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Polystyrene-Cross-Linking Triphenylphosphine on Porous Monolith: Enhanced Catalytic Activity for Aryl Chloride Cross-Coupling in Biphasic Flow

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ABSTRACT: Immobilized transition metals for continuous-flow catalyses are greatly in demand to achieve automation, scale-up, facile separation, regeneration, and energy-saving production with high level of sustainability and efficiency. Here, we report a tertiary phosphine immobilized on a macroporous monolith (**M-PS-TPP**) for challenging Pd-catalyzed cross-coupling reaction of aryl chloride in continuous-flow system. The monolithic and macroporous structure of **M-PS-TPP** was fabricated by bulk polymerization in the presence of high internal phase emulsion (HIPE) template. Owing to the large pore size and high porosity, the **M-PS-TPP** showed high permeability against continuous flow of mobile phase. Continuous-flow Suzuki-Miyaura cross-coupling reaction was realized by permeation of organic/aqueous media containing inorganic salt through Pd-loaded monolith (**M-PS-TPP**-Pd) column without serious clogging. Controlling coordination chemistry and hydrodynamics of **M-PS-TPP**-Pd boosted highly active phosphine-metal complex forming and fast mass transfer of reactants. Indeed, the **M-PS-TPP**-Pd column showed surprisingly higher yields (~93%) and turnover numbers (2704) in continuous-flow conditions than those in batch conditions (~6%).

INTRODUCTION

Continuous-flow syntheses of high-value organic molecules have attracted much attention for the production of pharmaceuticals, agrochemicals, fragrance, dyes, and organic electroluminescence devices.[1] The benefits of continuous-flow operation relate to the simplification and implementation of procedures, which facilitate automation, on-demand production, scale-up, and also make the reaction system safer compared with batch systems.[2] Transition-metal-catalyzed reactions are of great interest because of their high catalytic activities and selectivities, and various metals, ligands, and substrates have been studied in this respect. An immobilized metal catalyst in a continuous-flow reactor can potentially better facilitate separation and reuse processes than homogeneous catalysts.[3] Continuous-flow syntheses using an immobilized catalyst are important in fine chemical production as they provide a high level of sustainability and efficiency.

C–C or C–heteroatom cross-coupling reactions via transition-metal catalyses are strong tools for production of pharmaceuticals or agricultural drugs. Recently, the use of continuous-flow systems in cross-coupling reactions has attracted much attentions in both academia and industry.[4] Although aryl iodides, aryl bromides, or aryl triflates have been used as cross-coupling partners with aryl boronic acids, use of more inexpensive aryl chlorides is desired, where activation of C–Cl is very challenging.[5] Many researchers have demonstrated that sophisticated design of ligands toward metals can promote catalytic performance under mild conditions.[6] Among them, tertiary phosphines are important ligands for transition-metal catalysts and have been immobilized on support materials. In fact, the resulting immobilized catalyst systems exhibit high activity, durability, and easy separation in various cross-coupling reactions containing aryl chlorides.[7] However, while some reports continuous-flow system for cross-coupling reactions of aryl chlorides using immobilized catalysts, severe reaction conditions such as elevated temperature (> 80°C) or microwave assistance are needed.[8]

To obtain sustainable continuous-flow cross-coupling reaction, careful reactor design is necessary to avoid serious clogging of channel by insoluble salt in organic solvent during process.[9] Moreover, use of soluble organic base have resulted in very few successes and sometimes needs relatively high temperature (> 100°C) or microwave assistance.[10] One solution for this dilemma was proposed by Buchwald and co-workers, where organic/aqueous biphasic solvent was used to dissolve all the reactants in continuous-flow C–N cross-coupling reactions employing homogeneous Pd catalyst.[11] In biphasic reaction conditions, well mixing of reactants is necessary to maintain a large reaction interface during continuous-flow process, which leads to high productivity. To translate this biphasic condition into immobilized catalyst system, controlling hydrody-

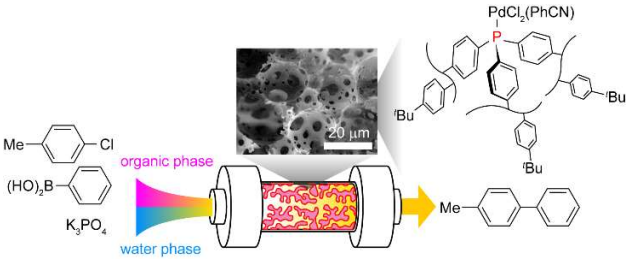


Figure 1. Macroporous polystyrene-triphenylphosphine monolith (**M-PS-TPP**) to Pd-catalyzed cross-coupling reaction containing aryl chloride in continuous-flow system.

namics of reactant solutions would be important for fast mass transfer and maximized performance of immobilized catalyst in continuous-flow reactor.[12]

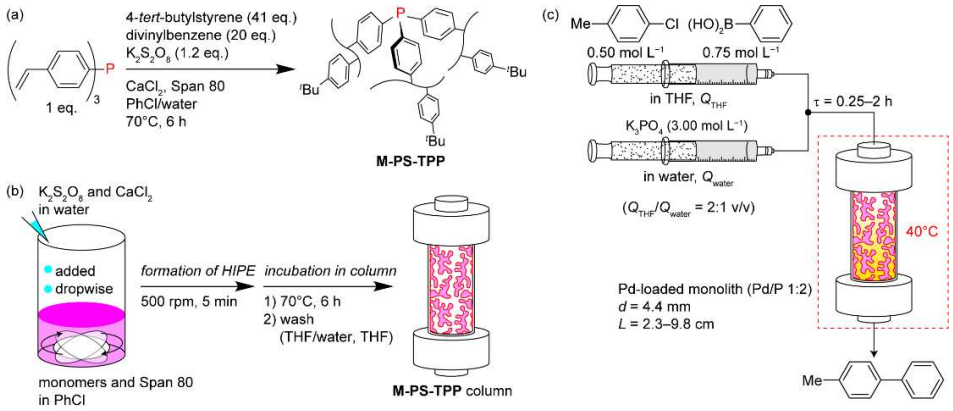
The combination of organic chemistry and material sciences has led to immobilized catalyst systems developed for challenging chemical transformations on the laboratory or industrial scale. Porous materials show great potential in catalytic systems because of their controllable pore size and large surface area, which can boost the performance of the immobilized catalyst.[13] Increasing demand for practical support materials has motivated the development of porous synthetic polymers because of their ease of preparation, flexible chemical functionalization, high stability, and insolubility.[14] For example, Zhan and co-workers reported a microporous organic polymer supporting a triphenylphosphine (TPP) ligand for the cobalt-catalyzed hydrosilylation reaction in a continuous-flow system.[15] In continuous-flow reactors using immobilized catalysts, packed-bed columns have been widely used. However, continuous-flow permeation through this column is accompanied by high pressure loss and broad residence time distribution (RTD), which is detrimental to the sustainability and efficiency of the process.[16] On the other hand, macroporous monoliths consist of a single column with flow-through macropores, and show low pressure loss and narrow RTD in continuous-flow applications because of their controlled and large pore size and high porosity.[17,18] We also believe that hydrodynamic properties of monolith allow fast mixing of biphasic reaction mixture to overcome mass transfer limitation in continuous-flow cross-coupling reactions, which show better catalytic efficiencies than those under batch conditions.

Here, we report a combination of sophisticated design of ligand and porous materials for challenging chemical transformation in continuous-flow manner. A three-fold cross-linking TPP on polystyrene monolith (**M-PS-TPP**) was fabricated by radical polymerization in the presence of a water-in-oil-type high internal phase emulsion (HIPE).[19,20] This monolithic material had a characteristic window and void structure with a large pore size and high porosity. ^{31}P CP/MAS NMR analyses were indicative of unique coordination behavior of the **M-PS-TPP** for mono-P-ligation toward Pd. To realize a continuous-flow system, a **M-PS-TPP** column was fabricated polymerizing the HIPE in a stainless-steel column. The resulting **M-PS-TPP** column showed excellent hydrodynamic properties such as high permeability and narrow RTD of feed. These features were attractive to continuous-flow cross-coupling reactions. In fact, continuous permeation of 4-chlorotoluene and phenylboronic acid in THF, and K_3PO_4 in water at 40 °C through a Pd-loaded **M-PS-TPP** (**M-PS-TPP**-Pd) column allowed the Suzuki-Miyaura cross-coupling reaction to proceed without clogging in the continuous-flow reactor (Figure 1). Controlling the hydrodynamic parameters in **M-PS-TPP**-Pd column provided the enhanced mass transfer, resulting in high productivity and durability during continuous-flow process. A proof-of-concept study demonstrated the advantages of the continuous-flow system using the monolith column supporting three-fold cross-linking TPP over the batch system and conventional TPP-grafted monolith column.

RESULTS AND DISCUSSION

Synthesis and Characterization of M-PS-TPP. To a solution of tris(4-vinylphenyl)phosphane (0.016 mmol, 1 eq.), 4-*tert*-butylstyrene (0.66 mmol, 41 eq.), divinylbenzene (0.32 mmol, 20 eq.), and surfactant Span 80 (0.061 mL) in chlorobenzene (0.19 mL) was added dropwise aqueous phase containing $CaCl_2$ (0.33 mmol), $K_2S_2O_8$ (0.019 mmol, 1.2 eq.), and water (3.3 mL) under vigorous stirring.[21,22] The ratio of organic phase to aqueous phase was 10:90 v/v. After addition of the aqueous phase, stirring was further continued for 5 min to give the HIPE. For characterization, **M-PS-TPP** was prepared in a glass vial (21.0 mm inner diameter) in which the HIPE was incubated at 70 °C for 6 h after removing the stirring bar (Scheme 1a).

Scheme 1. (a) Synthesis of M-PS-TPP, (b) Preparation of M-PS-TPP Column, and (c) Continuous-Flow Setup for Cross-Coupling Reaction between 4-Chlorotoluene and Phenylboronic Acid.



After carefully crushing the vial, the resulting polymer was washed successively by immersion in THF/water (2:1 v/v) and THF for > 1 day each. The high cross-linking density in the polymer phase resulted in the THF-swollen **M-PS-TPP** being self-standing (Figure 2a), which was a necessary characteristic of a monolith column. The diameter (*d*) of swollen **M-PS-TPP** differed in THF (*d* = 22.0 mm) and THF/water (*d* = 21.4 mm). These *d* values were larger than the inner diameter of the glass vial (21.0 mm) used as the mold. In a column reactor, the moderate swelling of **M-PS-TPP** would compensate for gaps between the column wall and monolith surface which could potentially allow a bypass flow of reactant.[23] The swollen **M-PS-TPP** was dried under vacuum at room temperature overnight, to give a white solid polymer (92 wt.% dry yield).[24] The amount of the TPP moiety incorporated ([P]) was 0.11 mmol g^{-1} based on the feed ratio of the monomers.

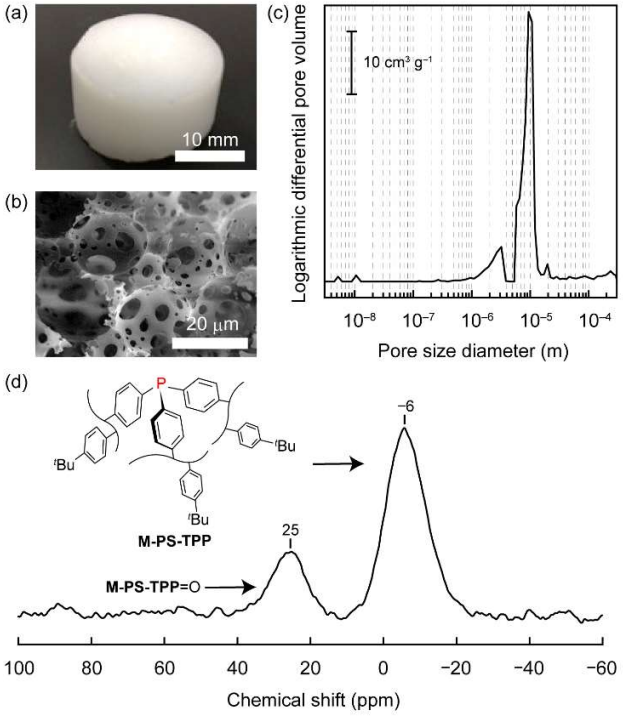


Figure 2. (a) THF-swollen photograph, (b) FE-SEM image, (c) Pore size distribution, and (d) ^{31}P CP/MAS NMR spectra of **M-PS-TPP**.

The dried **M-PS-TPP** was observed using FE-SEM, which revealed the characteristic window and void structure (Figure 2b). The observed voids were negative images of the aqueous phase in the HIPE, which were inter-connected with neighbors during polymerization.[21] Mercury intrusion porosimetry analysis indicated that **M-PS-TPP** had a bimodal pore size distribution curve with 1st- and 2nd-mode pore sizes of 10690 and 3600 nm, respectively (Table S2 and Figure 2c). The porosity of **M-PS-TPP** was 81%, which was smaller than the volume ratio of the aqueous phase (90 vol%) in the HIPE template. Nevertheless, the large flow-through pores and high porosity of **M-PS-TPP** were expected to provide continuous-flow catalysis in a column reactor. The ^{31}P CP/MAS NMR spectra (Figure 2d) of the **M-PS-TPP** confirmed the incorporation of coordinatively active TPP (−6 ppm) accompanied by some contents of TPP oxide (25 ppm) due to partial oxidation of the P atom during synthesis of monolith.

Coordination Behavior of M-PS-TPP. The coordination ability of **M-PS-TPP** toward Pd was confirmed by ICP-AES and ^{31}P CP/MAS NMR analyses after treatment with $[PdCl_2(PhCN)_2]$ in THF (Pd/P 1:2).[25] ICP-AES analysis indicated that the Pd source in THF was completely loaded on **M-PS-TPP** to give a Pd loading ([Pd]) of 0.05 mmol g^{-1}. ^{31}P CP/MAS NMR results were consistent with the formation of the TPP-Pd complex in the monolith, which indicated that **M-PS-TPP** favored a mono-P-ligated Pd^{II} complex (29 ppm) (Figure 3a). In contrast, a single-point grafting TPP on monolith (**M-PS-grafted-TPP**)[22] preferentially showed bis-P-ligation (24 ppm) toward Pd over mono-P-ligation (32 ppm) (Figure 3b). The selective mono-P-ligation of **M-PS-TPP** was attributed to three-fold cross-linking around TPP, which was site-isolated in polymer network and thus favored mono-P-ligation towards Pd^{II}. This mono-ligated TPP-Pd complex reportedly leads to excellent activity in challenging transition-metal-catalyzed reactions.[7a,b]

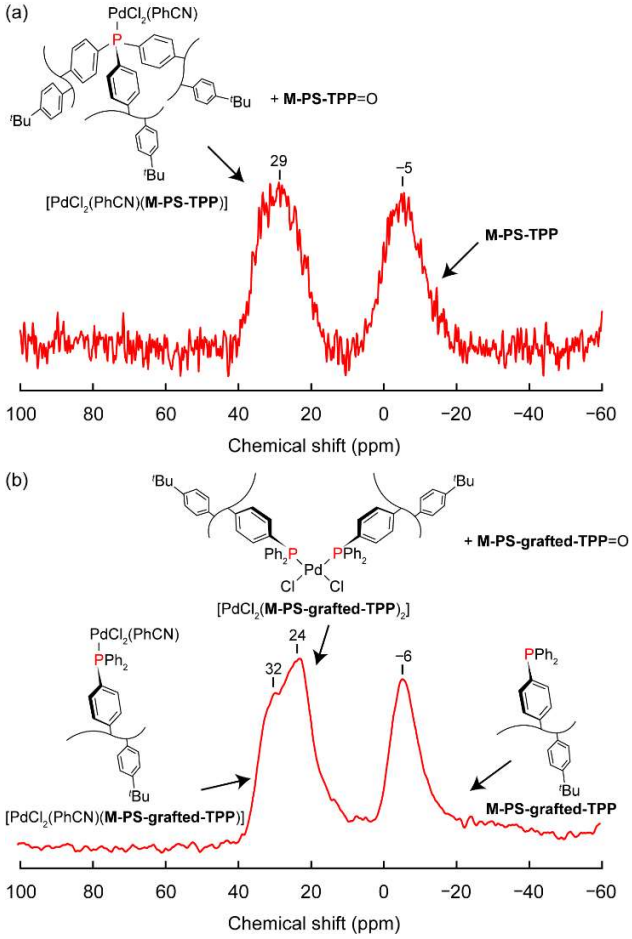


Figure 3. ^{31}P CP/MAS NMR spectra obtained (a) from **M-PS-TPP** and $[PdCl_2(PhCN)_2]$ (Pd/P 1:2), and (b) from **M-PS-grafted-TPP** and $[PdCl_2(PhCN)_2]$ (Pd/P 1:2).

Preparation and Characterization of Monolith Column for Continuous-Flow Application. Having confirmed the formation of flow-through macropores and selective mono-P-ligation in **M-PS-TPP**, **M-PS-TPP** was applied to

continuous-flow application in a column reactor.[26] Stainless-steel tube (4.4 mm inner diameter) was filled with monomer-containing HIPE using a syringe, and the column ends were then sealed with septa. Three different length of the stainless-steel tube (2.5, 5.0, or 10.0 cm length) was used to prepare **M-PS-TPP** columns with different lengths (L). After incubation at 70 °C for 6 h and subsequent permeation of THF/water (2:1 v/v) and THF for washing, a **M-PS-TPP** column was fabricated (Scheme 1b). In the continuous-flow reactor, the pressure loss (ΔP) through the **M-PS-TPP** column was monitored at residence times (τ) of 0.25–2.00 h by varying the linear velocity (u). During permeation of THF/water (2:1 v/v) or THF, ΔP reached steady state and was stable for more than 72 h. The steady-state value of ΔP increased proportionally with increasing u of the mobile phase, which showed the high mechanical stability of **M-PS-TPP** against continuous permeation through the column reactor. The Darcy's permeabilities (k_D) of monolith columns with L of 4.0 cm were 3.3×10^{-13} and 3.8×10^{-14} m^2 for THF/water (2:1 v/v) and THF, respectively. The **M-PS-TPP** column with shorter or longer L values (2.3 or 9.5 cm) had almost the same k_D (Figure 4a). When using **M-PS-grafted-TPP** column, the k_D were similar to that of **M-PS-TPP** column. These observation revealed that the absence of effect of ligand or column length on permeability of monolith column fabricated via HIPE template. Although pressure losses were rather greatly affected by monolith swelling in the mobile phase, the observed k_D values were comparable to those of a polystyrene monolith previously reported.[27] The continuous permeation of the mobile phase was achieved with low pressure loss because of the large pore size and high porosity of **M-PS-TPP**, which gave sustainable continuous-flow operation.

In order to understand and control the variables governing the hydrodynamics, **M-PS-TPP** column was characterized by means of RTD studies using pulse tracer. An inert tracer dye, methyl red, was injected into the stream of THF through the **M-PS-TPP** column and its distribution was continuously monitored using in-line UV-vis spectroscopy at the outlet over time.[28] Calculating the dimensionless time (θ) and dimensionless RTD function ($E(\theta)$), the flow behavior of methyl red was analyzed (Figure 4b). It was noteworthy that the narrow and high $E(\theta)$ curves were observed for **M-PS-TPP** column. Moreover, the flow patterns were independent on the τ of 0.25–2.00 h and repeated at least three times in each condition. These evaluations demonstrated that the flow-through porous structure of **M-PS-TPP** was very suitable for support material of immobilized catalyst in continuous-flow reactor, where the flow presents little axial dispersion and thus is closer to plug flow than in the case of packed-bed material.[18] Additionally, we estimated total porosity of **M-PS-TPP** column in continuous-flow reactor from the elution volume of pulse tracer,[28] and realized that **M-PS-TPP** had significantly higher porosity (91–98%) than those obtained from mercury intrusion porosimetry (81%). This was due to **M-PS-TPP** swelling in organic solvent,[29] which would provide the full molecular diffusion of reactants toward catalytic center and maximize the performance of continuous-flow reactor.[30]

Effect of Residence Time and Column Length on Productivity. The **M-PS-TPP**-Pd column was fabricated by the reaction of the **M-PS-TPP** column with $[PdCl_2(PhCN)_2]$ in THF under continuous-flow conditions.[31] After washing by permeating with THF, the concentration of Pd in the eluent from the column was below the ICP-AES detection limit (< 10 ppb), and the loading amount of Pd in **M-PS-TPP**-Pd was 0.05 mmol g^{-1} (Pd/P 1:2). The continuous-flow Suzuki-Miyaura cross-coupling reaction between 4-chlorotoluene (0.50 mol L^{-1}, 1 eq.) and phenylboronic acid (0.75 mol L^{-1}, 1.5 eq.) was used to evaluate the productivity of the **M-PS-TPP**-Pd column. THF solution of the aryl substrates and aqueous solution of K_3PO_4 (3.00 mol L^{-1}, 3 eq.) was pumped and mixed via a T-shaped mixer. The τ of the substrate solution was set in the range of 0.25–2.00 h by changing the Q while maintaining the ratio of the THF phase

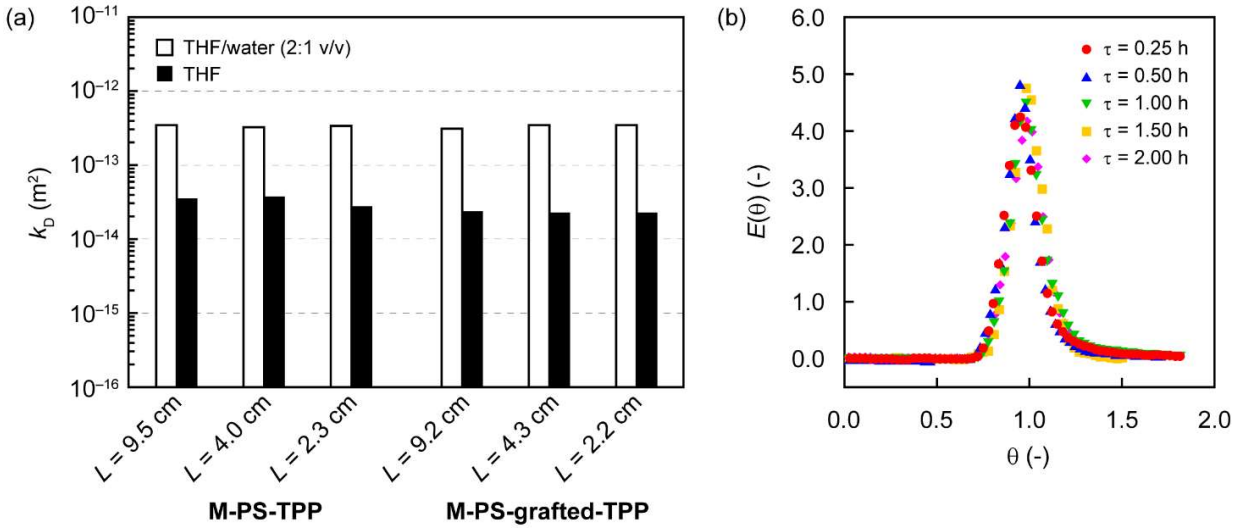


Figure 4. (a) Permeation coefficients (k_D) of monolith column with different mobile phase and column length (L). (b) Representative dimensionless residence time distribution function ($E(\theta)$) v.s. dimensionless time (θ) diagram for a pulse injection of methyl red in ethanol (1 g L^{-1}, 10 μL) into a THF stream through **M-PS-TPP** column (L = 4.5 cm).

(Q_{THF}) to water phase (Q_{water})at 2:1 v/v (Q = Q_{THF} + Q_{water}) (Scheme 1c). During elution from the column, macroscopic phase separation rapidly occurred, and the THF phase was analyzed using HPLC to confirm the production of 4-methylbiphenyl. Under the present conditions, byproducts such as biphenyl which might originate from homo-coupling of phenylboronic acids were not found. During permeation of the substrate solution at a time on stream of 4–10 h (early region), the yield of 4-methylbiphenyl was determined for each τ. The yield of 4-methylbiphenyl depended on the τ of the substrate solution (filled circle, filled triangle, and filled rectangle, Figure 5). The **M-PS-TPP**-Pd column with a short L (2.3 cm) gave a very poor yield (8%, filled rectangle) at a τ of 2.00 h. Increasing the L of the **M-PS-TPP**-Pd column drastically increased the yield within the same range of τ values. At a τ of 2.00 h, the **M-PS-TPP**-Pd column with longer L values (4.0 and 9.5 cm) achieved excellent yields of 86 and 88%, respectively.

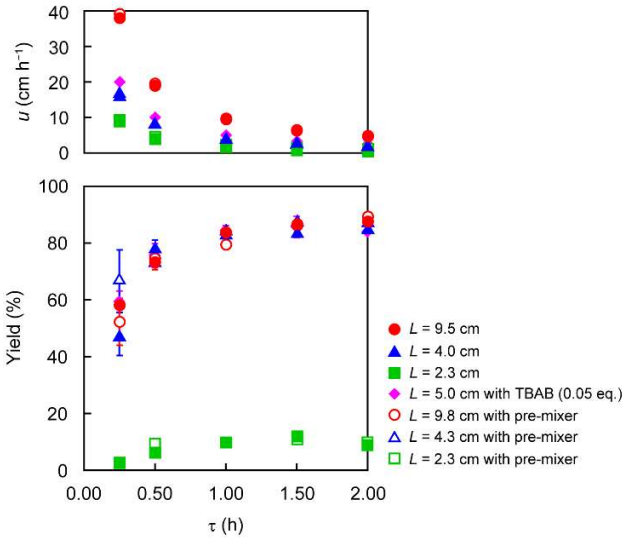


Figure 5. Effects of column length (L) of **M-PS-TPP**-Pd column and residence time (τ) on yield of 4-methylbiphenyl in continuous-flow Suzuki-Miyaura cross-coupling reaction using biphasic solvent. Conditions: 4-chlorotoluene (0.50 mol L^{-1}, 1 eq.) and phenylboronic acid (0.75 mol L^{-1}, 1.5 eq.) in THF, K_3PO_4 (3.00 mol L^{-1}, 3 eq.) in water, **M-PS-TPP**-Pd column (Pd/P 1:2), THF phase/water phase 2:1 v/v, 40°C.

Buchwald and co-workers reported that increasing the u improved the yield of the C–N cross-coupling reaction in toluene/water media using homogeneous Pd.[11] In our system, a higher u was realized using a longer L at the same range of τ (Figure 5). We assumed that this positive effect was attributed to the fast mass transfer at the organic/aqueous interface enhanced by higher u. To verify the importance of interfacial mass transfer for the biphasic media, glass beads (1.0–1.4 mm diameter) were packed in a stainless-steel tube (4.4 mm inner diameter, 5.0 cm length) as a pre-mixer, which was installed upstream of the **M-PS-TPP**-Pd column. However, the effect of pre-mixing on the yield was not obvious compared with the effect of the L of the **M-PS-TPP**-Pd column (blank circle, blank triangle, and blank rectangle, Figure 5). In the presence of tetra-*n*-butylammonium bromide (TBAB, 0.05 eq.) as a phase transfer catalyst in the biphasic reaction mixture, the productivity of the **M-PS-TPP**-Pd column was also evaluated (filled rhombus, Figure 5), which gave almost the same trend as that without using TBAB.

Unlike the previous study using a homogeneous catalyst,[11] the present results demonstrated that mass transfer at the liquid/liquid interface was not the rate-limiting step using the immobilized catalyst on the monolith reactor. Increasing the u accelerated the liquid/liquid interfacial mass transfer and also external diffusion on the **M-PS-TPP**-Pd surface.[32] This may have been the rate-limiting step in the continuous-flow system with a short L (~2.3 cm). With longer L values (4.0 cm or more), the yield profiles were almost the same, suggesting sufficiently fast diffusion at organic/aqueous interface, featuring efficient mixing through macropore of **M-PS-TPP**-Pd column. In addition to RTD behavior close to plug-flow (Figure 4b), the accelerated external diffusion of reactants also boosted productivity of monolith column.

Long-Term Durability of M-PS-TPP-Pd Column. At a τ of 2.00 h, the long-term durability of the **M-PS-TPP**-Pd column was evaluated using the Suzuki-Miyaura cross-coupling reaction under continuous-flow conditions (time on stream of 58 h) (Figure 6). From ICP-AES analyses, Pd leaching from the column was not observed (< 10 ppb) in any eluent (THF and water phase). This suggested the effective entrapment of Pd by the cross-linked polymer network in the **M-PS-TPP**-Pd column during long-term use.[30] The gradual decrease in the turnover numbers (TONs) of the monolith columns was observed along with permeation of the substrate solutions. TEM observations of original and spent Pd-loaded monoliths indicated the formation of clusters likely generated from Pd aggregation, which should be less active or inactive.[33] The **M-PS-TPP**-Pd column reached a very high TON of 2704 at a time on stream of 58 h in the continuous-flow cross-coupling reaction of aryl chloride.

Effect of TPP Moiety on Productivity. To confirm the importance of the three-fold cross-linking around TPP in **M-PS-TPP**-Pd on productivity, **M-PS-grafted-TPP**, where analogous TPP was covalently linked to a polystyrene chain via single-point grafting, was also used in the continuous-flow reaction at a τ of 2.00 h (Figure 6). The productivity of the **M-PS-grafted-TPP**-Pd column with a short L (2.2 cm) was poor, giving a TON of 90 at a bed volume of 17 (violet rhombus, Figure 6). As with the **M-PS-TPP**-Pd column system (Figure 5), increasing the L (4.3 cm) of the **M-PS-grafted-TPP**-Pd column significantly improved the yield and TON (gray square, Figure 6). However, further increasing the L (9.2 cm) did not give any meaningful enhancement (black triangle, Figure 6). The absence of external diffusion limitation in the monolith column was apparent at L values above 4.3 cm for the **M-PS-grafted-TPP**-Pd column. All **M-PS-grafted-TPP**-Pd columns showed drastic decreases in productivities of 4-methylbiphenyl with increasing time on stream, and no meaningful conversion was observed at bed volumes of 17 (5–10% yields). Surprisingly, the highly durable catalysis of the **M-PS-TPP**-Pd column produced biaryl (63% yield) at a bed volume of 17.

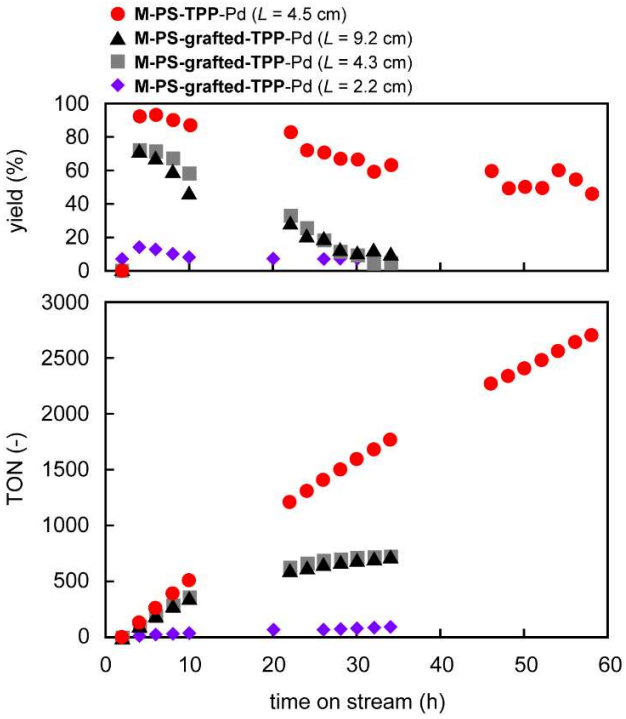


Figure 6. Long-term production of 4-methylbiphenyl using monolith reactors containing TPP-Pd complex. Conditions: 4-chlorotoluene (0.50 mol L^{-1}, 1 eq.) and phenylboronic acid (0.75 mol L^{-1}, 1.5 eq.) in THF, K_3PO_4 (3.00 mol L^{-1}, 3 eq.) in water, TPP-Pd on monolith column (Pd/P 1:2), THF phase/water phase 2:1 v/v, τ = 2.00 h, 40°C.

The efficient productivity of the **M-PS-TPP**-Pd column was apparent compared with those of the **M-PS-grafted-TPP**-Pd columns. This suggested that TPP-Pd complex species in the monolith column greatly influenced the catalytic efficacy in the continuous-flow cross-coupling reaction. The three-fold cross-linking around TPP, which facilitated the formation of the mono-ligated TPP-Pd complex, was essential for participation in conversion of the unactivated aryl chloride under mild conditions (40 °C).[7a,b] The final TON (2704) of the **M-PS-TPP**-Pd column corresponded to a turnover frequency (TOF) of 47 h^{-1} and space time yield of 0.45 kg L^{-1} day^{-1}. The potential of the **M-PS-TPP** column in Pd-catalyzed aryl chloride cross-coupling was comparable to that of a polymer-supported TPP bead column in similar cross-couplings of aryl bromides.[34] Using the **M-PS-TPP**-Pd column, 4-chlorotoluene was continuously processed to produce the cross-coupling product, 4-methylbiphenyl, with a total yield of 0.728 g (time on stream of 58 h). This yield could readily be scaled up using numbering up or size up strategies.[1]

Continuous-Flow Conditions v.s. Batch Conditions. The catalytic efficacy of **M-PS-TPP**-Pd was also evaluated in batch system[35] and compared with that in continuous-flow system. Indeed, the TON and TOF of **M-PS-TPP**-Pd was higher under continuous-flow conditions than those under batch conditions (Table 1). Interestingly, increasing the stirring rate and/or employing TBAB enhanced the reaction efficacy of batch cross-coupling reaction using **M-PS-TPP**-Pd. This indicated severe diffusion limitation at organic/aqueous interface in the batch system. Most of studies on cross-coupling reactions showed the lower productivities of immobilized catalysts under continuous-flow conditions than those under batch conditions,[36] which were probably due to low mixing and contact efficiency with catalyst. In our system, the merits of the macroporous architecture (Figure 2b and c) of the **M-PS-TPP**-Pd column for mass transfer were highlighted, where molecular diffusion at the liquid/liquid interface was accelerated by the biphasic media co-flowing through the micron-sized pores.[27] Moreover, the full accessibility of reactants toward catalyst was realized due to narrow RTD and swelling properties (Figure 4b) which also supported the high productivity of **M-PS-TPP**-Pd column. As far as we know, the present system is the first example of continuous-flow cross-coupling reaction of aryl chloride showing rather excellent efficacy and durability than that in batch system.

Table 1. Comparison of Catalytic Efficacies of M-PS-TPP-Pd for Aryl Chloride Cross-Coupling[a]

condition	yield (%)	TON (-)	TOF (h^{-1})
continuous flow[b]	46–93	2704[c]	47[c]
batch[d]	6	58	29

[a]Conditions: 4-chlorotoluene (0.50 mol L^{-1}, 1 eq.) and phenylboronic acid (0.75 mol L^{-1}, 1.5 eq.) in THF, K_3PO_4 (3.00 mol L^{-1}, 3 eq.) in water, THF phase/water phase 2:1 v/v, 40°C.

[b]**M-PS-TPP**-Pd column (Pd/P 1:2, *L* = 4.5 cm), τ = 2.00 h. [c]Time on stream = 58 h.

[d]**M-PS-TPP**-Pd (Pd/P 1:2, 0.1 mol% Pd), 2.00 h.

CONCLUSIONS

In summary, a macroporous polystyrene monolith containing three-fold cross-linking triphenylphosphine, **M-PS-TPP**, was synthesized and applied to challenging transition-metal catalysis in continuous-flow manner, which featured highly active phosphine-metal complex and enhanced hydrodynamic properties. Through radical polymerization in the presence of a HIPE, the characteristic window and void structure in **M-PS-TPP** was fabricated. **M-PS-TPP** in column format was applied to continuous-flow application and showed excellent permeability and narrow RTD of the feed. The feasibility of the **M-PS-TPP** column for continuous-flow synthesis was demonstrated in the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl chloride. Using organic/aqueous media, clogging in the continuous-flow reactor by salt formation was avoided. Controlling hydrodynamic properties in the **M-PS-TPP**-Pd column enhanced mass transfer and resulted in highly active and durable catalyst system without Pd leaching. The productivity of the **M-PS-TPP**-Pd column in the continuous-flow system was much higher than that in the batch system, with the former featuring efficient mixing of biphasic media and selective mono-P-ligation toward Pd^{II}. The **M-PS-TPP** system could be broadly extended to transition-metal catalysis in continuous-flow systems for efficient production of fine chemicals.

EXPERIMENTAL SECTIONS

Synthesis of M-PS-TPP for Characterization (Scheme 1a). A solution of tris(4-vinylphenyl)phosphane (5.5 mg,

0.016 mmol, 1 eq.), 4-*tert*-butylstyrene (106.0 mg, 0.66 mmol, 41 eq.), divinylbenzene (42.0 mg, 0.32 mmol, 20 eq.), and Span 80 (0.061 mL) in chlorobenzene (0.19 mL) was placed in a glass vial (21.00 mm inner diameter) equipped with a magnetic stirring bar (~20 mm). The organic phase was degassed by three freeze-pump-thaw cycles. Separately, $CaCl_2$ (36.9 mg, 0.33 mmol) and $K_2S_2O_8$ (5.2 mg, 0.019 mmol, 1.2 eq.) was dissolved in water (3.3 mL). The aqueous phase was degassed by nitrogen bubbling for > 0.5 h. Under vigorous stirring of organic phase (500 rpm), the initiator-containing aqueous phase was added dropwise using syringe. The ratio of organic phase to aqueous phase was 10:90 v/v. After addition of aqueous phase, stirring was further continued for 5 min to give HIPE. The HIPE was incubated in the vial at 70°C for various time (6 h) after removing stirring bar. Carefully crushing the vial, the resulting cylindrical polymer was washed successively by immersion in THF/water (2:1 v/v) and THF for > 1 day each. Using calipers, the *d* and *L* of swollen **M-PS-TPP** was measured to estimate a swelling volume. The yield of **M-PS-TPP** was determined after drying under vacuum at room temperature overnight, to give a white solid polymer (141.5 mg, 92 wt% dry yield). The [P] of **M-PS-TPP** was 0.11 mmol g^{-1} based on feed ratio of monomers.

Synthesis of M-PS-TPP Column for Flow Application (Scheme 1b). Stainless-steel tube (4.4 mm inner diameter) with different length (2.5, 5.0, or 10.0 cm) was filled with HIPE using syringe and sealed at the ends with septa. After incubation at 70°C for 6 h, the seals were removed, and the *L* of monolith column within stainless-steel column was measured using calipers. For flow application, the **M-PS-TPP** column was provided with fittings and attached to a syringe pump. THF/water (2:1 v/v) and THF were successively permeated through the column for wash (2.5 h each, τ = 0.50 h). At various *u* (τ = 0.25, 0.50, 1.00, 1.50, or 2.00 h), the pressure losses through the column were monitored for more than 48 h to reach steady-state condition. The k_D of monolith columns for each mobile phase were estimated.

Flow Suzuki-Miyaura Cross-Coupling Reaction in Biphasic Solvent System (Scheme 1c). $[PdCl_2(PhCN)_2]$ (0.005 mol L^{-1}) in THF was permeated through **M-PS-TPP** column (τ = 2.00 h). The molar ratio of Pd to P was 1:2, controlled by total elution volume of feed solution. After completion of the permeation, the column was washed by permeation of THF to afford **M-PS-TPP**-Pd (2.5 h, τ = 0.50 h). 4-Chlorotoluene (0.50 mol L^{-1}, 1 eq.) and phenylboronic acid (0.75 mol L^{-1}, 1.5 eq.) in THF, and K_3PO_4 (3.00 mol L^{-1}, 3 eq.) in water were separately prepared. TBAB (0.025 mol L^{-1}, 0.05 eq.) was dissolved in the THF phase with aryl substrates if needed. These solutions were loaded into syringes and attached to syringe pumps. Two syringe pumps were used to deliver the feed substrate solutions at controlled Q_{THF} and Q_{water}. The ratio of Q_{THF} to Q_{water} was 2:1. The two substrate solutions were pumped and mixed via T-shaped mixer. The mixture was continuously permeated through the **M-PS-TPP**-Pd column. The τ was calculated based on the total flow rate of THF-phase and water-phase substrate solutions ($Q = Q_{THF} + Q_{water}$). The elution from the column was continuously collected, and the THF-phase was analyzed using HPLC. During permeation of the substrate solution at a time on stream of 4–10 h (early region), the yield of 4-methylbiphenyl was determined for each τ. After run, THF/water (2:1 v/v) and THF was successively permeated through the column for washing. The eluent from the column was diluted in aqueous solution of HCl (1 mol L^{-1}) and analyzed using ICP-AES.

ASSOCIATED CONTENT

Experimental details, porous properties, NMR spectra, permeabilities, and other data for this study are available in Supporting Information and 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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