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Silica-Supported Palladium-Catalyzed Hiyama Cross-Coupling Reactions Using Continuous Flow System

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Palladium-catalyzed C-C bond formation reactions have been intensively studied and widely used in organic synthesis.[1] A variety of reaction methods have been developed utilizing the transformation methods. In particular, palladium-catalyzed biaryl cross-coupling reactions have been performed with a number of organometallics and a wide range of aryl halides.[2-4] In the homogeneous catalytic systems, electron-rich, bulky phosphine- and carbene-type ligands have been developed and showed high catalytic activity in the coupling reactions of the more challenging substrates such as aryl chloride, sterically demanding aryl halides and heteroaromatic substrates.[5-9] Although the cross-coupling reaction has mostly been carried out in homogeneous catalytic systems, these catalysts suffer some drawbacks such difficult catalyst recovery and separation problems. To address these problems, the immobilization of Pd catalysts on inorganic solid supports[10-12] or organic polymers[13-15] has been studied.

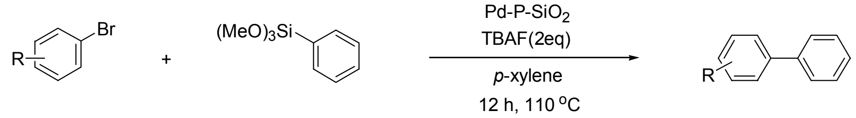
Recently, the continuous flow reaction technique has been used in organic transformation reactions to afford good reactivity and availability.[16-20] The continuous-flow microreactors have become an alternative to traditional batch reactors for scale-up due to their numerous advantages such as surface-area-to-volume ratio that enhances the surface contact between different phases when the reactor's line diameter is reduced.[21,22] Furthermore, the continuous flow system has been combined with the immobilized catalyst and applied to the palladium-catalyzed cross-coupling reactions. In the cross-coupling reactions, Suzuki,[23-25] Heck[26,27] and Sonogashira[28] reactions have been used in the continuous flow reaction with a variety of immobilized palladium catalysts.

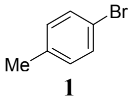
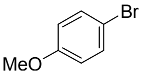
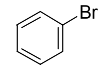
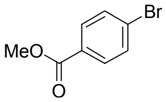
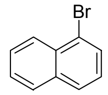
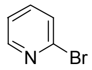
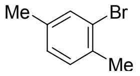
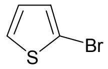
To the best of our knowledge, the Hiyama cross-coupling reaction has never been used in a continuous micro-flow reaction, despite the many advantages of the silyl reagent such as its stability in air stable, nontoxicity and easy availability.[29-33] Here, we report the first application of the Hiyama coupling reaction to the continuous flow reaction system.

Although polymer materials have also been used as solid-supported materials, we chose silica due to its advantages of mechanical and chemical strength and easily functionalization for modification.[34-36] A supporting material with smaller particles is known to be better than that with larger particles due to its larger surface area of catalyst. However, very small particles are not suitable as a packing material in the continuous flow system because of their plugging tendency and high-pressure drop. Therefore, we prepared two types of silica-supported palladium catalysts: large silica particles (6 ~ 12 mesh, 1.68 ~ 3.36 mm) and small silica particles (70 ~ 270 mesh, 0.053 ~ 0.21 mm). First, we attempted to introduce the diphenylphosphino bond group in the silica gel. The silica gel was reacted with $ClPPh_2$ in the presence of pyridine in THF at room temperature for 6 h. After washing with Et_2O, the diphenylphosphine-bounded silica gel was reacted with $Pd(acac)_2$ in THF solvent for 12 h. The phosphine/palladium complex with bounded silica gel was obtained. The amount of palladium in the silica gel was determined to be 5.92 wt % by ICP-MS method.

The potential recyclability of the silica-bonded phosphine/palladium complex (Pd-P-SiO_2) as the catalyst was explored in the model cross-coupling of 4-bromotoluene (**1**) and trimethoxysilyl benzene. The reaction was carried out under the same condition as that of our previous report[37]: 5 mol% of Pd in *p*-xylene at 120 °C for 12 h. The small, silica particle-bonded phosphine/palladium was employed as the catalyst. After cooling to room temperature, the organic product was filtered out and the yield was determined by gas chromatography (GC), with the results summarized in Table 1. The desired product of 4-methylbiphenyl was formed in 97% yield. The solid phase was washed with ether and then transferred to a new reaction bath flask containing fresh reagents. The catalytic system was efficient, giving two cycles of high yield (entry 1). Despite the decreased yield in the third run, a reasonable yield was achieved (entry 2). As expected, the larger silica particle-bonded catalyst showed very low yields, even when 5 mol% catalyst was loaded (entry 3). The silica-bonded, phosphine/palladium complex (Pd-P-SiO_2) was not sensitive to oxygen or moisture. Therefore, its efficiency was unaffected even when the Hiyama coupling reactions were carried out under aerobic conditions. When a variety of aryl bromides were reacted with trimethoxysilyl benzene in the presence of silica-supported palladium catalyst, most substrates exhibited good to excellent yields. Sterically demanding substrates such as 1-bromonaphthalene (**3**) and 2-bromo-*p*-xylene (**4**) afforded the desired product in 96% and 95% yields, respectively (entries 5 and 6). And electron donating substrate **5** and electron withdrawing substrate **6** also showed good reactivities (entries 7 and 8). However, heteroaromatic bromides such as 2-bromopyridine (**7**) and 2-bromothiophene (**8**) showed low conversion and gave 35% and 15% yields,

Table 1. Hiyama cross coupling reaction with Pd-P-SiO_2 in the batch reaction



Entry	ArBr	Conv. (%)^b	Yield (%)^c	Entry	ArBr	Conv. (%)^b	Yield (%)^b
1	 **1**	100(99)^d	97(95)^d	7	 **5**	100(89)^c	92(84)^c
2		98^e	91^e				
3		10^f	5^f				
4	 **2**	100(98)^c	98(98)^c	8	 **6**	100(95)^c	98(94)^c
5	 **3**	100(95)^c	96(94)^c	9	 **7**	66(35)^c	35(15)^c
6	 **4**	97(95)^c	95(91)^c	10	 **8**	32	15

^{a}Reaction condition : ArBr (0.3 mmol), $PhSi(OMe)_3$ (0.3 mmol), TBAF (0.6 mmol), 5 mol% Pd (calculated by ICP-MS), in 1.5 mL of *p*-xylene at 110 °C. ^{b}Conversions were determined by gas chromatography (GC) by comparison to an internal standard (naphthalene). ^{c}Yields were determined by gas chromatography (GC) by comparison to an internal standard (naphthalene), and all compounds were isolated and characterized by ^{1}H NMR and ^{13}C NMR. ^{d}Figures in parenthesis were in the second run. ^{e}Results were in the third run. ^{f}The larger particle size of silica (6 - 12 mesh) supported catalyst was employed.

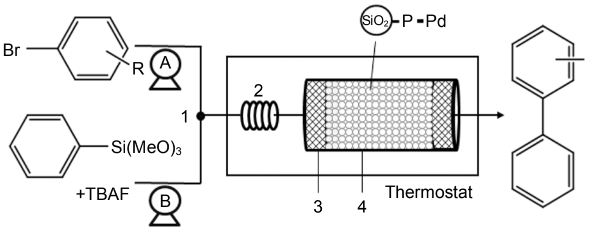


Figure 1. The continuous flow system for Hiyama coupling reactions. (1) Mixing T. (2) Preheating coil. (3) Filter. (4) Catalyst packed column.

respectively (entries 9 and 10).

Having successfully demonstrated the viability of the Pd-P-SiO_2-catalyzed Hiyama cross-coupling reaction in the heterogeneous batch reaction system, we then applied this reaction to the continuous flow system. The flow system allows the use of a packed bed catalyst, Pd-P-SiO_2 (silica gel, 6 - 12 mesh, 1.68 - 3.36 mm) with high conversion per unit mass of catalyst. The catalyst, Pd-P-SiO_2 was packed into a Teflon tube of 3.96 mm id × 1 m length, submerged in a thermostat silicon oil bath at a temperature of 120 °C. The total amount of Pd-P-SiO_2 material was 10.0 g which involves 0.013 g palladium. Aryl bromides with internal standard naphthalene in *p*-xylene and the mixture of $PhSi(OMe)_3$ and TBAF in *p*-xylene were pumped into the column at flow rates of 0.025 mL/min and 0.035 mL/min, respectively. The corresponding residence time was 180 min. We found that TBAF has to be with $PhSi(OMe)_3$ in the same reservoir, if it would be with others such as aryl bromide, the homogenous stock solution could not be prepared. The optimized ratio of aryl bromide, $PhSi(OMe)_3$ and TBAF, was 1 : 3 : 2. The flow system diagram was illustrated in Figure 1.

Flow-based chemical synthesis offers many benefits in terms of precise control of heat transfer, mass transfer, pressure, temperature, concentration, and residence time. These benefits significantly affect the reaction results by improving the yield and selectivity. A demonstration of the flow synthetic ability of the packed column reactor was readily obtained with the Hiyama coupling reaction. The flow synthesis of biphenyl derivatives was achieved through the coupling reaction of a series of aryl bromides. The results are summarized in Table 2. First, 4-bromotoluene (**1**) was employed as aryl halide. The experimental run was continued for forty hours after achieving the steady state conditions. The product was collected continuously after the column reached steady state conditions. The desired coupled product was afforded in 99% yield with the full conversion of 4-bromotoluene (entry 1). Based on this reaction result, we used the continuous flow system for the coupling of various aryl halides with trimethoxysilyl benzene. Electron neutral and withdrawing substrates such as bromobenzene (**2**) and methyl 4-bromoacetophenone (**6**) also afforded the desired coupled products in almost quantitative yields (entries 2 and 3). Sterically demanding aryl bromides such as 1-bromonaphthalene (**3**) showed no full conversion and 78% yield (entry 4). As expected, 2-bromopyridine (**7**) showed 43% yield of product and 2-bromo-

Table 2. The continuous flow reactions of aryl bromides with trimethoxysilylbenzene[a]

Entry	ArBr[b]	Conversion (%)[c]	Yield (%)[d]
1	4-Bromotoluene (**1**)	100	99
2	Bromobenzene (**2**)	100	99
3	Methyl 4-bromobenzoate (**6**)	100	99
4	1-Bromonaphthalene (**3**)	81	78
5	2-Bromopyridine (**7**)	72	43
6	2-Bromothiophene (**8**)	45	23

[a] Reaction condition: the reaction temperature was 120 °C and the flow rate was 0.45 mmol/h. [b] The mol ratio of $\mathrm{ArBr/ArSi(OMe)_3/TBAF}$ = 1/3/2. [c] Calculated by GC from the final product mixtures. [d] Isolated yield.

thiophene (**8**) gave the desired product in 23% yield (entries 5 and 6). The flow reactor enables the preparation of up to 12.0 mmol of product using smaller palladium than reactions promoted with general heterogeneous catalytic reaction. The turnover number of the latter catalytic system was 20, however, that of the former was almost 100.

In summary, a silica-bonded phosphine and palladium catalyst was successfully applied to the stationary phase for the Hiyama coupling reaction in a continuous flow reactor. This is the first example of a continuous flow reaction system that can be incorporated into any conventional HPLC system. The preparation of the supporting material was easy, simple and convenient for use in the continuous flow reactor. This method provided high yields of those desired products.

Experimental

4-Bromotoluene (2.38 g, 14.0 mmol) and naphthalene (0.896 g, 7.0 mmol) in *p*-xylene (48 mL) were added to the reservoir which connected to the pump A. $\mathrm{PhSi(OMe)_3}$ (8.32 g, 42.0 mmol) and TBAF (28.0 mL of 1 M solution, 28.0 mmol) in *p*-xylene (36 mL) were added to the reservoir which connected to the pump B. The pump A was flowed with 0.025 mL/min, and the pump B was flowed with 0.035 mL/min. The reaction mixtures were flowed into the catalyst packed bed at 120 °C. After 3 h later, the product mixture was collected and isolated using column chromatography.

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