** (296 mg, 84% yield) as a pale yellow solid, mp 80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, ^3J = 7.5 Hz, 2H), 7.43 (s, 2H), 7.40 (t, ^3J = 7.5 Hz, 1H), 2.79 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 153.8, 137.3, 131.3, 127.1, 122.4, 117.4, 19.2. LRMS (ESI): *m*/*z* (%) 351 (95) (M^++H), 353 (100) (M^++2+H), 373 (22) (M^++Na). Elemental analysis calcd (%) for $C_{14}H_{11}BrN_2S_2$: C, 47.87; H, 3.16; N, 7.97; found: C, 47.96; H, 3.18; N, 8.20.

*[Bromo-2,6-bis(2-methylthiazol-4-yl)phenylpalladium(II)] (**1**).* Under an argon atmosphere, a 25 mL Schlenk flask was charged with **1-bromo-2,6-bis(2-methylthiazol-4-yl)benzene** (106 mg, 0.3 mmol), $Pd(dba)_2$[39] (173 mg, 0.3 mmol), and dry benzene (15 mL). The reaction mixture was heated to reflux for 2 h, then cooled to room temperature and stirred for further 2 h. The resultant mixture was directly transferred on to a diatomite column and eluted first with hexane to remove dibenzylideneacetone (dba) and then with mixed solvent ($CHCl_3$/MeOH = 3:1). The collected target compound **1** was crystallized from $CHCl_3$/MeOH as a slight yellow amorphous solid. Yield 86%, mp >260 °C (decomp.). ^{1}H NMR (300 MHz, [D_6]DMSO): δ 7.96 (s, 2H), 7.43 (d, ^3J = 7.5 Hz, 2H), 7.20 (d, ^3J = 7.5 Hz, 1H), 3.15 (s, 6H). ^{13}C NMR (75 MHz, [D_6]DMSO): δ 174.7, 159.8, 154.6, 136.9, 125.8, 121.2, 111.0, 21.0. LRMS (ESI): *m*/*z* (%) 377 (64) (M^+−Br), 418 (46) (M^+−Br+CH_3CN), 801 (100) ($2M^+$+HCO_2−2Br), 835 (22) ($2M^+$−Br). HRMS (ESI) calcd for $C_{14}H_{11}N_2S_2Pd$ (M^+−Br): 376.9397; found: 376.9389. HRMS (ESI) calcd for $C_{28}H_{22}BrN_4S_4Pd_2$ ($2M^+$−Br): 832.7976; found: 832.7953. Elemental analysis calcd (%) for $C_{14}H_{11}BrN_2S_2Pd{\cdot}0.5H_2O$: C, 36.03; H, 2.59; N, 6.00; found: C, 36.02, H, 2.77; N, 5.88. The single crystals of **1** suitable for X-ray diffraction analysis were grown by slow diffusion of dichloromethane into its DMF solution.

*[2,6-Bis(2-methylthiazol-4-yl)phenylpalladium(II) acetate] (**2**).* A 25 mL flask was charged with AgOAc (86 mg, 0.51 mmol), **1** (80 mg, 0.17 mmol), and THF-H_2O (V:V = 60:1, 12 mL). The reaction mixture was stirred in the dark overnight, whereupon TLC analysis showed that bromide had been consumed, and then filtered through diatomite. The filter cake was washed with acetone three times and dried *in vacuo* to afford 57 mg of **2** as an off-white amorphous solid. Yield 76%, mp >160 °C (decomp.). ^{1}H NMR (300 MHz, [D_6]DMSO): δ 7.94 (s, 2H), 7.39 (d, ^3J = 7.2 Hz, 2H), 7.15 (d, ^3J = 7.3 Hz, 1H), 2.79 (s, 6H), 1.84 (s, 3H). The ^{13}C NMR of **2** was unsuccessful due to the complex's low solubility in the common solvent. LRMS (ESI): *m*/*z* (%) 377 (57) (M^+−OAc), 418 (28) (M^+−OAc+CH_3CN), 801 (100) ($2M^+$−2OAc+HCO_2). HRMS (ESI) calcd for $C_{14}H_{11}N_2S_2Pd$ (M^+−OAc): 376.9397; found: 376.9383. HRMS (ESI) calcd for $C_{28}H_{22}BrN_4S_4Pd_2$ ($2M^+$−OAc): 812.8926; found: 812.8940. Crystals of **2** suitable for X-ray diffraction analysis were grown by slow diffusion of EtOAc and hexane into a DMF-HOAc solution of **1**.

General Procedure for the Suzuki−Miyaura Couplings (Tables 1 and 2). A 10 mL reaction tube equipped with a condenser was charged with a mixture of organoboronic acid (1.5 mmol), aryl halide (1.0 mmol), anhydrous K_2CO_3 (3.0 mmol), an indicated amount of additive (if necessary), 1,4-dioxane (5.0 mL), and an indicated amount of complex **1**. If the amount of **1** was less than 1.0 mg, an appropriate volume of a solution of **1** was used (the solution at an initial concentration of 0.04 mol·L^{-1} in NMP was progressively diluted with dioxane), and the total volume of the solvents was 5.0 mL in each reaction. For the reactions in which inert atmosphere was not required, the outlet of the condenser was connected to a paraffin-filled bubble counter, while for those required, standard Schlenk-line techniques were applied under argon atmosphere. The mixture was heated at an indicated temperature (typically, at 110 °C) and continually stirred until the consumption of aryl halide (monitoring with TLC). After being cooled to the ambient temperature, it was diluted with 10 mL of deionized water, and extracted with EtOAc (three portions of 15 mL each). The combined organic phase was washed with deionized water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and then filtered and concentrated. The crude product was purified by column chromatography (silica, hexane or hexane/EtOAc mixture as eluent). The isolated coupling products were confirmed by ^{1}H and ^{13}C NMR.

*4-Methoxybiphenyl (**7a**).*[40−42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62−7.54 (m, 4H), 7.49−7.42 (m, 2H), 7.34 (tt, *J* = 1.6, 7.3 Hz, 1H), 7.02 (dt, *J* = 2.4, 8.7 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 140.7, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.3.

*(E)-4-Methoxystilbene (**7b**).*[43] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54−7.42 (m, 4H), 7.35 (t, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 6.8 Hz, 1H), 7.07 (d, *J* = 16.3 Hz, 1H), 6.99 (d, *J* = 16.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 137.6, 130.1, 128.6, 128.2, 127.7, 127.2, 126.6, 126.2, 114.1, 55.3.

*4-Methylbiphenyl (**7c**).*[40−42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62−7.57 (m, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.47−7.40 (m, 2H), 7.37−7.31 (m, 1H), 7.29−7.25 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 138.4, 137.0, 129.5, 128.7, 126.98, 126.96, 126.95, 21.1.

*4-(4-Chlorophenyl)toluene (**7d**).*[44] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 137.4, 137.0, 133.0, 129.6, 128.8, 128.1, 126.8, 21.1.

*Biphenyl (**7e**).*[40−42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.4 Hz, 4H), 7.44 (t, *J* = 7.4 Hz, 4H), 7.32 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 128.7, 127.2, 127.1.

*2-Methylbiphenyl (**7f**).*[41] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.35 (m, 2H), 7.35−7.28 (m, 3H), 7.28−7.20 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9 (C × 2), 135.3, 130.3, 129.8, 129.2, 128.0, 127.2, 126.7, 125.7, 20.5.

*2,6-Dimethylbiphenyl (**7g**).*[45] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.40 (m, 2H), 7.38−7.31 (m, 1H), 7.21−7.09 (m, 5H), 2.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9, 141.1, 136.1, 129.0, 128.4, 127.3, 127.0, 126.6, 20.9.

*4-Chlorobiphenyl (**7h**).*[40−42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 9.9 Hz, 2H), 7.46−7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 139.6, 133.3, 128.88, 128.86, 128.4, 127.6, 127.0.

*4-Nitrobiphenyl (**7i**).*[40−42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.65−7.60 (m, 2H), 7.54−7.41 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 147.0, 138.7, 129.1, 128.9, 127.8, 127.3, 124.1.

*4-(4-Nitrophenyl)chlorobenzene (**7j**).*[40] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 146.2, 137.1, 135.2, 129.3, 128.6, 127.6, 124.1.

*4-(4-Nitrophenyl)toluene (**7k**).*[40] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 146.8, 139.1, 135.8, 129.9, 127.4, 127.2, 124.1, 21.2.

*4-Phenylbenzonitrile (**7l**).*[41,42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76−7.66 (m, 4H), 7.62−7.57 (m, 2H), 7.52−7.39 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6, 139.1, 132.5, 129.1, 128.6, 127.7, 127.2, 118.9, 110.8.

*4-Acetylbiphenyl (**7m**).*[40−42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.7 Hz, 2H),

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7.51−7.37 (m, 3H), 2.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 145.6, 139.7, 135.6, 128.85, 128.81, 128.1, 127.13, 127.08, 26.6.

p-Terphenyl (7n).[42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 4H), 7.66 (d, J = 8.2 Hz, 4H), 7.47 (t, J = 7.3 Hz, 4H), 7.37 (t, J = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 140.1, 128.8, 127.5, 127.3, 127.0.

Synthetic Procedures of 3,5-Diphenylphenol (9a) and 3,5-Ditolylphenol (9b) (Scheme 1). *Miligram-Scale Synthesis.* A 15 mL reaction flask equipped with a condenser was charged with a mixture of phenylboronic acid (1.5 mmol), 3,5-dibromophenol (0.5 mmol), anhydrous K_2CO_3 (3.0 mmol), deionized water (3.0 mL), and 0.5 mL of the solution of **1** (5×10^{-4} mmol) in dioxane (the catalyst solution at an initial concentration of 0.04 mol·L^{-1} in NMP was progressively diluted into 1×10^{-3} mol·L^{-1} with dioxane). The outlet of the condenser was connected to a paraffin-filled bubble counter. The mixture was heated at 115 °C, and continually stirred until the consumption of aryl halide (monitoring with TLC). After being cooled to the ambient temperature, it was diluted with water (5 mL), neutralized with 1 mol·L^{-1} HCl, and extracted with EtOAc (three portions of 15 mL each). The combined organic phase was washed with distilled water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and then filtered and concentrated. The crude product was purified by column chromatography (silica, hexane/EtOAc mixture as eluent). The isolated coupling products were confirmed by ^{1}H NMR and ^{13}C NMR. For **3,5-diphenylphenol** (**9a**),[36,37] baby pink solid, yield, 98%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, ^3J = 7.2 Hz, 4H), 7.46 (t, ^3J = 7.3 Hz, 4H), 7.41−7.35 (m, 3H), 7.06 (d, ^4J = 1.4 Hz, 2H), 5.17 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 143.4, 140.7, 128.8, 127.6, 127.2, 118.9, 113.0. LRMS (ESI): m/z (%) = 115 (100) ($2CH_3CN$+MeOH+H$^+$), 247 (67) (M$^+$+H), 288 (36) (M$^+$+CH_3CN +H). For **3,5-ditolylphenol** (**9b**),[36] oyster white solid, yield 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, ^3J = 8.1 Hz, 4H), 7.36 (s, 1H), 7.26 (d, ^3J = 7.9 Hz, 4H), 7.01 (d, ^4J = 1.4 Hz, 2H), 5.02 (s, 1H), 2.40 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 143.2, 137.9, 137.4, 129.5, 127.0, 118.6, 112.6, 21.1; LRMS (ESI): m/z (%) 275 (100) (M$^+$+H), 316 (48) (M$^+$+CH_3CN+H).

Gram-Scale Synthesis. A 50 mL reaction flask equipped with a condenser was charged with a mixture of phenylboronic acid (15 mmol), 3,5-dibromophenol (5 mmol), anhydrous K_2CO_3 (30 mmol), deionized water (20 mL), and 2.3 mg of **1** (5×10^{-3} mmol). The outlet of the condenser was connected to a paraffin-filled bubble counter. The mixture was heated at 115 °C, and continually stirred until the consumption of aryl halide (monitoring with TLC). After being cooled to the ambient temperature, it was diluted with water (20 mL), neutralized with 1 mol·L^{-1} HCl, and extracted with EtOAc (three portions of 50 mL each). The combined organic phase was washed with distilled water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and then filtered and concentrated. The crude product was purified by column chromatography (silica, hexane/EtOAc mixture as eluent). The isolated coupling products were confirmed by ^{1}H NMR and ^{13}C NMR. For **9a**, yield, 94%; HPLC purity, > 98.1%. For **9b**, yield, 94%; HPLC purity, > 96.6%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental details, the crystal data for **1** and **2**, ^{1}H NMR, ^{13}C NMR, and MS spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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