

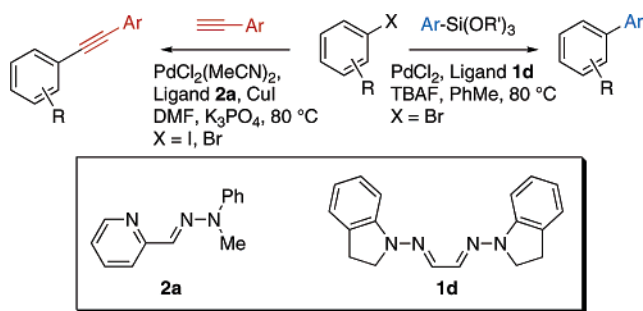
Palladium-Catalyzed Sonogashira and Hiyama Reactions Using Phosphine-Free Hydrazone Ligands

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Palladium/copper-catalyzed Sonogashira cross-coupling reaction of aryl halides with a variety of terminal alkynes under amine-free conditions in dimethylformamide (DMF) at 80 °C gave internal arylated alkynes using $\text{PdCl}_2(\text{MeCN})_2$ with phosphine-free hydrazone **2a** as a ligand and CuI as the cocatalyst in good yields. We also found PdCl_2 /hydrazone ligand **1d** in PhMe at 80 °C was a phosphine-free efficient catalyst system for a Hiyama cross-coupling reaction of aryl bromides with aryl(trialkoxy)silanes in good yields.

Palladium-catalyzed C–C coupling reactions have been recognized as powerful tools in multiple organic transformations.¹ We recently demonstrated air-stable phosphine-free

hydrazone as an effective ligand for the Suzuki–Miyaura² and Mizoroki–Heck cross-coupling reaction.³

The Sonogashira cross-coupling reaction of aryl halides with terminal acetylenes, which provides a powerful tool for the formation of alkynes, has been widely applied to such diverse areas as natural product syntheses and material science.⁴ The most common catalytic system for this reaction is using such palladium–phosphine complexes as $\text{PdCl}_2(\text{PPh}_3)_2$ and $\text{Pd}(\text{PPh}_3)_4$ in large amounts of amines as solvents or cosolvents with CuI as the cocatalyst.^{5–7} Recently a copper-free Sonogashira cross-coupling reaction was reported that used a combination of at least one phosphine as a ligand or an amine and a large amount of tetra-*n*-butyl ammonium salt as an activator.^{8–10} However, their phosphines in palladium complexes are often air-sensitive. Amines also have a characteristic foul smell and pungent flavor. We now report the use of air-stable phosphine-free hydrazone ligands **1** and **2** for an amine-free palladium/copper-catalyzed Sonogashira cross-coupling reaction.

We applied the coupling of 4-iodotoluene and phenyl acetylene in the presence of 2 mol % of $\text{PdCl}_2(\text{MeCN})_2$ with K_3PO_4 as a base under an argon atmosphere at 80 °C to determine the optimum reaction conditions (Table 1). The effect of various hydrazone ligands in this reaction was investigated (entries 1–5). In the presence of glyoxal bis(*N*-methyl-*N*-phenylhydrazone) (**1a**), which was the effective ligand for the

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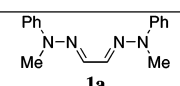
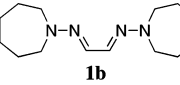
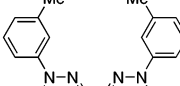
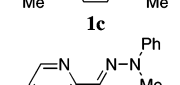
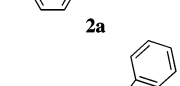
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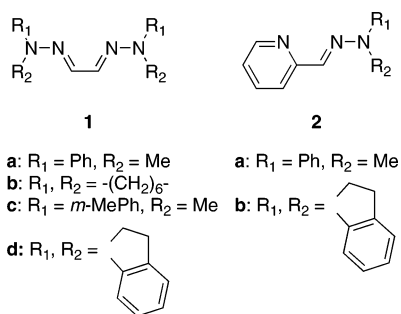
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TABLE 1. Optimization of Reaction Conditions on Sonogashira Reaction^a



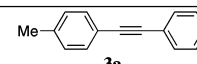


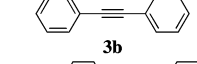


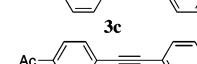


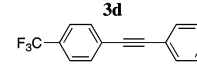


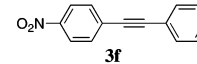


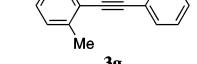


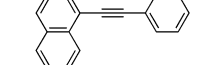


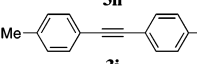


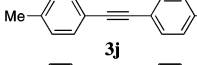


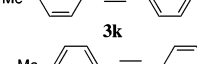


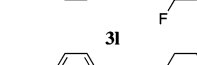


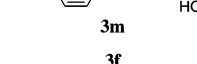


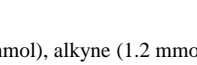


		Pd source Ligand, CuI base, solvent			
<i>p</i> -Tol-I + \equiv -Ph		80 °C, 5 h, Ar		<i>p</i> -Tol- \equiv -Ph 3a	
entry	ligand	base	solvent	Pd source	yield (%) ^b
1		K ₃ PO ₄	DMF	PdCl ₂ (MeCN) ₂	75
2		K ₃ PO ₄	DMF	PdCl ₂ (MeCN) ₂	37
3		K ₃ PO ₄	DMF	PdCl ₂ (MeCN) ₂	46
4		K ₃ PO ₄	DMF	PdCl ₂ (MeCN) ₂	93
5		K ₃ PO ₄	DMF	PdCl ₂ (MeCN) ₂	27
6	–	K ₃ PO ₄	DMF	PdCl ₂ (MeCN) ₂	41
7	2a	Cs ₂ CO ₃	DMF	PdCl ₂ (MeCN) ₂	76
8	2a	K ₂ CO ₃	DMF	PdCl ₂ (MeCN) ₂	37
9	2a	NaOAc	DMF	PdCl ₂ (MeCN) ₂	17
10	2a	KO ^t Bu	DMF	PdCl ₂ (MeCN) ₂	9
11	2a	K ₃ PO ₄	PhMe	PdCl ₂ (MeCN) ₂	4
12	2a	K ₃ PO ₄	MeCN	PdCl ₂ (MeCN) ₂	70
13	2a	K ₃ PO ₄	NMP	PdCl ₂ (MeCN) ₂	59
14	2a	K ₃ PO ₄	DMF	Pd(OAc) ₂	88
15	2a	K ₃ PO ₄	DMF	PdCl ₂	74
16	2a	K ₃ PO ₄	DMF	Pd ₂ (dba) ₃ ·CH ₂ Cl	83

^a Reaction conditions: 4-iodotoluene (1 mmol), phenyl acetylene (1.2 mmol), base (1.4 mmol), solvent (2 mL), palladium source (0.02 mmol), ligand (0.02 mmol), CuI (0.05 mmol). ^b Isolated yields.



Suzuki–Miyaura reaction, Sonogashira cross-coupling product **3a** was obtained in moderate yield (entry 1). Bishydrazone ligand **1b** with a seven-membered ring was not effective for this reaction. The use of **2a** as a ligand led to high yield for this reaction (entry 4). Without the presence of ligand **2a**, the reaction gave low yield of the desired product (entry 4 vs entry 6). The effect of various bases in the Sonogashira cross-coupling reaction was investigated (entries 4, 7–10). Among inorganic bases (K₃PO₄, Cs₂CO₃, and K₂CO₃), NaOAc, and KO^tBu examined in DMF (*N,N*-dimethylformamide), K₃PO₄ proved very effective. Other solvents proved less effective in this reaction than DMF (entry 4 vs entries 11–13). Several com-

TABLE 2. Sonogashira Reaction of Aryl Halides with Alkynes^a

entry	aryl halide	alkyne	time (h)	product	yield (%) ^b
1			5	 3a	93
2			5	 3b	94
3			5	 3c	87
4			5	 3d	74
5			5	 3e	81
6			5	 3f	84
7			5	 3g	83
8 ^c			5	 3h	95
9			5	 3i	83
10 ^c			5	 3j	70
11 ^c			5	 3k	48
12 ^c			5	 3l	95
13 ^{c,d}			5	 3m	73
14 ^c			24	3f	51

^a Reaction conditions: aryl halide (1 mmol), alkyne (1.2 mmol), K₃PO₄ (1.4 mmol), DMF (2 mL), PdCl₂(MeCN)₂ (0.02 mmol), ligand **2a** (0.02 mmol), CuI (0.05 mmol). ^b Isolated yields. ^c 4-Iodotoluene (0.5 mmol) and alkyne (1.0 mmol) were added. ^d This reaction was carried out at 70 °C. ^e This reaction used 2 equiv of phenyl acetylene.

monly used palladium sources were also tested (entries 4, 14–16); PdCl₂(MeCN)₂ preferred this reaction (entry 4).

The effect of various aryl iodides in the Sonogashira cross-coupling reaction was investigated using phenyl acetylene (entries 1–8, Table 2). Using 4-substituted aryl iodides led to good yields of the desired products (entries 1–6). Moreover, 2-substituted aryl iodides also led to good yields (entry 7). Using a 4 mol % palladium catalyst, the reaction of 1-iodonaphthalene with phenyl acetylene gave corresponding product with good yield (entry 8). The effect of varying alkynes was also investigated using 4-iodotoluene as the substrate (entries 9–13). Using 4-ethynyltoluene led to good yield of the corresponding product (entry 9). The reaction of 4-bromo-1-nitrobenzene with phenyl acetylene was necessary for longer reaction times such as 24 h (entry 14).

We next tried Hiyama cross-coupling of aryl bromides with aryl(trialkoxy)silanes using air-stable phosphine-free hydrazones **1** and **2** as a ligand. This reaction also provides a powerful tool for the C–C bond formation of biaryls, which has been widely

applied to such diverse areas as natural product and biologically active compound synthesis.¹¹ The use of such silicon-derived compounds as transmetalation reagents has attracted much attention as a viable option to these processes for its low cost, easy availability, nontoxic byproducts, and stability under many reaction conditions.¹² Generally, the Hiyama cross-coupling reaction is also carried out using an air-sensitive phosphine–palladium catalyst such as Pd(OAc)₂/PPh₃ and PdCl₂(MeCN)₂/(*o*-Tol)₃P.^{12f,i} We now report the use of air-stable hydrazone ligands **1** and **2** for phosphine-free palladium-catalyzed Hiyama cross-coupling reactions. We optimized the coupling conditions of 4-bromoacetophenone with phenyl(triethoxy)silane at 80 °C (Table 3). The effect of ligands in this reaction was investigated (entries 1–5). In the presence of **1d**, cross-coupling product **4a** was obtained in good yield (entry 3). Pyridine-type hydrazone ligands **2a** and **2b** were ineffective for this reaction. The effect of various solvents was investigated using ligand **1d** (entries 3, 6–10). Toluene proved very effective for 5 h (entry 10). Other solvents proved less effective in this reaction. Without the presence of ligand **1d**, the yield was decreased (entry 10 vs entry 11). Several commonly used palladium sources were also tested (entries 4, 12–14). We found the following optimized conditions: using the PdCl₂/hydrazone **1d** system, the reaction proceeded with 83% in toluene at 80 °C under an argon atmosphere (entry 14).

On the basis of those results, the Hiyama reaction of aryl bromides with various siloxanes was investigated (Table 4). The reaction of 4-bromoacetophenone and phenyl(triethoxy)silane gave corresponding product with 73% yield for 3 h (entry 2). Using phenyl(trimethoxy)silane, instead of phenyl(triethoxy)silane, also led to good yield (entry 3). Although a 4-methoxyphenyl bromide led to low yield (entry 6), the reactions of other 4-substituted aryl bromides gave good yields of the corresponding products (entries 5, 7, and 8). Moreover, 3-substituted aryl bromides and 1-bromonaphthalene also led to good yields (entries 9–11). We also investigated the reaction of 2-substituted aryl bromides. Using 3 equiv of phenyl(triethoxy)silane led to moderate yields of the corresponding products (entries 12 and 13). The reaction of bromobenzene with various aryl(triethoxy)silanes gave corresponding products with moderate to good yields (entries 14–17).

We found that hydrazone **2a** was useful as a phosphine-free ligand for the palladium/copper-catalyzed Sonogashira cross-coupling reaction of aryl halides with a variety of terminal alkynes under amine-free conditions in DMF at 80 °C with PdCl₂(MeCN)₂. We also found that Pd(OAc)₂/hydrazone ligand **1d** in PhMe at 80 °C was a phosphine-free efficient catalyst

TABLE 3. Optimization of Reaction Conditions on Hiyama Reaction^a

entry	ligand	time (h)	solvent	Pd source	yield (%) ^b
1		20	Dioxane	Pd(OAc) ₂	55
2		20	Dioxane	Pd(OAc) ₂	49
3		20	Dioxane	Pd(OAc) ₂	57
4		20	Dioxane	Pd(OAc) ₂	23
5		20	Dioxane	Pd(OAc) ₂	45
6	1d	20	BuOH	Pd(OAc) ₂	0
7	1d	20	DMF	Pd(OAc) ₂	38
8	1d	20	DMSO	Pd(OAc) ₂	40
9	1d	5	<i>m</i> -Xylene	Pd(OAc) ₂	54
10	1d	5	PhMe	Pd(OAc) ₂	68
11	–	5	PhMe	Pd(OAc) ₂	58
12	1d	5	PhMe	Pd(dba) ₂	82
13	1d	5	PhMe	PdCl ₂ (MeCN) ₂	79
14	1d	5	PhMe	PdCl ₂	83(76) ^c

^a Reaction conditions: *p*-bromoacetophenone (0.5 mmol), phenyl(triethoxy)silane (1.0 mmol), TBAF (1.0 mmol) in THF (1 M, 1 mL), solvent (1.5 mL), palladium source (0.02 mmol), ligand (0.03 mmol). ^b GC yields. ^c Isolated yields.

system for Hiyama cross-coupling reaction of aryl bromides with aryl(trialkoxo)silanes in good yields.

Experimental Section

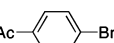
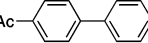

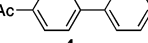
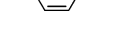
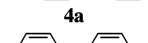

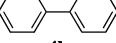
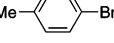
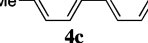
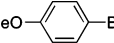
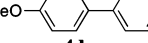
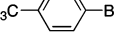
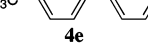
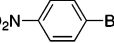
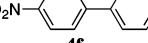

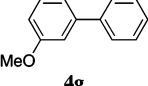
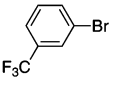
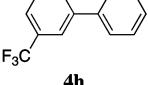

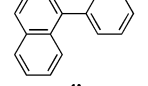

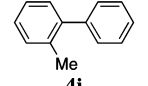

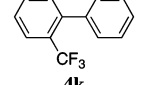



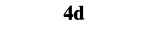

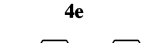

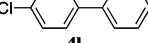
Preparation of Glyoxal Bis(*N*-methyl-*N*-3-tolylhydrazone) (1c). A solution of *N*-methyl-*N*-3-tolylhydrazine (0.163 g, 1.2 mmol) in MeOH (2 mL) was added to 40 wt % of glyoxal in water (0.073 g, 0.5 mmol) at 0 °C. The mixture was stirred for 5.5 h at room temperature. The yellow solid precipitated and was collected by filtration, washed with hexane, and dried under reduced pressure: 0.140 g, 0.48 mmol, 95% as a yellow solid; mp 157–159 °C; IR (KBr) 1542 cm⁻¹; ¹H NMR (CDCl₃) δ 2.36 (s, 6H), 3.37 (s, 6H), 6.71–6.81 (m, 2H), 7.03–7.11 (m, 2H), 7.14–7.23 (m, 4H), 7.51 (s, 2H); ¹³C NMR (CDCl₃) δ 21.8, 33.5, 112.4, 116.1, 121.7, 128.9, 133.7, 138.9, 147.6; FAB-MS *m/z* (rel. intens.) 294 (M⁺, 80); HRMS (FAB-MS) *m/z* calcd for C₁₈H₂₂N₄ 294.1844, found 294.1818.

Preparation of *N,N*-Bis(indolin-1-yl)ethane-1,2-dimine (1d). A solution of *N*-aminoindoline (1.47 g, 11 mmol) in MeOH (5 mL) was added to 40 wt % of glyoxal in water (0.725 g, 5 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature. The yellow solid precipitated and was collected by filtration, washed with hexane, and dried under reduced pressure: 1.349 g, 4.65 mmol, 93% as a yellow solid; mp 251–253 °C; IR (KBr) 1532 cm⁻¹; ¹H NMR (CDCl₃) δ 6.81 (t, *J* = 7.3 Hz 2H), 3.19–3.25 (m, 4H), 3.80–3.86 (m, 4H), 7.07–7.19 (m, 6H), 7.34 (s, 2H); ¹³C NMR (CDCl₃) δ 27.0, 48.2, 108.6, 120.3, 124.8, 127.5, 127.8, 134.4, 147.5; EI-

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TABLE 4. Hiyama Reaction of Aryl Bromides with Siloxanes^a

entry	aryl bromide	siloxane	time (h)	product	yield (%) ^b
1		PhSi(OEt) ₃	5		76
2		PhSi(OMe) ₃	3		73
3		PhSi(OMe) ₃	3		69
4		PhSi(OEt) ₃	3		80
5		PhSi(OEt) ₃	3		64
6		PhSi(OEt) ₃	3		63
7		PhSi(OEt) ₃	3		87
8		PhSi(OEt) ₃	3		70
9		PhSi(OEt) ₃	3		74
10		PhSi(OEt) ₃	3		74
11		PhSi(OEt) ₃	3		72
12 ^c		PhSi(OEt) ₃	3		60
13 ^c		PhSi(OEt) ₃	3		50
14		<i>p</i> -MePhSi(OEt) ₃	3		71
15		<i>p</i> -MeOPhSi(OEt) ₃	3		58
16		<i>p</i> -CF ₃ PhSi(OEt) ₃	3		90
17		<i>p</i> -ClPhSi(OEt) ₃	3		79

^a Reaction conditions: aryl bromide (0.5 mmol), siloxane (1.0 mmol), TBAF (1.0 mmol) in THF (1 M, 1 mL), PhMe (1.5 mL), PdCl₂ (0.02 mmol), ligand **1d** (0.03 mmol). ^b Isolated yields. ^c This reaction used 3 equiv of phenyl(triethoxy)silane.

MS *m/z* (rel. intens.): 290 (M⁺, 24); HRMS (FAB-MS) *m/z* calcd for C₁₈H₁₈N₄ 290.1531, found 290.1531; X-ray diffraction analysis data of **1d** (Figure S1 of the Supporting Information). Yellow cubic crystals from hexane–chloroform, monoclinic space group *P*2₁/*c*, *a* = 12.9030(4) Å, *b* = 10.4680(3) Å, *c* = 11.7384(4) Å, α = 90°, β = 112.6840(10)°, γ = 90°, *V* = 1462.84(8) Å³, *Z* = 4, ρ = 1.318 g/cm³, μ (Mo Kα) = 0.81 cm⁻¹. The structure was solved by the direct method of full matrix least-squares, where the final *R* and *R*_w were 0.051 and 0.168 for 5462 reflections, respectively.

Preparation of *N*-(Indolin-1-yl)(pyridin-2-yl)methanimine (2b). Under an atmosphere of argon, a solution of *N*-aminoindoline (0.067 g, 0.5 mmol) in MeOH (1.5 mL) was added to 2-pyridin-

ecarboxaldehyde (0.032 g, 0.3 mmol) at room temperature. The mixture was stirred for 24 h at 50 °C. The mixture was directly concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 1/1): 0.022 g, 0.10 mmol, 33% as a yellow solid; mp 111–112 °C; IR(KBr) 1557 cm⁻¹; ¹H NMR (CDCl₃) δ 3.27 (t, *J* = 8.3 Hz, 2H), 3.92 (t, *J* = 8.2 Hz, 2H), 6.86 (dt, *J* = 1.4 and 7.2 Hz, 1H), 7.11–7.26 (m, 5H), 7.46 (s, 1H), 7.66 (dt, *J* = 1.7 and 7.7 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 8.52 (d, *J* = 4.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 27.1, 48.0, 109.1, 118.9, 120.9, 121.9, 125.0, 127.8, 127.9, 133.3, 136.1, 147.3, 149.1, 155.6; EI-MS *m/z* (rel. intens.): 223 (M⁺, 18); HRMS (FAB-MS) *m/z* calcd for C₁₄H₁₃N₃ + H 224.1188, found 224.1182.

Sonogashira Cross-Coupling Reaction of Aryl Halides with Alkynes (Table 2). Under an atmosphere of argon, alkyne (1.2 mmol) was added to the mixture of aryl halide (1 mmol), K₃PO₄ (1.4 mmol), PdCl₂(MeCN)₂ (0.02 mmol), ligand (0.02 mmol), and CuI (0.05 mmol) in DMF (2 mL) at room temperature. The mixture was stirred at 80 °C. After 5 h, the mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography.

(4-Fluorophenyl)-4-tolylacetylene (3j). 70% as a white solid; mp 91–92 °C; IR (KBr) 2216 cm⁻¹; ¹H NMR (CDCl₃) δ: 2.36 (s, 3H), 6.96–7.08 (m, 2H), 7.15 (d, *J* = 7.84 Hz, 2H), 7.41 (d, *J* = 7.65 Hz, 2H), 7.42–7.52 (m, 2H); ¹³C NMR (CDCl₃) δ 21.5, 87.6, 89.2 (d, *J* = 1.1 Hz), 115.6 (d, *J* = 22.1 Hz), 119.6 (d, *J* = 3.5 Hz), 120.0, 129.1, 131.4, 133.4 (d, *J* = 8.3 Hz), 138.5, 162.4 (d, *J* = 249.2 Hz); EI-MS *m/z* (rel. intens.): 210 (M⁺, 100); HRMS (FAB-MS) *m/z* calcd for C₁₅H₁₁F 210.0845, found 210.0840.

(2-Fluorophenyl)-4-tolylacetylene (3l). 95% as a white solid; mp 55–56 °C; IR (KBr) 2219 cm⁻¹; ¹H NMR (CDCl₃) δ 2.36 (s, 3H), 7.05–7.19 (m, 4H), 7.22–7.35 (m, 1H), 7.41–7.56 (m, 3H); ¹³C NMR (CDCl₃) δ 21.5, 82.0, 94.6 (d, *J* = 3.2 Hz), 112.1 (d, *J* = 15.6 Hz), 115.5 (d, *J* = 21.0 Hz), 119.8, 123.9 (d, *J* = 3.7 Hz), 129.1, 129.7 (d, *J* = 8.0 Hz), 131.6, 133.4 (d, *J* = 0.9 Hz), 138.8, 162.6 (d, *J* = 251.3 Hz); EI-MS *m/z* (rel. intens.): 210 (M⁺, 100); HRMS (FAB-MS) *m/z* calcd for C₁₅H₁₁F 210.0845, found 210.0833.

6-*p*-Tolylhex-5-yl-1-ol (3m). 73% as a colorless liquid; IR (KBr) 2231 and 3357 cm⁻¹; ¹H NMR (CDCl₃) δ 1.46 (s, 1H), 1.58–1.82 (m, 4H), 2.33 (s, 3H), 2.45 (t, *J* = 6.6 Hz, 2H), 3.71 (t, *J* = 6.1 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 19.2, 21.4, 25.0, 31.9, 62.5, 80.9, 89.0, 120.7, 128.9, 131.4, 137.5; EI-MS *m/z* (rel. intens.): 188 (M⁺, 15); HRMS (FAB-MS) *m/z* calcd for C₁₃H₁₆O 188.1201, found 188.1205.

Hiyama Cross-Coupling Reaction of Aryl Bromides with Siloxanes (Table 4). Under an atmosphere of argon, siloxane (1.0 mmol) and TBAF (1.0 mmol) in THF (1 M, 1 mL) were added to the mixture of aryl bromide (0.5 mmol), PdCl₂ (0.02 mmol), and ligand (0.03 mmol) in PhMe (1.5 mL) at room temperature. The mixture was stirred at 80 °C. After 3 h, the mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography.

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Supporting Information Available: ORTEP drawing **1d** (Figure S1), ¹H and ¹³C NMR spectra of all compounds, and X-ray crystallographic file (CIF) for **1d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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