JOC *Note*

$Pd(OAc)_2$-Catalyzed Fluoride-Free Cross-Coupling Reactions of Arylsiloxanes with Aryl Bromides in Aqueous Medium

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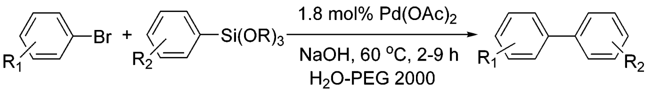

Mild conditions have been developed to achieve the $Pd(OAc)_2$-catalyzed fluoride-free cross-coupling between the aryl bromides and arylsiloxanes in good to high yields in aqueous medium. The success of the reactions requires the presence of poly(ethylene glycol) (PEG) and 3 equiv of sodium hydroxide. The product was easily separated with ethyl ether extraction, and the catalytic system can be reused eight times with high efficiency.

The palladium-catalyzed cross-coupling transformations between aryl halides and organometallic species constitute the most efficient methodologies for the construction of biaryl subunits[1−3] and are extensively used in the synthesis of pharmaceutical intermediates, bioactive molecules, and functional materials.[4] Among the various organometallic coupling partners, the organoboranes (Suzuki)[5] and organostannanes (Stille)[6] are the most routinely employed reagents because of their high reactivity and wide functional group tolerances. However, the toxicity of organostannanes and the difficulty of purification of organoboranes can present hurdles to large-scale implementation. The development of viable substitutes for organostannanes and organoboranes becomes the important objective.

Organosilanes (Hiyama) have emerged as premier agents for effecting this type of cross-coupling reaction currently because they are environmentally benign and stable to many reaction conditions.[7−9] The potential of the aqueous Hiyama reaction was recognized with the development of sodium hydroxide as an efficient promoter, and several examples of the Hiyama reaction in aqueous medium were recently demonstrated.[10] For example, Wolf and Lerebours reported the Hiyama reaction in water promoted by NaOH using a palladium−phosphinous acid complex.[11] Jesús et al. employed the palladium complex of formula $[PdCl_2L_2]$, where L was a crown-ether-containing triarylphosphane ligand, to give the synthetically useful yields of the Hiyama reaction in water.[12] Very recently, the fluoride-free Hiyama reaction was reported using palladium salts and oxime-derived palladacycles in concentrated aqueous sodium hydroxide solution under heating at 120 °C in a pressure tube or under microwave irradiation.[13] Although the aqueous Hiyama reaction has been developed with significant success, the ligands and/or high temperature (often in a sealed tube) are generally required. Herein, we report the development of a practical and efficient set of conditions for the fluoride-free Hiyama reaction

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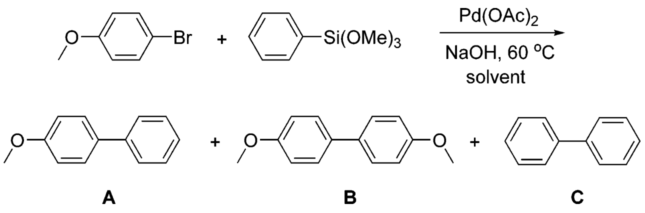
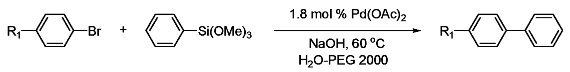
TABLE 1. Effect of Solvent, Base, and Temperature on the Hiyama Reaction[a]

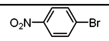
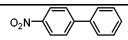
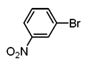
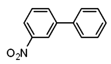
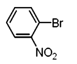
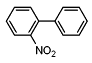
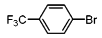
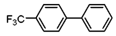
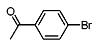
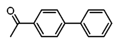
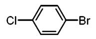
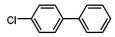
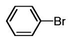
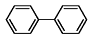
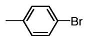
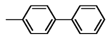
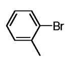
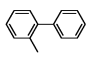
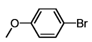
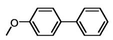
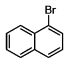
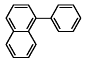
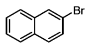
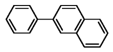
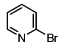
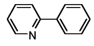
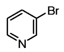
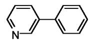
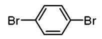
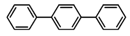
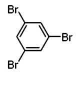
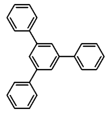


entry	solvent (g)	conv (%)	Yield (%)		
			A[b]	B[b]	C[c]
1	H_2O (6)	87	74	12	22
2	H_2O:dioxane (3:3)	98	90	7	3
3	H_2O:acetone (3:3)	74	66	6	5
4	H_2O:THF (3:3)	85	72	11	4
5	H_2O:[BMIM]BF_4 (3:3)	0	0	0	0
6	H_2O:[BMIM]PF_6 (3:3)	0	0	0	0
7	H_2O:PEG (3:3)	100	92	5	trace
8	H_2O:PEG (5:1)	95	80	13	15
9	H_2O:PEG (4:2)	97	80	11	6
10	H_2O:PEG (2:4)	100	24	45	trace
11	H_2O:PEG (1:5)	100	15	30	0
12	PEG (6)	3	0	0	0
13[d]	H_2O:PEG (3:3)	96	79	11	3
14[e]	H_2O:PEG (3:3)	78	60	12	8
15[f]	H_2O:PEG (3:3)	27	17	5	trace
16[g]	H_2O:PEG (3:3)	75	69	6	10
17[h]	H_2O:PEG (3:3)	100	79	16	4

[a] Reaction conditions: 1-bromo-4-methoxybenzene (1 mmol), trimethoxy(phenyl)silane (1.2 mmol), NaOH (3 mmol), $Pd(OAc)_2$ (1.8 mol %), 60 °C, 6 h. [b] GC yields based on 1-bromo-4-methoxybenzene. [c] Isolated yields based on trimethoxy(phenyl)silane. [d] KOH (3 mmol). [e] NaOH (2 mmol). [f] NaOH (1 mmol). [g] 25 °C, 24 h. [h] 80 °C, 4 h.

TABLE 2. Cross-Coupling of Aryl Bromides with Trimethoxy(phenyl)silane (a)[a]



entry	aryl bromide	product	time (h)	yield (%)[b]
1			2	95
2			2	96
3			2	99
4			2	95
5			2	71
6			2	94
7			2	85
8			4	94
9			24	62
10			6	81
11			24	66
12			4	73
13[c]			24	63
14			6	98
15			6	85
16			6	88

[a] Reaction conditions: aryl bromide (1 mmol), trimethoxy(phenyl)silane (1.2 mmol), NaOH (3 mmol), $Pd(OAc)_2$ (1.8 mol %), H_2O:PEG 2000 = 3:3 g, 60 °C. [b] Isolated yields. [c] 100 °C.

using $Pd(OAc)_2$ as the catalyst in aqueous medium under mild reaction conditions (60 °C).

The coupling reaction between 1-bromo-4-methoxybenzene (1 mmol) and trimethoxy(phenyl)silane (1.2 mmol) was examined in pure water with 3 equiv of NaOH and 1.8 mol % of $Pd(OAc)_2$ at 60 °C for 6 h in air. The desired cross-coupling product was obtained in 74% along with the formation of a large amount of side products from the self-coupling of 1-bromo-4-methoxybenzene and trimethoxy(phenyl)silane (Table 1, entry 1). Various cosolvents were examined (Table 1, entries 2−7), and it was found that PEG 2000 significantly improved the reaction, and the generation of the homocoupling byproducts was suppressed markedly (Table 1, entry 7). Similar to the Suzuki reaction in this catalytic system,[14] the amount of the PEG 2000 had a strong influence on the activity of the reaction, and the low yields were obtained when an excess amount of PEG was presented in the catalytic system (Table 1, entries 8−11). In the neat PEG, no reactions were observed (Table 1, entry 12). Of the bases tested, KOAc, K_2CO_3, K_3PO_4, and piperidine presented poor activity, and KOH was also inferior compared to NaOH (Table 1, entry 13). In addition, KF and TBAF, which were well-known promoters for the Hiyama coupling in organic solvents, were inactive in the H_2O−PEG system, and no product was detected. The amount of the base influenced the reactions, and the decrease of the amount of NaOH led to poor yields (Table 1, entries 14 and 15). The excess NaOH might have implications with the activation of arylsilanes and the hydrolysis of methoxysilane, which should be beneficial to the increase of reaction rate. Raising or lowering the reaction temperature did not improve the yields (Table 1, entries 16 and 17).

The scope and limitation of this catalytic system for various aryl bromides were studied as summarized in Table 2. The electronic property of the substituent group has a strong influence on the reactivity of aryl bromides. The electron-deficient aryl bromide showed the excellent reactivity and furnished the products in high yields in short reaction times (Table 2, entries 1−7), while prolonged reaction time was required for the electron-rich aryl bromide (Table 2, entries 8−10). It was also noted that the catalytic system could tolerate many functional groups, such as NO_2, CF_3, COMe, Me, and

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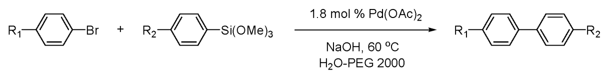
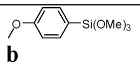
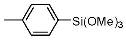
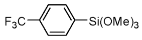
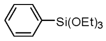
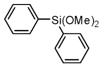
[14] (a) Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122. (b) Xin, B.; Zhang, Y.; Liu, L.; Wang, Y. *Synlett* **2005**, *20*, 3083. (c) Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2006**, *71*, 5725.

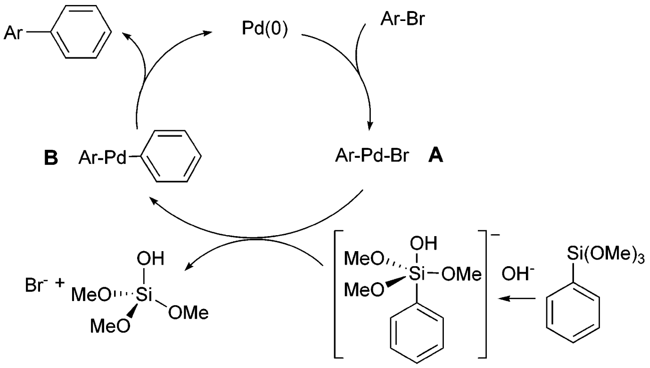
TABLE 3. Hiyama Coupling Reaction of Aryl Bromide with Various Arylsiloxane[a]



entry	R_1	siloxane	time(h)	yield [b](%)
1	4-OCH_3	 **b**	6	85
2	H	**b**	6	70
3	4-NO_2	**b**	2	80
4	3-Py	**b**	6	95
5	4-CH_3	 **c**	8	93
6	H	**c**	8	73
7	4-NO_2	**c**	2	90
8	3-Py	**c**	9	81
9	4-OCH_3	 **d**	6	73
10	H	**d**	6	72
11	4-NO_2	**d**	3	92
12	3-Py	**d**	9	65
13	4-OCH_3	 **e**	8	75
14	H	**e**	4	60
15	4-NO_2	**e**	2	87
16	3-Py	**e**	6	96
17	4-OCH_3	 **f**	6	92 [c]
18	H	**f**	6	82 [c]
19	4-NO_2	**f**	3	78 [c]
20	3-Py	**f**	6	93 [c]

[a] Reaction conditions: aryl bromide (1 mmol), siloxane (1.2 mmol), NaOH (3 mmol), $Pd(OAc)_2$ (1.8 mol %), H_2O:PEG 2000 = 3:3 g, 60 °C. [b] Isolated yields. [c] Siloxane (0.6 mmol).

SCHEME 1



OMe. Furthermore, coupling of 4-bromochlorobenzene with the trimethoxy(phenyl)silane gave exclusively 4-chlorobiphenyl in 94% yield, showing the good chemoselectivity (Table 2, entry 6). The sterically demanding aryl bromides delivered poor yields even after prolonged the reaction time (Table 2, entries 9 and 11), while the coupling of 1-bromo-2-nitrobenzene with trimethoxy(phenyl)silane afforded the desired product in nearly quantitative yield (Table 2, entry 3), which might have implications with the strong electron-withdrawing effect of NO_2. 3-Bromopyridine was efficiently coupled with trimethoxy(phenyl)silane to give 3-phenylpyridine in 98% yield (Table 2, entry 14). The 2-bromopyridine was less active and gave lower yield even at 100 °C for 24 h (Table 2, entry 13). It should be noted that the coupling of 1,4-dibromobenzene and 1,3,5-tribromobenzene with trimethoxy(phenyl)silane afforded the polyaryls in high yields in this catalytic system (Table 2, entries 15 and 16). Thus, the present reactions offered a convenient method for synthesizing polyaryls, which have wide applications in material and biological science, from di- and tribromoaromatics.

The reactivity of various arylsiloxanes on the Hiyama reaction was studied, and no obvious differences have been found, as shown in Table 3. It can be seen that arylsiloxane either with an electron-donating group or with an electron-withdrawing group exhibited high reactivity and delivered good yields (Table 3, entries 1−12). Satisfying results were also obtained when triethoxy(phenyl)silanes were replaced with trimethoxy(aryl)silanes (Table 3, entries 13−16). Both aryl groups of dimethoxydiphenylsilane worked as a coupling partner with aryl halides, and good to high yields were obtained under the reaction conditions (Table 3, entries 17−20).

The fluoride is known to play the key role in the Hiyama reaction via the in situ formation of the pentacoordinate arylsilicate anion,[15] which is found to be more reactive than the corresponding tetracoordinated silane.[16] In the absence of fluoride, the generation of pentavalent silicate under basic aqueous conditions through nucleophilic attack of a hydroxide ion at the arylsiloxane is thought to play the key role to promote the cross-coupling reaction. On the basis of the previous studies,[11] the following mechanism is proposed in the sodium hydroxide aqueous solution. The initial oxidative addition of aryl bromide to Pd(0) generates the arylpalladium intermediate **A**, which reacts with the pentavalent silicate formed in situ in sodium hydroxide solution to afford the (aryl)(aryl)-palladium(II) species **B**. The subsequent reductive elimination liberates the biaryl product with the regeneration of the active Pd(0) to complete the catalytic cycle (Scheme 1). For practical applications, the level of reusability of the catalyst is very important. To clarify this issue, we established the experiments to test the reusability efficiency of the catalytic system in the coupling reaction of 3-bromopyridine and 1-bromo-4-nitrobenzene with trimethoxy(phenyl)silane using 1.8 mol % of $Pd(OAc)_2$. The product was easily isolated by simple extraction with diethyl ether, and the $Pd(OAc)_2$−PEG−H_2O was subjected to the second run by charging it with the same substrates in the remnant. The catalytic system could be recycled eight times with a small decrease in activity without the need for activation or addition of the catalyst or PEG (Scheme 2). The presence of water increased the solu-

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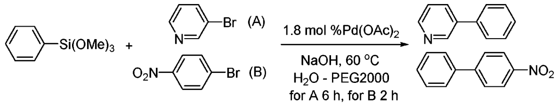
SCHEME 2



Run No.	1	2	3	4	5	6	7	8
Isolated yield for A (%)	98	97	90	85	87	90	85	81
Isolated yield for B (%)	95	93	90	91	87	87	84	83

bility of the sodium hydroxide in this catalytic system, which should facilitate the coupling reaction, and indeed the reaction was sluggish in the neat PEG (Table 1, entry 7). The reaction, however, was not so successful in water alone (Table 1, entry 1). Thus, the combination of water and PEG was found to be an efficient medium for the reaction. On the other hand, the solubility of the organic substrates in water was greatly promoted by PEG,[17] which led to the enhancement of the reaction rate, as well. In addition, PEG might act as the ligand and/or stability reagent of palladium in the reaction process and construct the recyclable catalytic system.[17]

In summary, the PEG−H_2O solvent system was proved to be a useful and alternative reaction medium for cross-coupling of arylsiloxanes and aryl bromides, avoiding the use of fluoride. The substrates show significant increase in reactivity, reducing the reaction times and improving the yields substantially under the mild reaction conditions. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this reaction medium are expected to contribute to the development of a green strategy for the preparation of biaryls.

Experimental Section

General Procedure for the Hiyama Reaction: A mixture of NaOH (0.120 g, 3 mmol), $Pd(OAc)_2$ (4 mg, 1.8 mol %), aryl bromide (1 mmol), arylsiloxane (1.2 mmol), distilled water (3 mL), and PEG 2000 (3 g) was stirred at 60 °C for the indicated time. Afterward, the reaction solution was cooled to room temperature and extracted four times with diethyl ether (4 × 15 mL). The combined organic phase was analyzed by GC and GC/MS. Further purification of the product was achieved by flash chromatography on a silica gel column.

In the recycling experiment, the residue was subjected to a second run of the Hiyama reaction by charging it with the same substrates (3-bromopyridine or 1-bromo-4-nitrobenzene, trimethoxy(phenyl)-silane, NaOH) without further addition of $Pd(OAc)_2$ or PEG 2000. In the third, fifth, and seventh runs, another 0.5 mL of distilled water was added to the reaction mixture.

3-Phenylpyridine[12] [T2−14]: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.83 (d, 1H), 8.55−8.56 (m, 1H), 7.80−7.83 (m, 1H), 7.53−7.55 (m, 2H), 7.42−7.45 (m, 2H), 7.29−7.38 (m, 2H); MS (EI) *m*/*z* (%) 155 (100) [M^+], 154 (22), 153 (15), 76 (9).

1,3,5-Triphenylbenzene[18] [T2−16]: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.85−7.86 (d, 3H), 7.76−7.78 (m, 6H), 7.52−7.56 (m, 6H), 7.43−7.47 (m, 3H); MS (EI) *m*/*z* (%) 307 (81) [M^+ + 1], 306 (100) [M^+], 289 (33), 276 (9), 228 (26), 202 (10), 153 (9), 77 (8).

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Supporting Information Available: The experimental procedure and spectroscopic data (^{1}H NMR and MS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] Paul, S.; Clark, J. H. *Green Chem.* **2003**, *5*, 635.