

Pd/C-catalyzed and Water-mediated Hiyama Cross-coupling Reaction Using an Electron-deficient Phosphine Ligand

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The Pd/C-catalyzed Hiyama cross-coupling reaction between a variety of aryl halides and aryltriethoxysilanes was developed. Since only small amounts of the 10% Pd/C (0.5 mol %) and phosphine ligand (1.0 mol %) are required for efficient reaction, the protocol would be practical for the construction of biphenyl derivatives.

The palladium-catalyzed cross-coupling reactions of aryl halides or halide equivalents with organometallic compounds are widely used for the construction of carbon–carbon bonds.¹ The use of organosilanes^{2,3} as organometallic compounds, which was initially explored by Hiyama,³ is drawing increasing attention as one of the most attractive approaches, since organosilanes are easy to handle and environmentally friendly due to their air-stability and low toxicity. The Hiyama coupling has generally been catalyzed by homogeneous palladium complexes. Heterogeneous catalysts have been recently recognized as alternatives in a variety of organic synthetic fields due to their air-stability and recoverability.⁴ In particular, palladium on carbon (Pd/C), which is a commercially available heterogeneous catalyst widely employed for hydrogenation,⁵ has been in use for various kinds of cross-coupling reactions, such as carbon–carbon and carbon–nitrogen bond formations.⁶ During the preparation of this manuscript, a comparative study on the activity of Pd/Cs from various vendors regarding the cross-coupling reactions, including the Hiyama coupling, was reported.⁷ However, the conditions for the Hiyama coupling, such as solvents and ligands, were not well investigated and were only for the nonsubstituted phenylation of bromoarenes. In this paper, we describe efficient conditions for the Pd/C-catalyzed Hiyama cross-coupling reaction between a variety of aryltrialkoxysilanes and aryl halides as well as the role of a small amount of water for effective reaction.

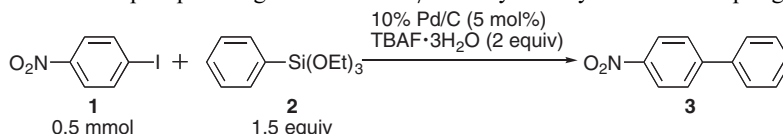
The cross-coupling between 4-iodonitrobenzene (**1**) and phenyltriethoxysilane (**2**, 1.5 equiv) in boiling toluene in the presence of 10% Pd/C^{7–9} (5 mol %) and tetrabutylammonium fluoride (TBAF, 2 equiv) was accelerated by the addition of 1,1-bis(diphenylphosphino)ferrocene (DPPF, 10 mol %) (Table 1, Entries 1 vs. 2). However, the use of DMF, dioxane, or THF as a solvent (Entries 3–5) or metal fluorides, such as sodium fluoride (see Supporting Information²¹) instead of TBAF, impeded the cross-coupling reaction, and significant quantities of the homocoupling products (4,4'-dinitrobiphenyl and biphenyl) were observed by TLC analysis.¹⁰ Triphenylphosphine (Entry 6) and tris(4-tolyl)phosphine (Entry 7) were effectively employed as a ligand (20 mol %), while the addition of tris(4-methoxyphenyl)phosphine (Entry 8) or trialkylphosphines (Entries 9 and 10) indicated only a slight enhancing effect. Furthermore, the use of tris(4-chlorophenyl)phosphine or tris(4-fluorophenyl)phosphine [(4-FC₆H₄)₃P], possessing a hal-

ogen atom on the benzene ring, significantly improved the reaction rate, and the reaction was completed within 6 h (Entries 11 and 12). Particularly, in the case of (4-FC₆H₄)₃P, a favorable isolated yield of **3** (83%) was obtained.^{11,12}

Although TBAF is highly hygroscopic, and absorbed water usually poses a potential risk of deactivating the fluoride ion by the formation of hydrogen bonds, the yield of **3** decreased to 70% when using dried TBAF,¹³ which might indicate the importance of water in the reaction (Entry 13). The addition of 50 or 100 μ L of water to 1 mL of anhydrous toluene in the 0.5 mmol scale cross-coupling of **1** significantly enhanced the reaction efficiency, while the further addition of water (200 μ L) rather delayed the reaction (Entries 14–16). The amounts of 10% Pd/C and (4-FC₆H₄)₃P could be reduced to 0.5 and 1 mol %, respectively, and the yield was eventually improved to 90% due to the suppression of the homocoupling reaction (Entry 17).^{14,15} The reaction was obviously impeded by a decrease in the reaction temperature (80 °C), and a significant amount (24%) of the unchanged starting material **1** remained (Entry 18). Furthermore, the reaction was depressed by using 0.5 mol % Pd(OAc)₂ in place of 10% Pd/C owing to the formation of nitrobenzene by the deiodination of **1** and 4,4'-dinitrobiphenyl (Entry 19).¹⁶

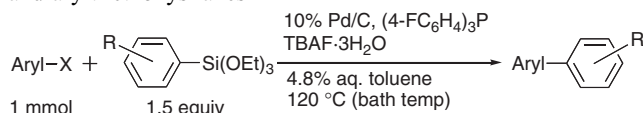
We next applied the optimized conditions indicated in Table 1, Entry 17, to the cross-coupling reaction between a wide range of substituted aryl halides and aryltriethoxysilanes (Table 2). Both 4-iodonitrobenzene (Entries 1–3) and 4-iodoanisole (Entries 4–6) were effectively cross-coupled with either the phenyl- (Entries 1 and 4), *p*-tolyl- (Entries 2 and 5), or 4-chlorophenyltriethoxysilane (Entries 3 and 6), to give the corresponding biphenyl derivatives in good to excellent yields.¹⁷ Aryl bromides possessing an electron-withdrawing nitro, acetyl, formyl, or cyano functionality on the benzene ring were also found to be good substrates for the cross-coupling (Entries 8–11). 4-Bromoanisole as well as the 3- and 2-bromoanisoles could also react with phenyl- or *p*-tolyltriethoxysilane to give the desired biaryl derivatives in good yields (Entries 12–15). These results indicated that the present Pd/C-catalyzed Hiyama coupling reaction is not affected by the substitution position and electron-withdrawing or -donating nature of the substituents on the benzene nuclei of the aryl halides. 3-Iodopyridine and 3-bromopyridine were also good substrates, and the desired 3-phenylpyridine could be smoothly obtained (Entries 7 and 16). It should be noted that the present conditions could be applied to the cross-coupling of 4-chloronitrobenzene with phenyltriethoxysilane, while the reaction efficiency obviously decreased (Entry 17) compared to the reaction of the 4-iodo- and 4-bromonitrobenzene (Entries 1 and 8).

The low level of Pd-leaching (3.8% of total Pd amount) in the filtered reaction media of the 10% Pd/C-catalyzed cross-coupling reaction between 4-bromonitrobenzene and phenyl-

Table 1. Effect of phosphine ligands on the Pd/C-catalyzed Hiyama cross-coupling reaction

Entry	Solvent/1 mL	Ligand/20 mol %	Water additive/ μL	Bath temp/ $^{\circ}\text{C}$	Time/h	Yield/% ^a
1	toluene	—	—	120	24	52
2 ^b	toluene	DPPF	—	120	14	64
3 ^b	DMF	DPPF	—	120	1	16
4 ^b	dioxane	DPPF	—	130	2	5
5 ^b	THF	DPPF	—	90	1	7
6	toluene	PPh ₃	—	120	20	63
7	toluene	tris(4-tolyl)phosphine	—	120	20	66
8	toluene	tris(4-methoxyphenyl)phosphine	—	120	24	50
9	toluene	tricyclohexylphosphine	—	120	12	58
10	toluene	2-(di- <i>t</i> -butylphosphino)biphenyl	—	120	24	41
11	toluene	tris(4-chlorophenyl)phosphine	—	120	6	69
12	toluene	tris(4-fluorophenyl)phosphine	—	120	6	83
13 ^c	toluene	tris(4-fluorophenyl)phosphine	—	120	17	70
14	toluene	tris(4-fluorophenyl)phosphine	50 (4.8% aq. toluene)	120	4	83
15	toluene	tris(4-fluorophenyl)phosphine	100 (9.1% aq. toluene)	120	4	80
16	toluene	tris(4-fluorophenyl)phosphine	200 (17% aq. toluene)	120	24	64
17 ^d	toluene	tris(4-fluorophenyl)phosphine	50 (4.8% aq. toluene)	120	6	90
18 ^{d,e}	toluene	tris(4-fluorophenyl)phosphine	50 (4.8% aq. toluene)	80	24	66
19 ^f	toluene	tris(4-fluorophenyl)phosphine	50 (4.8% aq. toluene)	120	2	72

^aDetermined by ¹H NMR using 1,4-dioxane as an internal standard. ^b10 mol % of DPPF was employed. ^cTBAF was dried under vacuum at 90 $^{\circ}\text{C}$ for 0.5 h prior to use. ^d0.5 mol % of 10% Pd/C and 1 mol % of (4-FC₆H₄)₃P were employed. ^e4,4'-Dinitrobiphenyl was obtained as a by-product in 8% yield together with the recovered **1** in 24% yield. ^f0.5 mol % of Pd(OAc)₂ instead of 10% Pd/C and 1 mol % (4-FC₆H₄)₃P were used. 4,4'-Dinitrobiphenyl was obtained in 5% yield.

Table 2. The Hiyama cross-coupling of various aryl halides and aryltriethoxysilanes^a

Entry	Aryl-X	R	Time/h	Yield/% ^b
1	4-NO ₂ -C ₆ H ₄ I	H	6	88
2	4-NO ₂ -C ₆ H ₄ I	4-Me	12	80
3	4-NO ₂ -C ₆ H ₄ I	4-Cl	6	75
4	4-MeO-C ₆ H ₄ I	H	6	85
5	4-MeO-C ₆ H ₄ I	4-Me	12	79
6	4-MeO-C ₆ H ₄ I	4-Cl	9	83
7	3-iodopyridine	H	12	85
8	4-NO ₂ -C ₆ H ₄ Br	H	6	81
9	4-Ac-C ₆ H ₄ Br	H	12	86
10	4-CHO-C ₆ H ₄ Br	H	12	86
11	4-CN-C ₆ H ₄ Br	H	12	85
12	4-MeO-C ₆ H ₄ Br	H	24	83
13	4-MeO-C ₆ H ₄ Br	4-Me	24	77
14	3-MeO-C ₆ H ₄ Br	H	12	90
15	2-MeO-C ₆ H ₄ Br	H	17	80
16	3-bromopyridine	H	18	81
17	4-NO ₂ -C ₆ H ₄ Cl	H	18	47

^aThe reactions were carried out in the presence of 0.5 mol % of 10% Pd/C, 1.0 mol % of (4-FC₆H₄)₃P, and 2 equiv of TBAF·3H₂O. ^bIsolated yield.

triethoxysilane in the presence of (4-FC₆H₄)₃P was confirmed based on an inductively coupled plasma-atomic emission spectrometric analysis.¹⁸ This suggests that the leached Pd species could be actual catalysts and the Pd/C may act as a reservoir of the leached and soluble active Pd species.¹⁹ The obtained 4-nitrobiphenyl was not contaminated with Pd species after the simple purification using silica gel column chromatography.¹⁸

A plausible mechanism is illustrated in Figure 1. Denmark et al. reported that arylsilanol derivatives are likely to be more reactive than arylalkoxysilanes for the Hiyama coupling reaction.^{2,3} The aryltriethoxysilanes (**A**) in Figure 1 would be partially hydrolyzed by a small amount of water to give a mixture of the corresponding arylsilanol derivatives (**B**). The electrophilicity of the silicon atoms would be enhanced by the hydrolysis of **A** presumably due to the decrease in both the electron density and steric hindrance around the silicon atom, leading to the easy generation of the active silicate complex (**C**) by the fluoride attack derived from TBAF. On the contrary, the addition of an excess amount of water would accelerate the formation of the inactive cage-shaped silanol polymer (**D**) that causes the low efficiencies of the Hiyama coupling reaction (Table 1, Entry 16).²⁰

In summary, we have developed a Pd/C-(4-FC₆H₄)₃P-catalyzed and water-mediated Hiyama cross-coupling reaction as an effective method for the preparation of biaryls. This reaction system can be easily performed by the use of only 0.5 mol % of 10% Pd/C, is applicable to the cross-coupling of various aryl

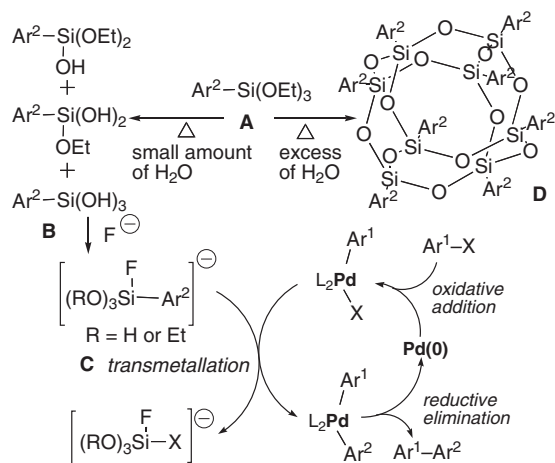


Figure 1. Plausible mechanism of the Pd/C-catalyzed Hiyama cross-coupling reaction.

halides and arylalkoxysilanes, and is readily applicable to the large-scale synthesis of asymmetric biaryls derivatives.

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