

Development of Monolithic and Porous Polymer Gel Catalyst for Continuous-Flow Synthesis of Fine Chemicals

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**Development of Monolithic and Porous Polymer Gel Catalyst
for Continuous-Flow Synthesis of Fine Chemicals**

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Chapter 1

Introduction

Chapter 1 Introduction

1.1 Background of Fine Chemical Production

1.1.1. Fine Chemical Industries

With advances in science and medical technologies, the demand for health and well-being has greatly expanded with the increased interests in “fine” and “specialty” chemicals than those in commodity (bulk) chemicals. Fine chemicals generally refer to starting materials for specialty chemicals such as pharmaceuticals, dyes, cosmetics, perfumes, surfactants, adhesives, agrochemicals, and electronic devices. Though there are no universally accepted definitions of bulk, fine, and specialty chemicals, a useful working definition is based on their price and production amount (Table 1-1). The fine chemicals are produced mainly by traditional organic synthesis and/or biosynthesis in multipurpose plants in limited volumes for each reactions ($< 10^6$ kg year⁻¹) and at relatively high prices (> 10 US dollars kg⁻¹).^[1]

Table 1-1. Definition of Bulk, Fine, and Specialty Chemicals

	bulk chemicals	fine chemicals	specialty chemicals
identity	single pure chemical substances		mixtures
price (US dollars kg ⁻¹)	~10	> 10	~10 ⁵
production amount per reaction (kg year ⁻¹)	> 1000	< 1000	undifferentiated
plant type	dedicated, continuous	multipurpose, batch	formulation (dissolution, mixing)
sales channel	business to business	business to business	business to consumer

The fine chemical industries provides important intermediates in a variety of fields such as automotive, paint, textile, electrical/electronic, and medical industries (Figure 1-1).^[2] Within the chemical universe, the fine chemical industry is positioned between the commodity and specialty chemical industries, which are their suppliers and customers, respectively.

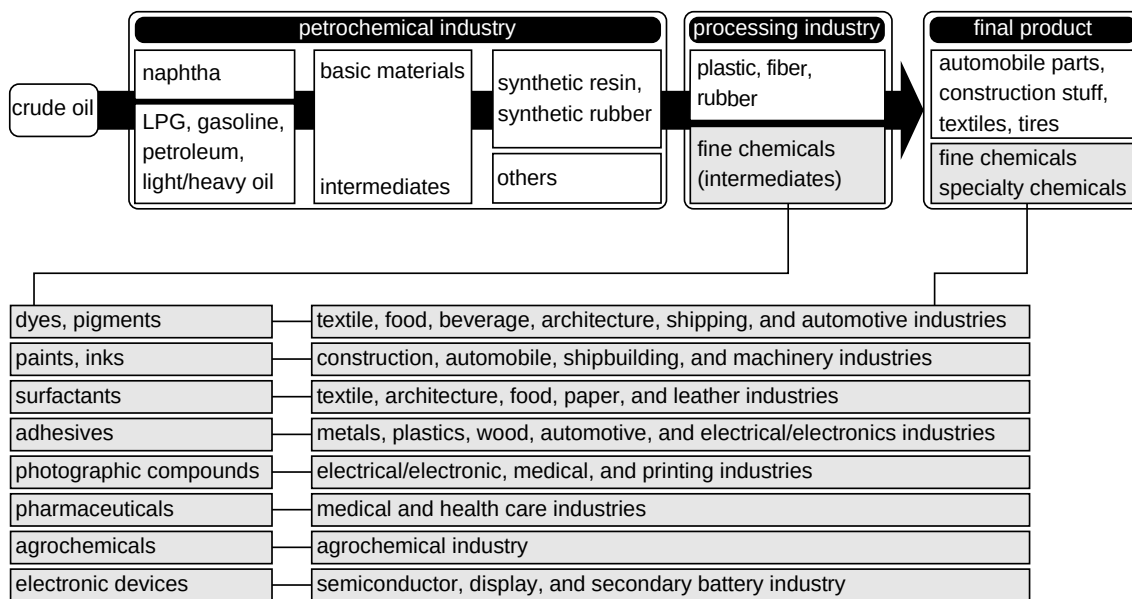


Figure 1-1. Relationship between fine chemicals, upstream/downstream industries, and related industries.

According to the latest pharmaceutical market forecast report released by IQVIA, global spending on pharmaceuticals reached \$1.2 trillion in 2018, up from \$1.1 trillion in 2017, and is set to be just under \$1.3 trillion by 2019, with 4–5% growth rate globally. Those global spending on pharmaceuticals is expected to exceed \$1.5 trillion by 2023 (Figure 1-2). The global growth of pharmaceuticals spending through 2023 will primarily be driven by markets in developed countries and their adoption of a wave of newly launched innovative products including not only (synthetic) small or middle molecules but also biologics (antibodies and enzymes) and drug combinations.^[3,4]

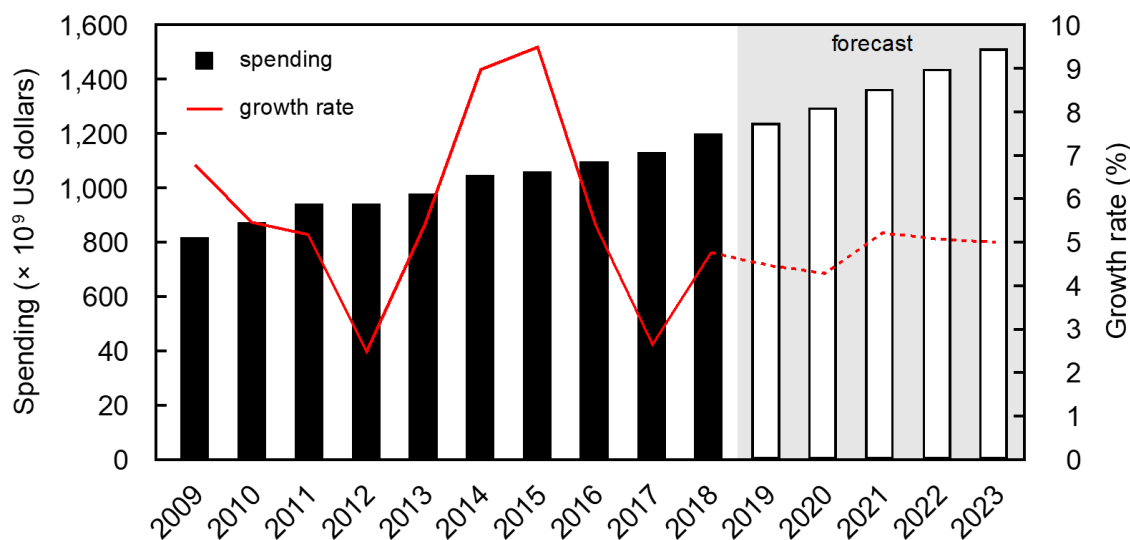


Figure 1-2. Global pharmaceuticals spending and growth 2009–2023.

Recent people's interests in the environmental issues and sustainable development have motivated the emergence of chemical manufacturing with high yield and selectivity while reducing wastes and energy. Typically, the process cost of fine chemicals is high and the mass of waste per the mass of product is also larger than those of bulk chemicals.^[5,6] This illustrates that the modern fine chemical industries are facing with serious resource and environmental problems to maintain and go further beyond the high standard of living in our societies. To evaluate the environmental impact of the manufacturing process, an *E* (Environment) coefficient was proposed in the latter half of 1980 as follows:

$$E = \frac{\text{mass of waste}}{\text{mass of products}} \quad (1-1)$$

which expresses the mass of waste per the mass of products. The *E* factors emphasize the seriousness of waste problems in various sectors of the chemical industry, especially in fine chemicals (Table 1-2).^[6] Not only conventional requirement based on chemical yield, but also resource efficiency, the mass of waste per reaction, and greener synthetic routes should be searched for highly efficient and environmentally friendly organic syntheses in chemical manufacturing.

Table 1-2. *E* Factors in the Chemical Industries

	oil refining	bulk chemicals	pharmaceuticals	fine chemicals
total production amount (kg year ⁻¹)	10 ⁹ –10 ¹¹	10 ⁷ –10 ⁹	10 ³ –10 ⁶	10 ⁵ –10 ⁷
<i>E</i> factor (kg-waste kg-product ⁻¹)	< 0.1	< 1–5	25– >100	5–50

1.1.2. *Switching from Batch to Continuous-Flow System*

Modern organic chemistry is constantly evolving to develop new synthetic routes to fine chemicals. For hundred years, chemists have addressed these requests on the basis of chemical reaction in flask, which is a technique suitable for many reaction systems (Figure 1-3a). However, in response to the above-mentioned social conditions, chemistry (even in the laboratory) is facing a turning point when the chemical reaction should be carried out in waste-reducing, safe, and preferably automated fashion. Switching the modern chemical reaction from a batch system to a continuous-flow system helps researchers pursue this vision (Figure 1-3b).^[7] Historically, continuous-flow systems have been adopted in the large-scale syntheses of bulk chemicals in reactions of gas reactants; the synthesis of ammonia through the Haber–Bosch process^[8] is one of famous example. Recently, most reactions using microreactors have been conducted by using flow methods (Figure 1-3c).^[9]

To date, the continuous-flow chemistry has thrived in academic and industrial laboratories for production of fine chemicals and functional materials, which is supported by efficient and innovative synthesis methods. The continuous-flow systems are advantageous over batch systems in terms of high heat exchange efficiency, mixing efficiency, and controllability of reaction time.^[7] In addition, the continuous-flow systems incorporate reaction scale-out at the early stage of science. This enables effective on-demand production in compact and reconfigurable setups supported by computer- and/or

artificial intelligence-aided automated system. As a result, this field has diversified and expanded to provide new and practical solutions to organic chemistry,^[9–11] biochemistry,^[12] polymer chemistry^[13,14] and materials science (Figure 1-3d).^[15–17]

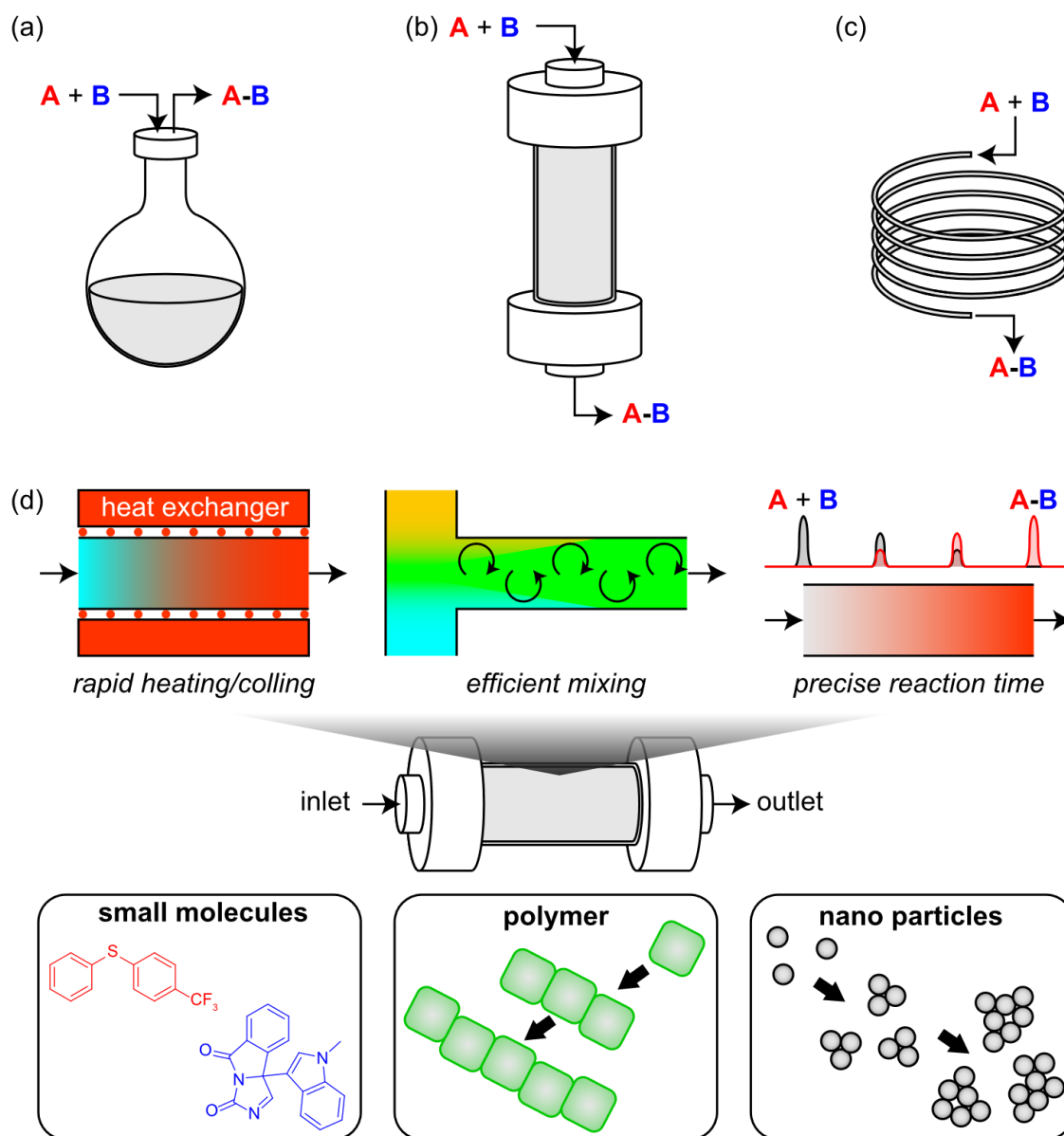


Figure 1-3. (a) Conventional batch reactor, (b) continuous-flow reactor, and (c) microflow reactor.

(d) Continuous-flow productions with high heat and mixing efficiency, and precisely controlled reaction time for small molecules, polymers, and nanomaterials.

1.1.3. Catalytic C–C and C–Heteroatom Bond Formations by Transition Metals

C–C bonds are backbone of most of organic compounds, and the functions of the molecules are mainly derived from the presence of heteroatoms such as nitrogen, oxygen and sulfur, which are ligated to these molecules by C–heteroatom bonds. Thus, the synthetic routes via C–C or C–heteroatom bond formations have been recognized as strong tools for production of fine chemicals.^[18] For example, pharmaceuticals and conductive polymers often contain amine C–N bonds,^[19] and almost all the natural products contain ether, ketone, and/or ester C–O bonds.^[20] Heterocyclic compounds which have C–N, C–O, or C–S bonds in the ring structures are found in all applications of chemistry.^[21–23] Moreover, useful intermediates often contain C–B or C–Si bonds that are easily converted into C–C, C–O, or C–N bonds in the final products.^[24,25] Nowadays, the linking of these reactions to catalytic processes, especially using transition metals, has been a recent focus of organic syntheses through alkylation, oxidation, arylation, vinylation, amination, azidation, formylation, acylation, benzylation, borylation, and silylation (Figure 1-4).^{24–34} Continuous-flow systems have also adopted for some of these useful catalytic reactions.^[36–41] The catalytic properties of the metals will be explained in detail in the later section.

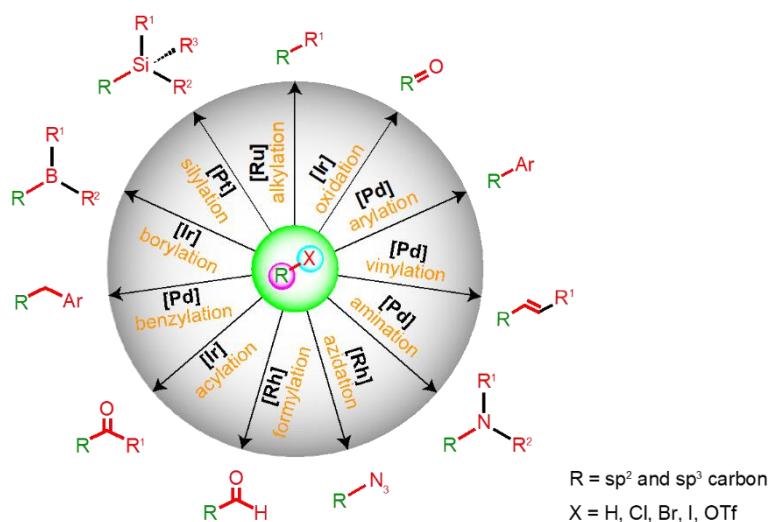


Figure 1-4. Synthetic strategies for C–C and C–heteroatom bond formations catalyzed by transition-metal catalysts.

1.2 Transition-Metal Catalyst

1.2.1. Catalytic Properties of Transition Metals

Transition-metal catalyses have gained great interests for their many applications in industrial and laboratory scales. Transition-metal reactions are important in many thermodynamically possible processes because these reactions accelerate by opening low-energy pathways. Among them, noble metals such as Pd, Pt, Ag, Au, Rh, Ru, and Ir have been recognized as frontrunners for in race to find a clean and efficient synthetic route for fine chemicals.^[42,43] Nowadays, they are covering the wide range of reaction scopes (Figure 1-4). Considering the limited availability, high price, and high toxicity of the noble metals, reactions catalyzed by first-row transition metals such as Sc, Ti, V, Cr, Mn, Fe, Co, Ni, and Zn have also attracted much attentions due to their inexpensiveness, easiness in handling, safety for health, and low environmental loading (Table 1-3).^[44,45]

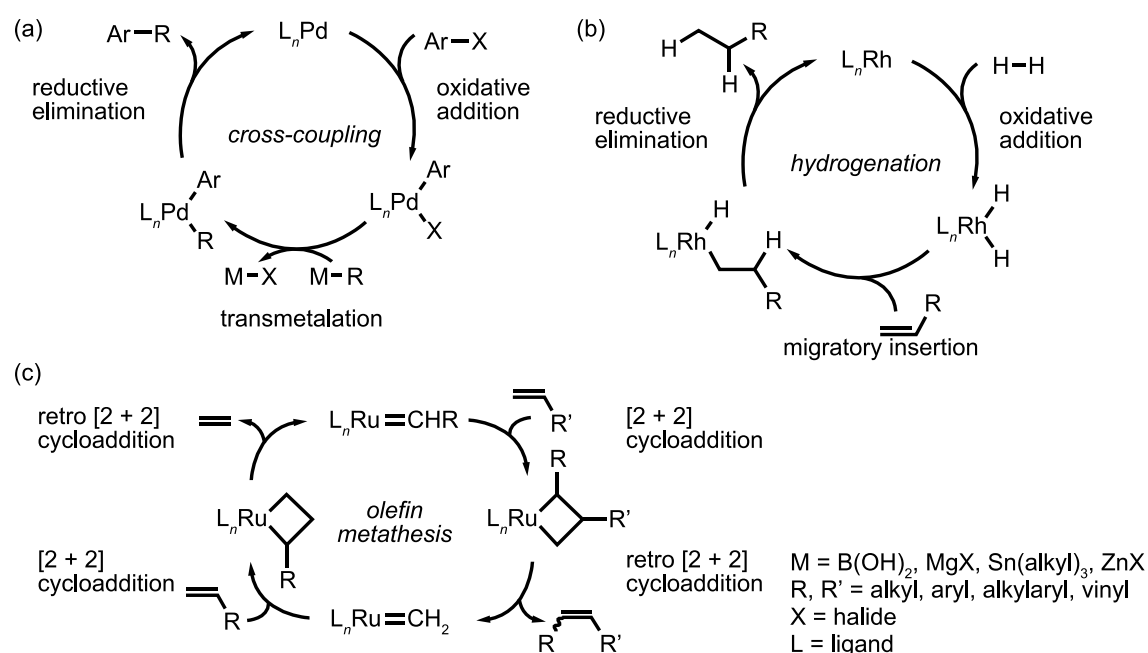
Table 1-3. Comparison between Noble Metals and First-Row Transition Metals

	noble metals	first-row transition metals
price (€ kg ⁻¹)	< 5 × 10 ⁴	< 4 × 10 ³
tolerance in drugs (ppm)	< 10 ¹	< 10 ³
abundance in earth's crust (ppm)	10 ⁻⁴ –10 ⁰	10 ¹ –10 ⁵

These metal-centered reactions contain the formations of organometallic complex, which is organic groups attached to a central metal through metal–C (M–C) bonds. To give a desired final product, the organometallic complex undergoes one or more elementary reactions such as substitution, oxidative addition, reductive elimination, migratory insertion, hydrogen exchange, β-hydrogen transfer, σ-bond metathesis, transmetalation, and nucleophilic addition. Many experimental and theoretical studies have been conducted to understand these fundamental transformations.^[46,47] These

elementary reactions (and several others) have been used to create hundreds of catalytic processes. For example, cross-coupling follows a sequence of steps containing the oxidative addition of an organic halide, transmetalation between the generated organometallics, the reductive elimination of catalyst center to give a coupling product (Scheme 1-1a). Hydrogenation often occurs by a combination of oxidative addition of the H–H bond in H₂ to metal, olefin insertion to form the first C–H bond, and reductive elimination to form the second C–H bond (Scheme 1-1b). The metathesis of olefins occurs by a series of [2 + 2] and retro [2 + 2] cycloadditions (Scheme 1-1c).^[18]

Scheme 1-1. Mechanisms of Common Catalytic Organometallic Processes, (a) Cross-coupling, (b) Hydrogenation, and (c) Olefin Metathesis



1.2.2. Transition-Metal Complexes

In the research field of organometallic chemistry, the molecular design of organic ligands to boost the catalytic activity and selectivity of transition metals has fascinated organic chemists for hundreds of years. To date, vast numbers of organic ligands have been developed to formulate a transition-metal

complexes which carried out fascinating and challenging catalytic reactions in terms of turnover frequency (TOF), turnover number (TON), regio- or enantio-selectivity, durability, atom economy, and other reaction conditions.

HSAB Rule

One of the primitive selection criteria for ligands is a theory of hard and soft acids and bases (HSAB), which systematized the strengths of metal-ligand bonds in 1963 by Pearson.^[48,49] This approach assumes that all bonds between heteroatoms are considered to have portions of acidity and basicity. Essentially, this acidity and basicity depends on the number of valence electrons attached to the species and the ease with which they can be rearranged. The main principle behind HSAB theory is that strong bonds are only formed between hard acids and hard bases or between soft acids and soft bases. Hard-soft bonds are either very weak or do not exist. Some properties employed in classifying a species as hard or soft, acid or base (Table 1-4) and these are employed to classify the common transition metals and ligands (Table 1-5).^[50]

Table 1-4. Classification of Hard and Soft Acids and Bases-Acid

acid (electron acceptor)			base (electron donor)		
<i>hard</i>	<i>property^a</i>	<i>soft</i>	<i>hard</i>	<i>property^a</i>	<i>soft</i>
low	polarizability	high	low	polarizability	high
high	electropositivity	low	high	electropositivity	low
large	positive charge or oxi. state	small	large	negative charge	small
small	size	large	small	size	large
ionic, electrostatic	types of bond	covalent, π	ionic, electrostatic	types of bond	covalent, π
few and not easily excited	outer electrons on donor atoms	several, easily excited	high energy and inaccessible	available empty orbitals donor atom	low-lying on and accessible

^aThese properties may be used as guidelines for classifying species. The whole column need not be satisfied for a species to be called hard or soft but the more properties that are true, the greater the degree of hardness or softness.

Table 1-5. HSAB Classification of Lewis Acids and Bases

	metal (electron acceptor)	ligand (electron donor)
<i>hard</i>	Mn ⁴⁺ , V ⁵⁺ , Mo ⁶⁺ , Mn ²⁺ , Cr ³⁺ , Co ³⁺ , Fe ³⁺ , Ti ⁴⁺	O ²⁻ , OH ⁻ , H ₂ O, CO ₃ ²⁻ , NO ₃ ⁻ , NH ₃ , RNH ₂ , RCOO ⁻ , RO ⁻ , ROH, N ₂ H ₄ , PO ₄ ³⁻ , ROPO ₃ ²⁻ , (RO) ₂ PO ²⁻ , Cl ²⁻
<i>borderline</i>	Fe ²⁺ , Ni ²⁺ , Co ²⁺ , Cu ²⁺ , Zn ²⁺	NO ²⁻ , imidazole (Im), pyridine (py), N ₂ , SO ₃ ²⁻ , Br ⁻ , N ₃ ⁻
<i>soft</i>	Cu ⁺ , Mo ²⁺ , Cd ²⁺ , Pd ²⁺ , Au ⁺ , Tl ⁺ , Hg ²⁺ , Pt ²⁺ , M ⁰ (metal atoms), bulk metals	R ₂ S, R ₃ P, RS ⁻ , I ⁻ , CN ⁻ , RSH, RNC, SCN ⁻ , CO, benzene, ethylene, H ⁻ , R ^{-a}

^aStands for an alkyl or aryl group.

18-Electron Rule

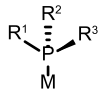
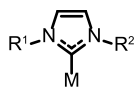
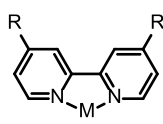
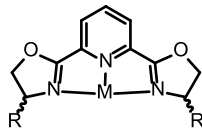
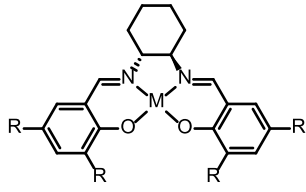
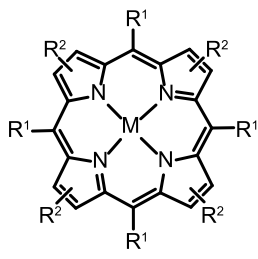
A simple and effective approach to discuss the stability of transition-metal complexes is the 18-electron rule first formulated in 1921 by Langmuir.^[51] This is an extension of the so-called octet rule to metal. Langmuir derived an equation relating the number of shared electrons or the covalence (v_c) of a given atom in a compound or complex ion to the difference between the number of valence electrons (e) in the isolated atom and the number of electrons (s) required for completion of its valence shell:

$$v_c = s - e \quad (1-2)$$

In the case of “pure” organic compounds, the component atoms obey the octet rule ($s = 8$), whereas in the case of the transition-metal complexes, the component metals fulfill the 18-electron rules ($s = 18$). If v_c is less than 18 (coordinationally unsaturated), the metal center is open to accept further guest, which is a very important concept to consider the catalytic reactivity of organometallic complexes. One of the important points of catalyst design is how the coordination unsaturated state can be incorporated

into the catalyst system. In order to interact with the coordinatively saturated transition metal, an empty coordination is necessary, and in many cases, a part of the ligand dissociates in the solution to form the coordinatively unsaturated active complex.^[52] Indeed, for activation of transition metals via effective formulation of coordinatively unsaturated species, a variety of ligand scaffolds have been proposed due to their electron-donation ability to metal, structural robustness, and diversity of functionalization (Table 1-6).^[53-60]

Table 1-6. Representative Scaffolds for Ligands to Transition Metals

ligand	M	scope of reaction
 tertiary phosphine	Pd, Pt, Ru, Rh, Ir, Mn, Fe, Co, Ni, Cu, Ag, Au, Zn, Cd, Hg	hydrogenation, C–C or C– heteroatom cross-coupling, borylation, hydroformylation, metathesis
 N-heterocyclic carbene (NHC)	Pd, Tl, Rh, Ru, Ir, Ni, V, Ag,	hydrogenation, C–C or C– heteroatom cross-coupling, metathesis
 bipyridine (bpy)	Pd, Ni, Cu, Fe, Ru,	hydrogenation, C–C cross- coupling, metathesis, borylation
 bis(oxazolonyl)pyridine (pybox)	Ni, Fe, Zn, Cu, Ru, Rh	C–C or C–heteroatom cross- coupling, hydrosilylation
 salen	Mn, Co, Cu, Ru, Fe, Ni, Cr	oxidation, aziridination, cycloaddition
 porphyrin	Zn, Fe, Co, Ru	oxidation, hydroxylation

1.2.3. Tertiary Phosphine Ligands

Tertiary phosphines are the most widely used organic ligands for various types of transition-metal catalyses, and the number of different phosphines has been developed by organic chemists displaying a wide range of applicability in catalytic systems. The coordination behavior of a phosphine ligand is primarily defined by steric and electronic properties, which were first systematically explained in 1970 by Tolman.^[61,62] These features of phosphines provides insights into the fine tuning of the catalytic properties of transition-metal complexes in terms of activity and selectivity.^[63] For example, it has been demonstrated that the steric bulkiness and electron donation of phosphine ligand are important for the formation of coordinatively unsaturated Pd species and stabilization of Pd⁰ in the C–C or C–N cross-coupling reactions.^[64]

Steric Parameter (Tolman Angle)

The most frequently used steric parameter of a phosphine ligand is the Tolman cone angle (Θ),^[61] which was defined as the apex angle of a cylindrical cone centered 2.28 Å from the P atom and tangent to the van der Waals radius of the outermost atom of the three substituents on the P atom (Figure 1-5a and b). If there are internal degrees of freedom (e.g., rotation about P–C bonds), the substituents are folded back to give a minimum cone. For $\Theta \geq 180^\circ$, measurements may be made more conveniently by trigonometry (Figure 1-5c). Θ can be defined for an unsymmetrical ligand $PX_1X_2X_3$, by using a model to minimize the sum of half-angles (Figure 1-5d):

$$\Theta = \frac{2}{3} \sum \frac{\theta_i}{2} \quad (1-3)$$

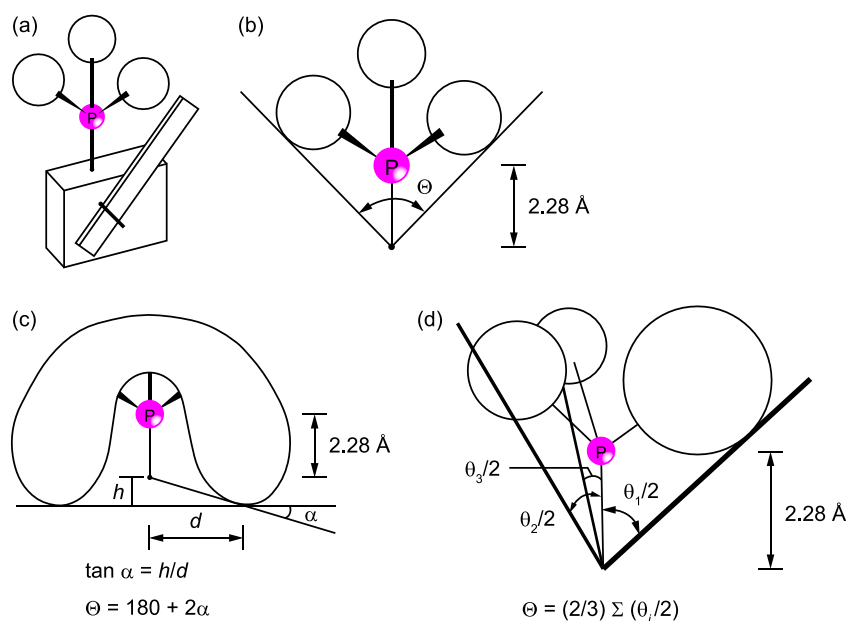


Figure 1-5. (a) Primitive measuring kit for Θ and the their definitions in (b) the symmetrical ligands with $< 180^\circ$ or (c) $\geq 180^\circ$, and (d) the asymmetrical ligands.

Tolman conducted a series of ^{31}P nuclear magnetic resonance (NMR) analyses for ligand exchange reactions between various phosphorus ligands (L) with different bulkiness and $[\text{NiL}_4]$.^[61] A good correlation between Θ and binding ability of phosphine ligands to Ni^0 could be observed (Figure 1-6). Displacement of CO from $\text{Ni}(\text{CO})_4$ by various phosphorus ligands confirmed the expectation that the degree of replacement decreased as the size of the ligand increased. Independent experiments using infrared (IR) spectroscopy (see next paragraph) confirmed the lack of correlation between binding ability to Ni^0 complex and the electronic nature of the phosphorus ligands. Since the limitations of Tolman's approach have been recognized due to the deviation between the actual Θ and one predicted by space-filling model, some different models have been proposed.^[65,66] A structural information from X-ray analyses has also supported the evaluation of Θ .^[67]

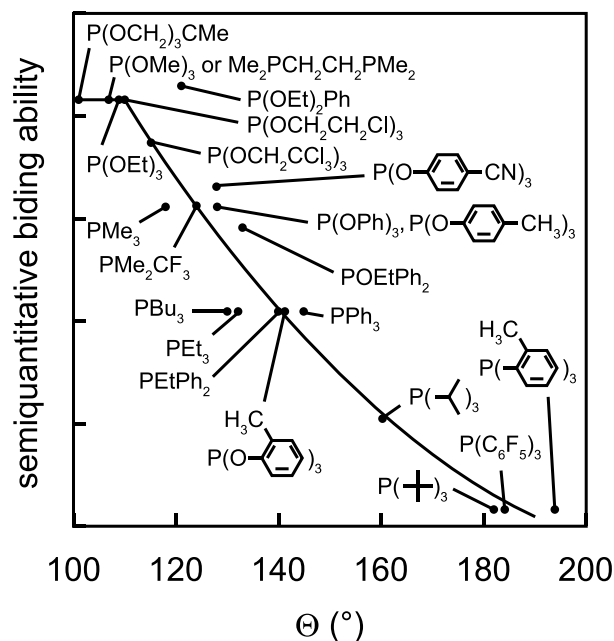


Figure 1-6. Relationship between semiquantitative binding ability in formation of $[\text{NiL}_4]$ complexes and Θ of phosphorus ligands determined by ligand competition experiments using ^{31}P NMR analyses.

Tolman Electronic Parameter

Tolman also correlated the electronic properties of the phosphine ligand to the CO stretching frequency (ν_{CO}) in the IR spectrum of the corresponding complex $[\text{Ni}(\text{CO})_3\text{L}]$ in CH_2Cl_2 .^[62] The ν_{CO} depends on the combination of the σ -donating and π -accepting properties of L for the metal center. The electron density donated by L enhances the back donation from the metal center to the lowest unoccupied molecular orbital (LUMO) of the CO ligand, which results in a decrease in ν_{CO} . The stronger electron-donating property of phosphine corresponds to the lower ν_{CO} . Tolman electronic parameter (χ) was defined as the difference between the ν_{CO} observed for L and that for the strongest electron-donating phosphine, $\text{P}(\text{tBu})_3$. From the series of experiments, the substituent contribution on phosphorus (χ_i) for any $[\text{Ni}(\text{CO})_3\text{PX}_1\text{X}_2\text{X}_3]$ were determined by following equation:

$$\nu_{\text{CO}} = 2056.1 + \sum \chi_i \quad (1-4)$$

The obtained χ_i values reflected the electron-donating property of the interested phosphine ligand,

where lower χ_i values meant the stronger electron-donating property (Table 1-7).

Table 1-7. Substituent Contribution to ν_{CO} of $[\text{Ni}(\text{CO})_3\text{PX}_1\text{X}_2\text{X}_3]$

X_i	$\chi_i (\text{cm}^{-1})$	X_i	$\chi_i (\text{cm}^{-1})$
$-\text{tBu}$	0.0	$-\text{p-PhOCH}_3$	3.4
$-\text{cyclohexyl}$	0.1	$-\text{Ph}$	4.3
$-\text{o-PhOCH}_3$	0.9	$-\text{p-PhF}$	5.0
$-\text{iPr}$	1.0	$-\text{p-PhCl}$	5.6
$-\text{Bu}$	1.4	$-\text{OMe}$	7.7
$-\text{Et}$	1.8	$-\text{H}$	8.3
$-\text{Me}$	2.6	$-\text{OPh}$	9.7

Another convenient experimental method for evaluating the electronic properties of phosphine ligands is to measure the coupling constants ($^1J_{\text{P,Se}}$) in the ^{31}P NMR spectra of the corresponding phosphine selenides.^[68] This $^1J_{\text{P,Se}}$ is related to the degree of the s-orbital character in the lone-pair electrons of the P atom. The energy level of the highest occupied molecular orbital (HOMO) associated with lone-pair electrons is generally high for phosphine, and the s-orbital characteristic of the lone electron pair is lower. This means that the electrons are easily available for bonding to transition metal atoms, and thus the phosphine ligand is a strong σ donor. Stronger σ donors modulated by electron-donating substituents give more basic phosphine ligand and thus smaller $^1J_{\text{P,Se}}$.

1.2.4. Transition-Metal Nanoclusters

Nanoclusters, which are generally close to monodispersed particles less than 10 nm (100 Å) in diameter,^[69] have attracted strong interest in the past few decades. One reason for this is that nanoclusters have unique properties, in part due to the fact that these particles and their properties lie

somewhere between bulk and single particle species. These attractive possibilities have propelled research into photochemical pattern applications such as quantum dots,^[70] chemical sensors,^[71] light emitting diodes,^[72] and conductive films.^[73] Nanoclusters also have great potential as new types of highly active and selective catalysts.^[74–76]

Two reasons why nanoclusters hold the potential to be more active and selective catalysts than those of bulk materials are that a large percentage of metal atoms lie on the surface, and the metal atoms on the surface do not necessarily order themselves in the same way that those in the bulk do. For example, metal clusters which have a complete and regular outer geometry are designated full-shell, or ‘magic number’, clusters (Figure 1-7). Full-shell clusters are constructed by successively packing layers or shells of metal atoms around a single metal atom. The total number of metal atoms (y) per the order of shell (n) is given by the following equation:

$$y = 10^n + 2 \quad (n > 0) \quad (1-5)$$

Thus, full-shell metal clusters contain M_{13} ($1 + 12 = 13$), M_{55} ($13 + 42 = 55$), M_{147} ($55 + 92 = 147$), M_{309} , M_{561} , M_{923} (and so on) metal atoms. Furthermore, the electrons in a nanocluster are confined to spaces that can be as small a few atom-widths across, giving rise to quantum size effects. Perhaps most importantly, the nanoclusters provide the possibility of controlling both the nanocluster size and the surface ligands in a more quantitative and modifiable manner than those of bulk metals.^[77]

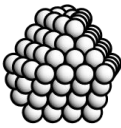
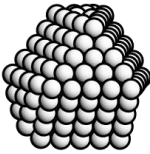
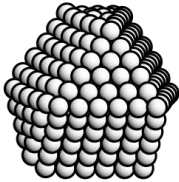
full-shell 'magic number' clusters					
numbers of shells	1	2	3	4	5
numbers of atoms in cluster	M_{13}	M_{55}	M_{147}	M_{309}	M_{561}
percentage of surface atoms	92%	76%	63%	52%	45%

Figure 1-7. Idealized representation of hexagonal close-packed full-shell 'magic number' clusters.

Each metal atom has the maximum number of nearest neighbors, which imparts some degree of extra stability to full-shell clusters. Note that as the number of atoms increases, the percentage of surface atoms decreases.

1.3 Immobilized Catalyst

1.3.1. Immobilization Method of Transition Metals

As mentioned above, transition metals play important roles as catalysts in the wide range of key steps for fine chemicals. However, especially for noble metals, their costs are relatively expensive, which increases the total process costs of desired products. Much effort has gone into the immobilization of homogeneous catalysts based on the idea that the catalysts could be not only separated more easily from the product but also reused several times, thus reducing the process costs in both batch and continuous-flow processes.^[78] In the system using immobilized catalyst, a catalytically active species is commonly immobilized onto a solid support, which can be easily separated from the reaction system by filtration, decantation, and so on. Some unique researches have proposed the liquid-supported catalysts using ionic liquids^[79] or fluorous solvents^[80] as separable liquid phases, followed by combination with solid-supported liquid systems.^[81,82] Several methods for the immobilization of catalysts onto solid supports have been developed over the years, most often based on covalent and ionic bonding, adsorption, or encapsulation (Figure 1-8). The catalyst can be incorporated within a specific support applying various chemical or physical processes, such as decomposition, impregnation, precipitation, co-precipitation, adsorption, or ion exchange.

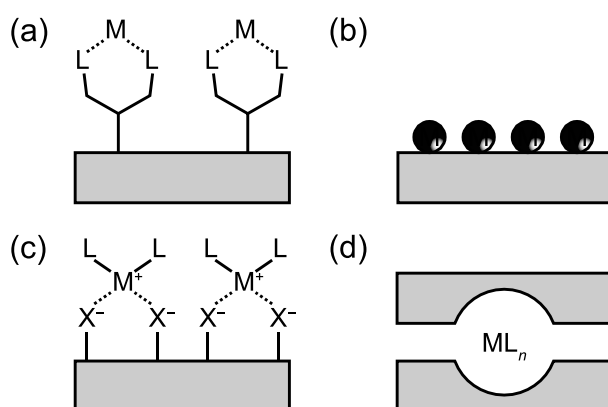


Figure 1-8. Most common immobilization techniques for supported metal catalyst systems: a) covalent bonding, b) adsorption, c) ionic bonding, and d) encapsulation.

1.3.2. Mass Transport Issue

In the immobilized catalyst systems, mass transport limitations generally play an important role in determination of the reaction efficiency because the catalyst is supported on a different phase, which usually is on a solid, and employed in a liquid or gaseous reaction mixture. As a result, the reaction rate depends mainly on mass transfer or diffusion between these phases. Immobilized catalysis occurs when the reactants contacts the active site, usually located inside the catalyst pores (Figure 1-9). The classical seven steps for catalytic reactions have been proposed; (i) diffusion of reactants from the bulk phase (boundary layer) to the outer surface of the catalyst (external film diffusion), and (ii) diffusion of reactants from the pore mouth through the catalyst pores to the vicinity of active site (pore diffusion), (iii) adsorption of the reactant on the inner catalyst surface, (iv) molecular conversion by the active site on surface, (v) desorption of the product from the inner surface, (vi) diffusion of the product from the inside into the pore mouth, and (vii) diffusion of the product from the outer surface into the bulk fluid.^[83]

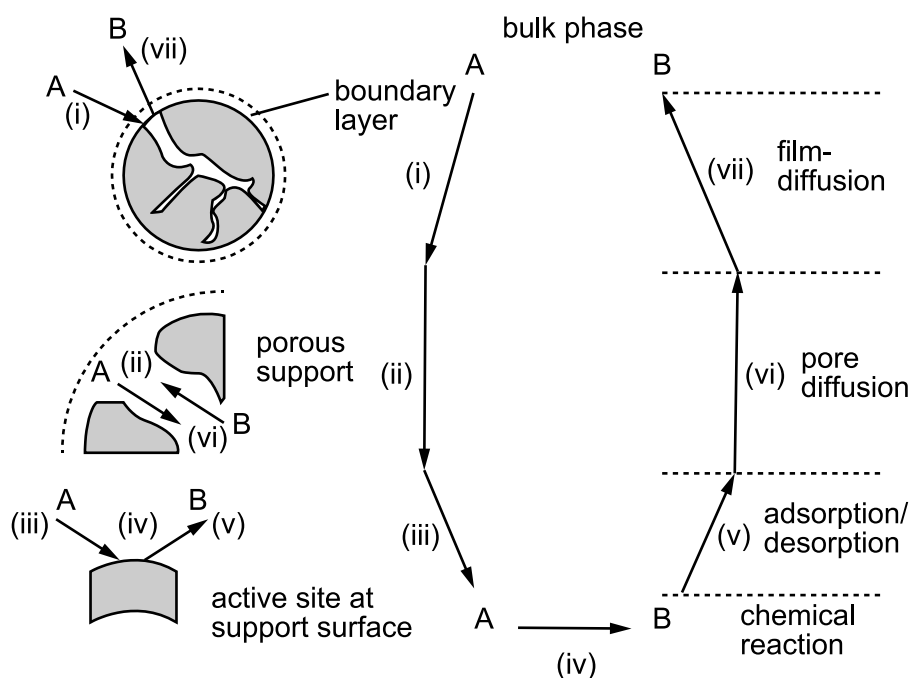


Figure 1-9. Elementary steps of a simple, heterogeneous catalytic fluid–solid reaction ($A \rightarrow B$) carried out on a porous support.

When diffusion or mass transfer (steps (i), (ii), (vi), and (vii)) are very fast, there is no resistance for the mass transfer from the bulk to the particle surface and from the surface to the active site. The concentration around the catalyst sites is considered to be the same as that of the bulk. Under these conditions, the elementary steps relating to mass transfer do not affect the overall reaction rate.

When diffusion from the bulk to the catalyst surface (steps (i) and (vii)) is slow, the external mass transfer resistance is high and significantly influences on the overall reaction rate. For a given component, the reaction rate can be defined as:

$$r_A = k_{cA}(x_A^b - x_A^s) \quad (1-6)$$

where r_A , k_{cA} , x_A^b , and x_A^s are the reaction rate, mass transfer coefficient in a binary system, mole fraction in fluid bulk, and mole fraction in equilibrium with adsorbed species of component A. k_{cA} is correlated to the Sherwood ($Sh = k_c d_p / D$), Schmidt ($Sc = \mu / \rho D$), and Reynolds ($Re = d_p u \rho / \mu$) numbers, where d_p , D_A , ρ , μ , and u are the diameter of catalyst particle, diffusion coefficient of component A, density and viscosity of the fluid, and superficial linear velocity, respectively. Another dimensionless number, Colburn “ J ” factor (J_D), is defined as follows:

$$J_D = \frac{Sh}{Re Sc^{1/3}} \quad (1-7)$$

J_D is a function of the Reynolds number. For the liquid reactants by which $55 < Re < 1500$ and $0.35 < \text{interparticle porosity } (\epsilon) < 0.75$:

$$J_D \epsilon = 0.357 Re^{-0.359} \quad (1-8)$$

and for the liquid reactants with $0.0016 < Re < 55$:

$$J_D \epsilon = 1.09 Re^{-0.67} \quad (1-9)$$

The external mass transfer resistance is also strongly depended on the flow conditions such as temperature and pressure, relating to the D_A , ρ , and μ .^[83,84]

When the internal diffusion effects are significant and there is no external mass transfer resistance, the concentration profile of component varies across the porous support for catalyst. When the

diffusion in the pore is slow, the reaction occurs only at the support surface. Then, only few catalysts localized close to the surface of support is used for the reaction, and the inside is not used. This problem was first analytically solved in 1939 by Thiele.^[85] For a first-order catalytic reaction, the reaction rate referred to the unit bulk volume of catalyst particle (V) is given by:

$$r_A/V = k_s S_v C_A \quad (1-10)$$

where k_s , S_v , and C_A are the reaction rate constant, specific surface area per unit volume, and concentration of component A. For a spherical catalyst pellet with a radius (R), the C as a function of distance from the center of support (r) can be calculated using a mass balance of which referred to the spherical shell region from r to $r + dr$ (Figure 1-10a). The integration was managed by introducing dimensionless term, Thiele modulus (Φ), as follows:

$$C_A = \frac{C_{sA}}{r \sinh(\Phi)} \sinh\left(\frac{r\Phi}{R}\right) \quad (1-11)$$

$$\Phi = R \sqrt{\frac{k_s S_v C_{sA}^{\nu-1}}{D_e}} \quad (1-12)$$

where C_{sA} , ν , and D_e are the concentration of component A at the external particle surface, reaction order, and effective diffusion coefficient, respectively. This parameter Φ represents the ratio of reactivity over diffusivity of the reactants. The lower the value of Φ is, the higher the concentration anywhere in the pore is. In other words, the diffusion is much higher than the chemical reaction. The concentration is uniform throughout the pores and is approximately equal to the C_A . The chemical reaction is much slower than the diffusion, hence, a surface reaction is the rate-determining step in the case of low Φ value. When the value of Φ is large, the chemical reaction is faster than the diffusion. The internal diffusion rate produces a characteristic concentration gradient.

To compare the relationship between diffusion and reaction limitations, the catalyst effectiveness factor (η) is defined by:

$$\eta = \frac{\text{actual reaction rate}}{\text{reaction rate assuming no diffusion resistance}} \quad (1-13)$$

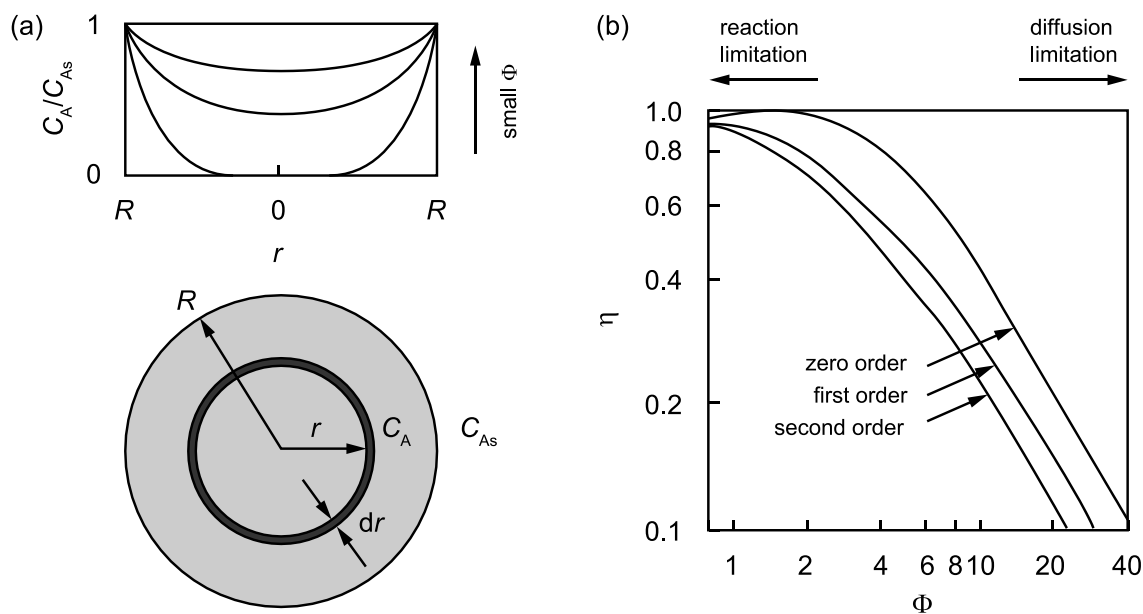


Figure 1-10. (a) Shell balance on a spherical support of catalyst. (b) η for ν th-order kinetics on a spherical catalyst supports.

The magnitude of the η ranges from 0 to 1. For a first-order reaction on a spherical supported catalyst, the effectiveness factor can be explained as follows:

$$\eta = \frac{3}{\Phi^2}(\Phi \coth(\Phi) - 1) \quad (1-14)$$

The magnitude of η ranges from 0 to 1 (Figure 1-10b). The relationship between η and Φ indicates the reaction limitation and diffusion limitation in the catalytic system at lower and larger Φ regions, respectively.^[83,86] To accelerate r_A/V in the internal-diffusion-limiting system (Equation 1-10), not only increasing S_v but also decreasing R and/or increasing D_e (Equation 1-12) are important to acquire low Φ and hence high η (Equation 1-14).

1.3.3. Inorganic Supports

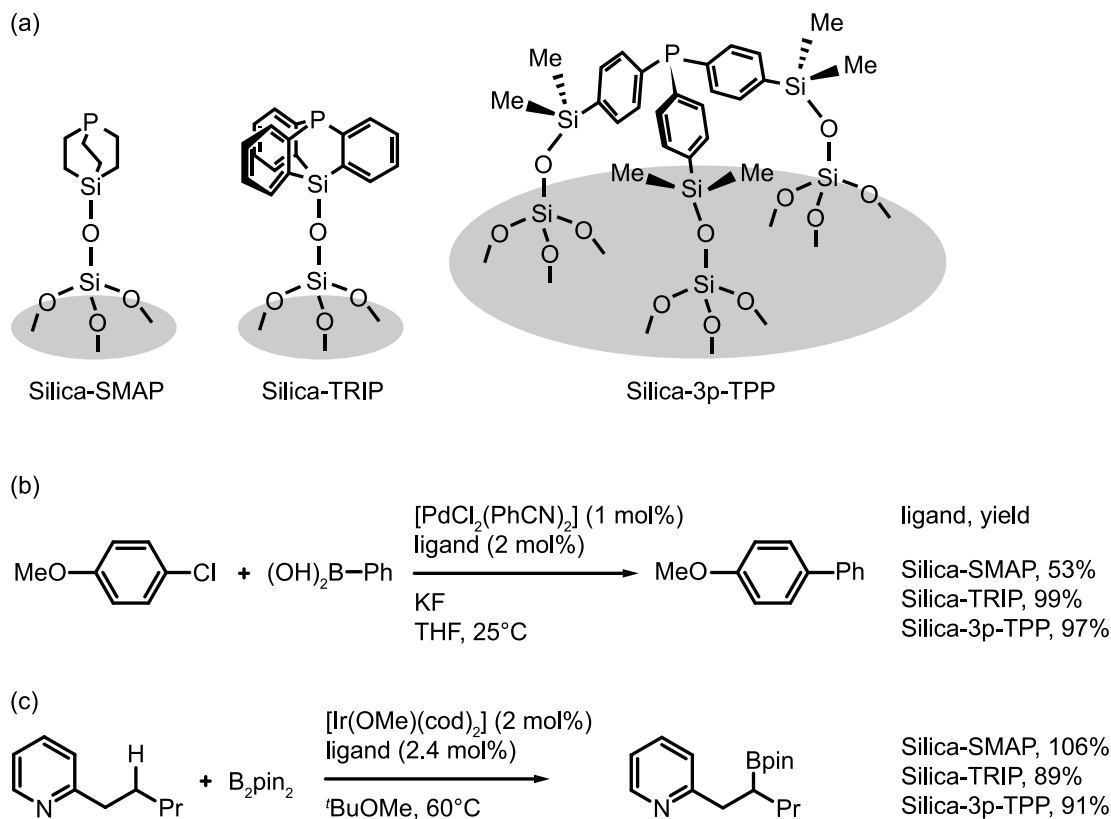
A number of inorganic materials such as silica,^[87–89] metal silicate,^[90] and metal oxide^[91–94] have been used to immobilize transition metals for fine chemical syntheses. The motivation to use these

inorganic supports basically lies on their superior thermal and physical stability, though these conventional inorganic solids suffer from their poor chemical stabilities.^[87] Among them, silica is the first choice of researchers for support of catalysts due to its wide accessibility, various processing methods, excellent thermal stability, tunable porosity and size, and availability of surface modification to introduce functional groups as ligands.^[95]

Surface-Modified Silica

The well-studied technique of surface functionalization of silica is the grafting of functional groups using a trichloro- or trialkoxy-organosilane, which are silane coupling reagents. Sawamura and co-workers attached various phosphine ligands, which had cage (Silica-SMAP^[96–98] or Silica-TRIP^[99–101]) or tripodal shape (Silica-3p-TPP),^[102,103] on silica particles (Scheme 1-2a). Owing to the highly restricted mobility, the supported phosphines could not aggregate and were site isolated from each other. These solid-support-assisted strategies enabled to formulate a coordinatively unsaturated metal complexes, and thus exhibited excellent performance in challenging chemical transformations such as Pd-catalyzed C–C cross-coupling reactions of aryl chlorides (Scheme 1-2b) and Ir-catalyzed C(sp³)–H borylation reactions (Scheme 1-2c). Specialty of these immobilized catalysts were highlighted in comparison with their homogeneous counterparts, meaning the poorer catalytic efficiencies of homogeneous catalyst systems. Unfortunately, these silica-surface modification methods sometimes underwent metal leaching, probably due to the low chemical stability of silica matrix under basic conditions.^[101]

Scheme 1-2. (a) Silica-Supported Ligands System for Site-Isolation of Phosphine and Application to (b) Aryl Chloride Cross-Coupling^a and (c) *N*-Adjacent C(sp³)-H Borylation^b



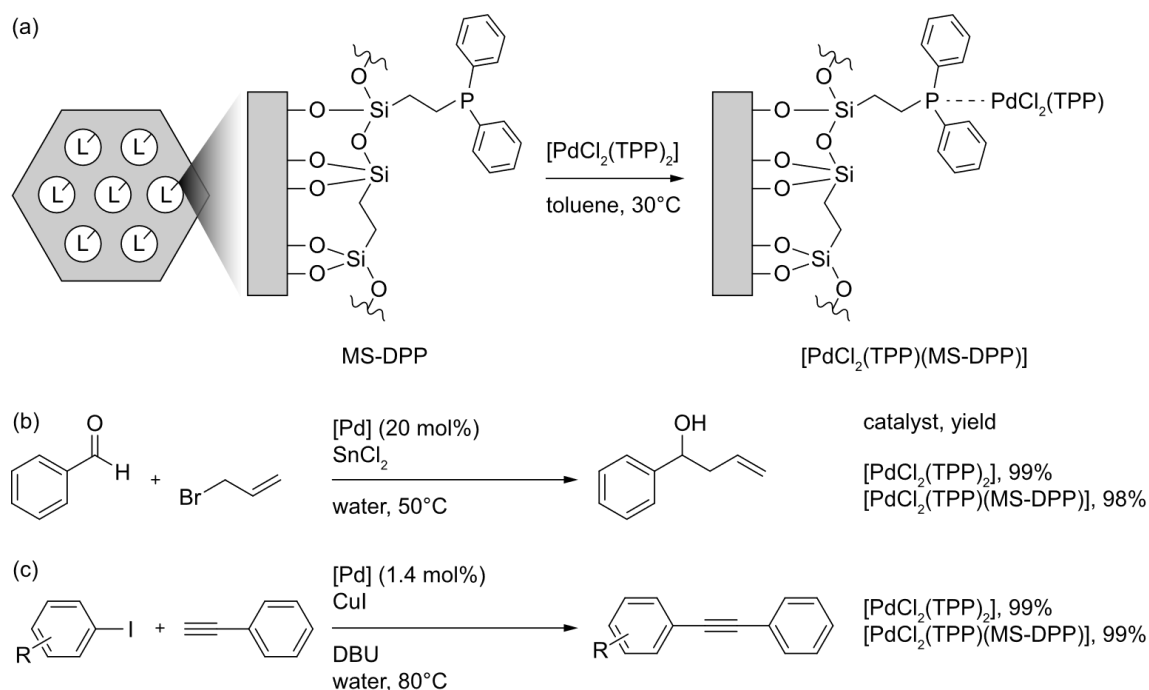
^aTHF = tetrahydrofuran. ^bB₂pin₂ = bis(pinacolato)diboron, cod = 1,5-cyclooctadiene.

Co-Condensed Silica

A highly promising approach to the preparation of silicas with organic ligands groups lies in the incorporation of functional groups in the silica matrix during its preparation via sol-gel process. This can be achieved via co-condensation of ligand-tethering silane coupling reagents with a silica precursor.^[104] These co-condensation methods have also been applied to the synthesis of organic-functionalized mesoporous silicas (MS) featuring the uniform distribution and high incorporation rate of ligands compared with surface modification methods.^[105,106] Kang and co-workers developed an ethyl-bridged MS functionalized with diphenylphosphino (MS-DPP) ligands by co-condensation methods and used as a supported ligand toward Pd^{II} (Scheme 1-3a). The combination of the MS-DPP

and $[\text{PdCl}_2(\text{TPP})_2]$ formulated an immobilized Pd catalyst showing high activity in water-medium C–C coupling reactions comparable with homogeneous $[\text{PdCl}_2(\text{TPP})_2]$ (Scheme 1-3b and c). The high activity could be attributed to the fast molecular diffusion through highly Pd-dispersed mesopores and promoted adsorption of organic reactants on ethyl-bridged MS backbone.^[106]

Scheme 1-3. (a) Schematic Diagram of Immobilization of Pd^{II} on MS-Supported Silica,^a and Application to Pd-Catalyzed (b) Barbier Reaction and (c) Sonogashira Cross-Coupling^b



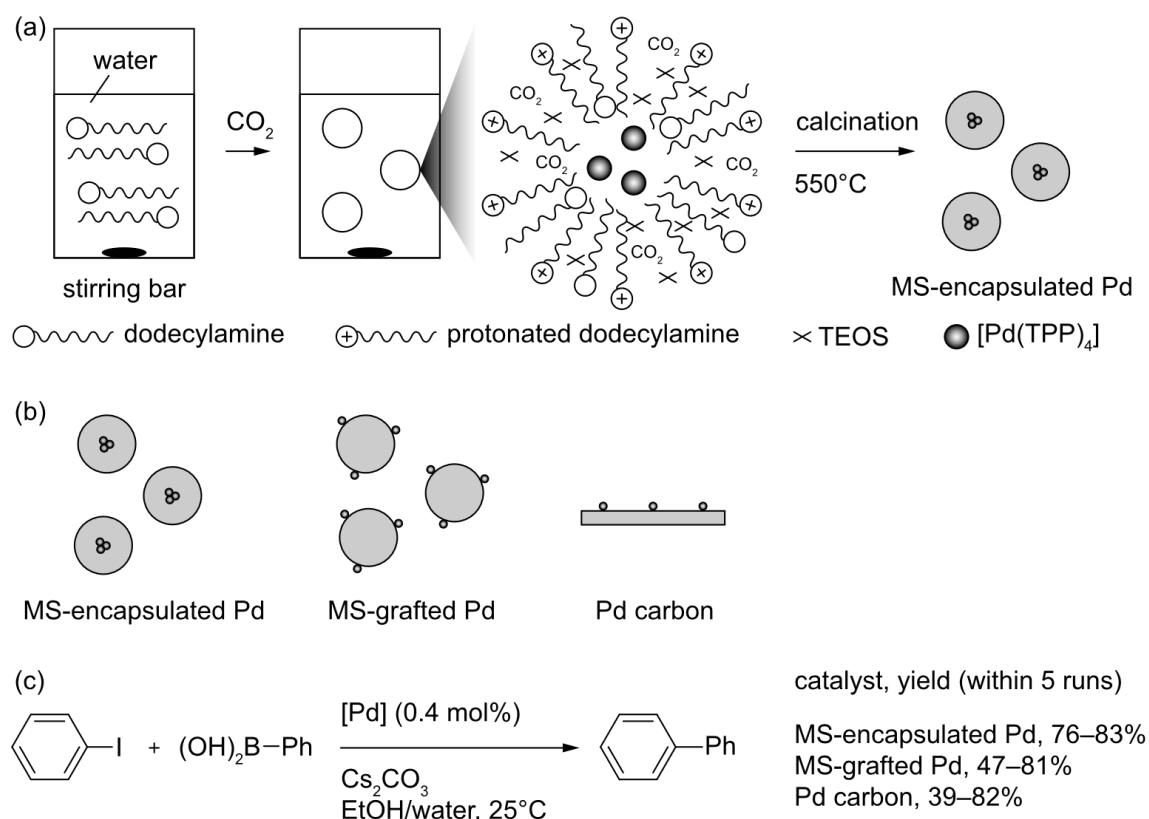
^aTPP = triphenylphosphine. ^bDBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Silica Capsules

Physical encapsulation of transition metals within silica supports is often used because it ideally requires no modification of organic ligands and the active species can behave like a homogeneous counterparts.^[104] Guo and co-workers developed an MS-encapsulated Pd prepared via compressed- CO_2 -in-water microemulsion in the presence of cationic surfactant (Scheme 1-4a). $[\text{Pd}(\text{TPP})_4]$ was

encapsulated inside the spherical MS and formed Pd nanoclusters with the size of 2.8 nm through one-pot approach. The MS-encapsulated Pd showed higher catalytic durability in Suzuki coupling reaction than those of surface-supported Pd (MS-grafted Pd) and Pd carbon (Scheme 1-4b and c). A proof-of-concepts experiment was conducted by pore blocking treatment of MS-encapsulated Pd by *n*-octyl groups and demonstrated deteriorated catalytic efficiency, meaning almost all Pd nanoclusters were entrapped inside the MS matrix.^[107]

Scheme 1-4. (a) Proposed Formation Mechanism of MS-Encapsulated Pd,^a (b) Comparison of MS-Supported Pd, and (c) Application to Suzuki-Miyaura Cross-Coupling



^aTEOS = tetraethyl orthosilicate.

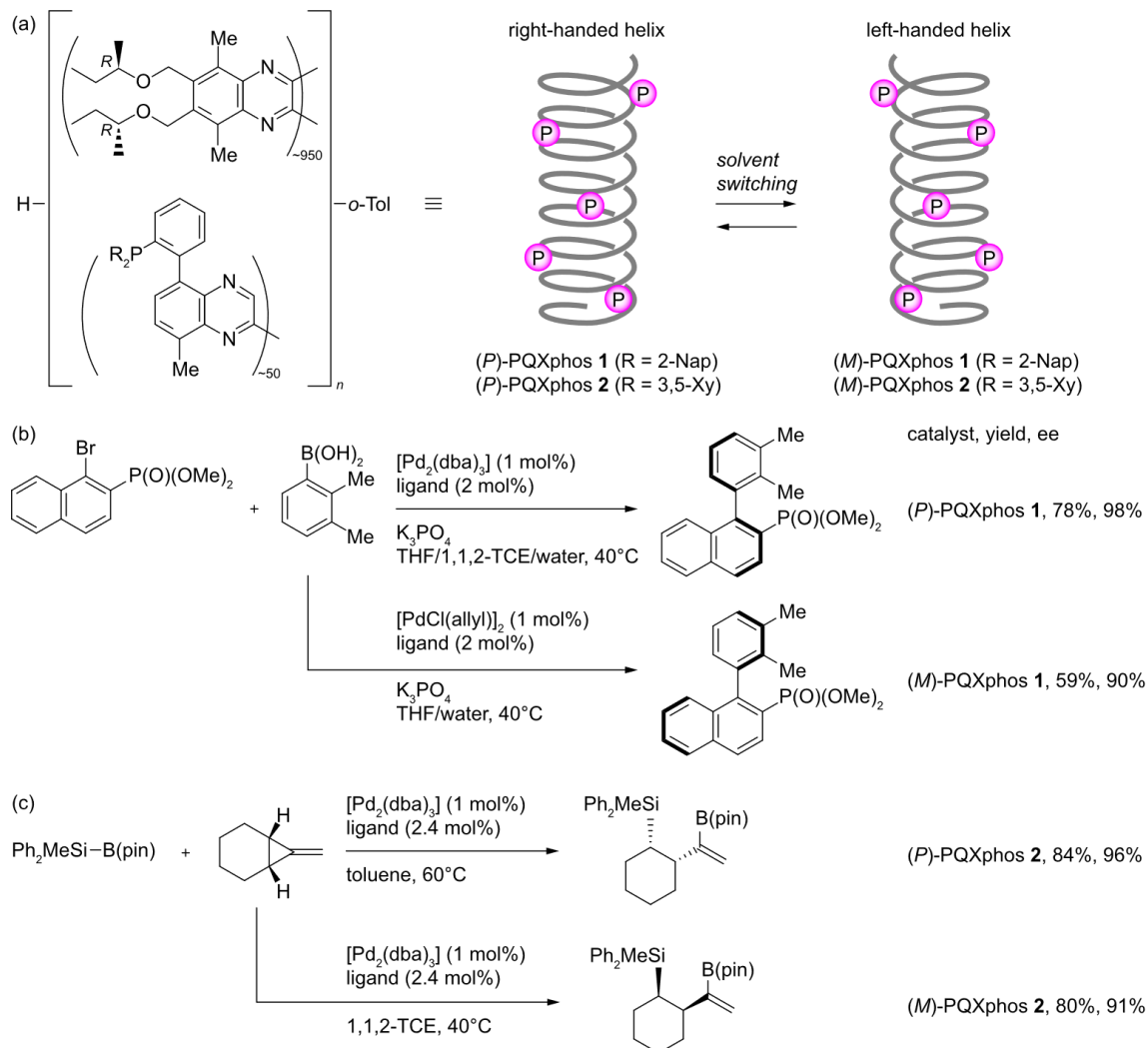
1.3.4. Organic Supports

The immobilization of transition-metal catalysts on organic scaffold offers a number of advantages over inorganic ones in terms of functionalization and variety of backbone. Especially, organic polymers have driven the progress of immobilized catalysts featuring their ease of recovery, high chemical stability, and low costs.^[108,109] Similar to the inorganic supports, organic polymers also adopt the incorporation of functional groups via surface-grafting, co-polymerization, or encapsulation methods. To date, various types of organic supports for transition metals have been developed such as linear polymers,^[110–113] cross-linked polymers (resins),^[114–117] polymer capsules,^[118–121] self-assembly,^[122] dendrimers,^[123,124] and covalent organic frameworks (COFs).^[125–127] Some of these have demonstrated excellent catalytic performance compared with those of inorganic-support or homogeneous catalysts.

Linear Polymer

Suginome and co-workers have reported the elegant polymer-supported chiral phosphine ligands based on poly(quinoxaline-2,3-diyl)-type helical polymers (PQXphos) with reversible and perfect switching properties of helical chirality by solvent effect (Scheme 1-5a).^[110–113] The PQXphos were prepared by copolymerization of achiral or chiral phosphine ligands and spacer co-monomers initiated by chiral or achiral organometallic initiators, respectively. The inversion of helical chirality of PQXphos provided a unique reaction platform for Pd-catalyzed asymmetric chemical transformations to obtain different enantiomers from a single catalyst (Scheme 1-5b and c).^[112,113] Moreover, the PQXphos acted as highly efficient chiral ligand/catalysts with high TOF and enantiomeric excess (ee) comparable with or better than the chiral homogeneous catalysts. The helical structure of PQXphos might attribute to “long-range steric effect” which would make coordinatively unsaturated and hence catalytically active Pd.

Scheme 1-5. (a) PQXphos with Switchable Helical Chirality by Solvent and Application to Pd-Catalyzed (b) Asymmetric Suzuki-Miyaura Cross-Coupling^a and (c) Silaboration^a



^a1,1,2-TCE = 1,1,2-trichloroethane, dba = dibenzylideneacetone

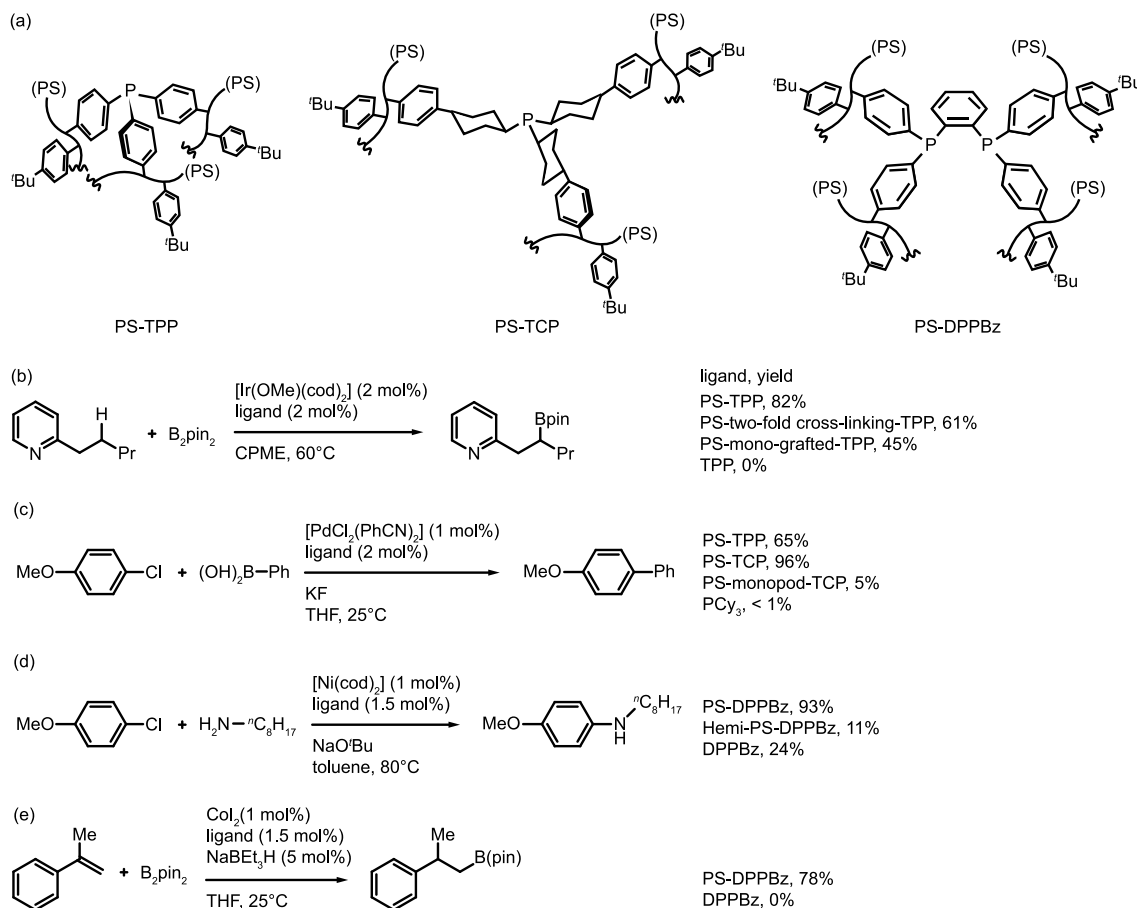
Cross-Linked Polymer

Following the development of ion exchange resins based on suspension polymerization during the 1950s, many key large-scale chemical processes have been established, particularly employing polystyrene (PS)-supported sulfonic acid resins as the immobilized catalysts. The functional cross-linked polymer can be prepared by copolymerization of matrix, functional, and multi-vinyl (cross-

linking) monomers to give intrinsic insolubility in reaction media.^[128] The incorporated functional groups have generally significant mobility even in the cross-linking network and exhibit similar to those of their homogeneous counterparts. In many cases, this flexibility causes unfavorable steric effects on the catalytic environment, resulting in reduced catalyst efficiency.

Sawamura and co-workers developed a series of multi-fold cross-linking phosphine ligands, mono-phosphine (PS-TPP or PS-TCP) and bis-phosphine (PS-DPPBz), by a suspension polymerization of styrene monomers (Scheme 1-6a) to give polymeric beads.^[114–117] The resulting cross-linked polystyrene had coordination centers at cross-linking points and thus enabled effective site-isolation of phosphine ligands from each other. These multi-fold cross-linking strategies around phosphine ligands favored the formulation of coordinatively unsaturated transition-metal complexes. In fact, excellent catalytic activities were highlighted in challenging transformations such as C–C or C–N cross-couplings, and C(sp³)–H borylations catalyzed by Pd, Ir, Rh,^[114,115,117] and also first-row transition metals (Scheme 1-6b–e).^[116] The importance of multi-fold cross-linking around these unique ligands were demonstrated by comparison with their homogeneous counterparts and polymers incorporating more flexible phosphine ligands. The cross-linked polymer endured the Pd-catalyzed C–N cross-coupling under harsh basic conditions without metal leaching and cleavage of ligand groups, while inorganic counterparts failed.^[114]

Scheme 1-6. (a) Multi-Fold Cross-Linking Phosphine Ligands Supported Copolymerized in Polystyrene and Application to (b) C(sp³)-H Borylation,^a (c) C-C or (d) C-N Cross-Couplings, and (e) C(sp²)-H Borylation Catalyzed by Transition Metals



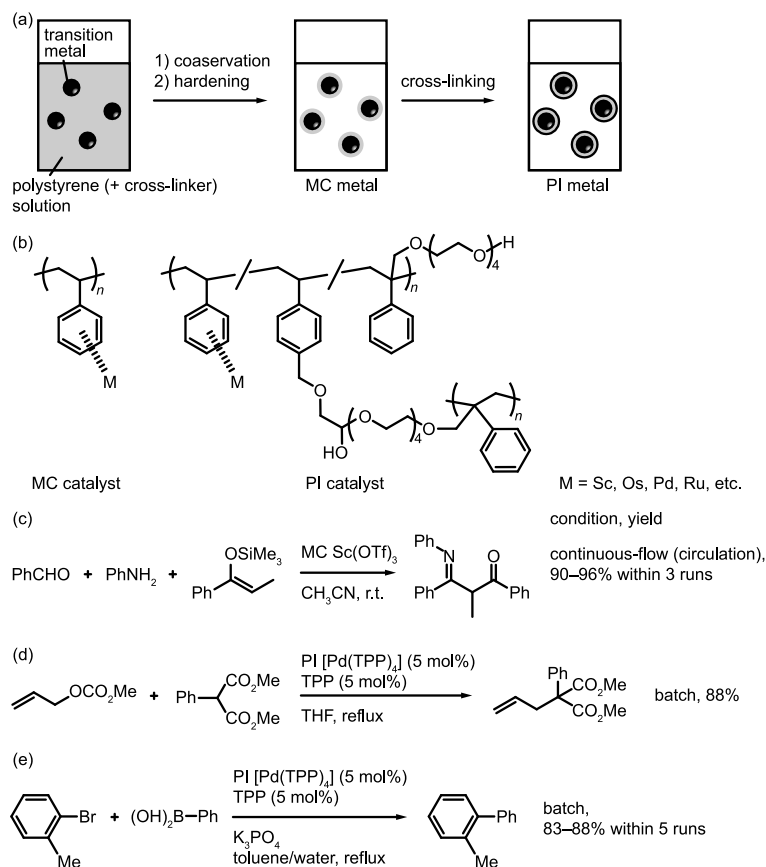
^aCPME = cyclopentyl methyl ether

Polymer Capsules

Microencapsulation techniques, which have been used for coating and isolating pharmaceuticals and fragrance, were successfully applied to immobilized catalyst systems.^[129] Kobayashi and co-workers developed immobilized transition metals enveloped by polystyrene thin films, where physical entrapment and π -d interaction between the benzene rings of the polystyrene and the vacant orbitals of the metals were featured.^[118–121] The microencapsulated (MC) metals were prepared by

“coaservation” in a dense polystyrene solution^[130] and obtained as hard capsules after shrinking treated by poor solvent (Scheme 1-7a). The benzene rings of the polystyrene were essential to immobilize the core metals, which was supported by control experiments using polybutadiene or polyethylene (immobilized amounts of 43 and 0% for polybutadiene and polyethylene compared with that (100%) of polystyrene).^[118] The obtained MC metals could be stored at room temperature for more than several months. Additionally, the polymer shell around the MC metals could be cross-linked to afford the more stable PI metals using epoxide-containing co-polymer (Scheme 1-7b). These MC^[118,119] and PI^[120,121] metals showed high activities against high durability and recyclability without any leaching of the metals in continuous-flow or batch reactions (Scheme 1-7c–e).

Scheme 1-7. (a) Microencapsulation of Transition Metals for (b) MC and PI Catalysts, and Application to (c) Mannich-Type Reaction, (d) Allylic Substitution, and (e) Suzuki-Miyaura Cross-Coupling under Continuous-Flow or Batch Conditions

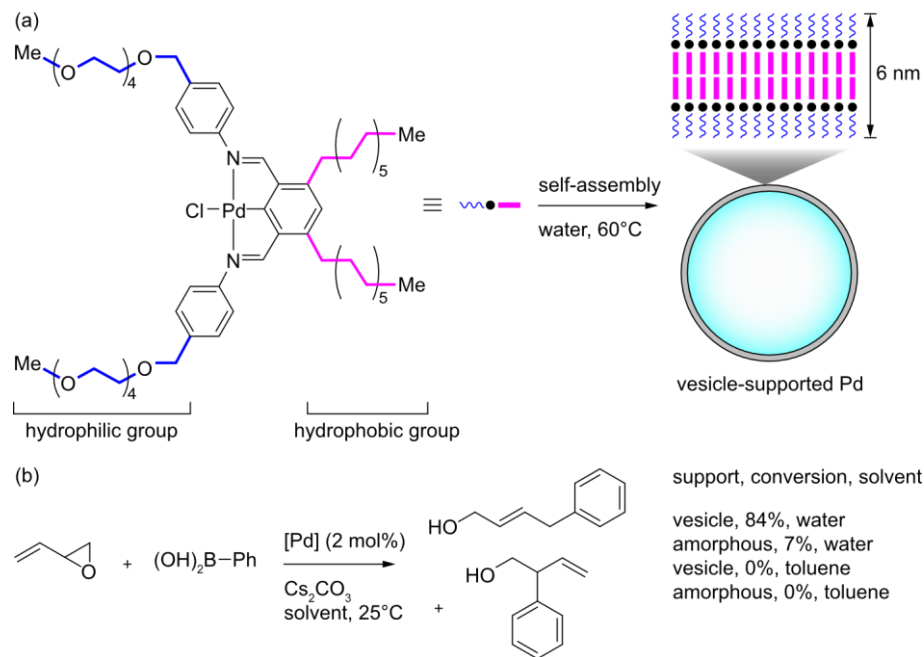


Self-Assembly

Biological membranes are known to play important roles in the control of life-related molecular functions (e.g. active/passive transport, diffusion, filtration, selective permeation, etc.). Lipid bilayer vesicles, that is liposomes, are small aggregates of amphipathic molecules with both hydrophilic and hydrophobic groups. If molecular catalysts with low activity self-assembles to form vesicles and would acquire the higher catalytic activity concentrating reactants and catalysts in the hydrophobic interior in a certain reaction media.^[131]

Uozumi and co-workers reported the formation of a vesicle from an amphipathic pincer Pd complex through self-assembly and application to Pd-catalyzed C–C bond formations under ambient conditions (Scheme 1-8a).^[122] The pincer Pd complex was treated with water at 60°C then cooled to self-assemble into a vesicle with size and membrane thickness of 550 and 6 nm, respectively. The obtained vesicle adopted the molecular diffusion of hydrophobic molecules into/out of the bilayer region confirmed observing fluorescent molecules. By centrifugation and decantation, the vesicle-supported catalyst could be recovered and employed to Pd-catalyzed oxirane ring opening with phenylboronic acid in aqueous media (Scheme 1-8b). The vesicle-supported Pd showed significantly higher catalytic activity than that of amorphous powder. Interestingly, homogeneous catalyst systems using the vesicle or the amorphous powder in toluene did not give any products because both supports disassembled and dissolved in the reaction mixture. Thus, the self-concentration of organic reactants in the hydrophobic region and localization of Pd complex in a very thin bilayer membrane provided the fully accelerated molecular diffusion and catalytic reactions in the aqueous media.

Scheme 1-8. (a) Formation of Vesicle by Self-Assembly of Pincer Pd Complex and (b) Application to Oxirane Ring Opening with Phenylboronic Acid



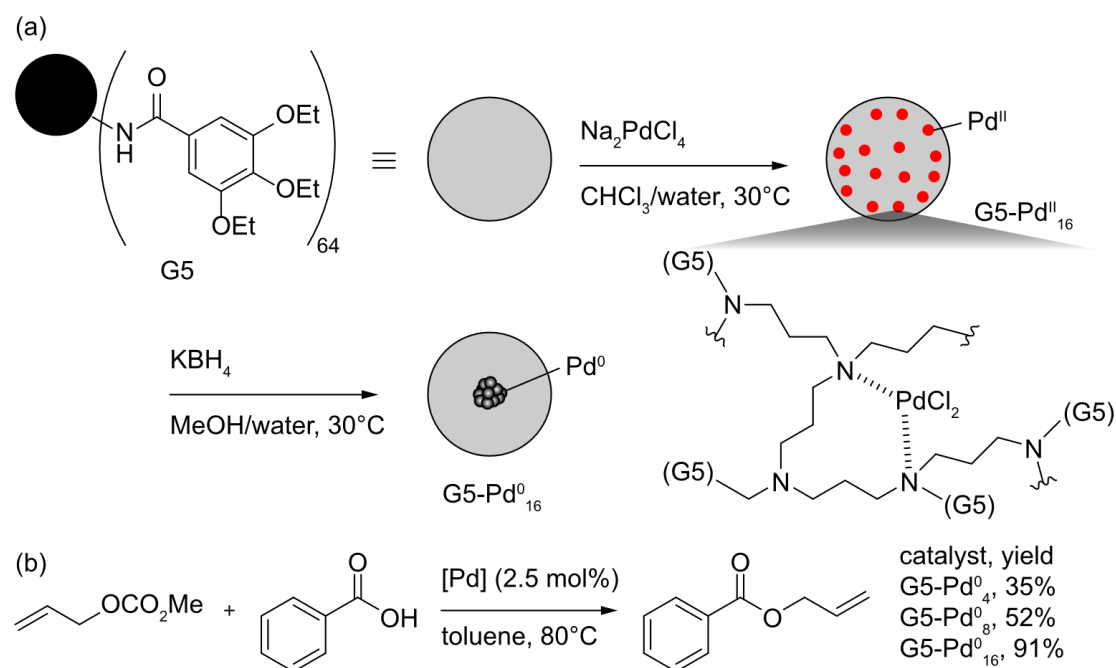
Dendrimer

Dendrimers are spherical organic polymers which have well-regulated units branched from the core to the periphery. Their chemical and physical properties can be adjusted by changing the units. The preparation of well-defined immobilized catalysts has been realized adopting dendrimers as supports.^[132] A considerable number of catalyst systems including dendrimers have been reported in the past few years, where ease of recycling by precipitation and "dendritic effect" were emphasized. This dendritic effects on catalytic performance can be seen in cooperative effects due to the high local catalyst concentration and site isolation in periphery-functionalized and core-functionalized dendrimers, respectively.^[133]

Kaneda and co-workers precisely controlled the number of atoms of Pd nanoclusters and investigated their electronic, geometric, and catalytic properties using poly(propylene imine)-based dendrimers as supports.^[123,124] The nanoclusters, Pd₄, Pd₈, and Pd₁₆, were prepared using the 5th-

generation dendrimers whose periphery were functionalized with 3,4,5-triethoxybenzamide groups (G5). The loading amount of Pd^{II} was tuned based on the amount of Pd source to give the desired number of Pd atoms in one G5. The Pd K-edge X-ray absorption fine structure (XAFS) confirmed that the G5-supported Pd^{II} (G5-Pd^{II}) are ligated by two Cl and two N atoms of the dendritic branch. After reduction of G5-Pd^{II} into G5-supported Pd⁰ (G5-Pd⁰), the coordination number of Pd–N did not change while Pd–Pd newly generated, suggesting that Pd⁰ nanoclusters formed and located within the voids of G5 (Scheme 1-9a). A series of spectroscopic analyses using Pd L₃-edge X-ray absorption near edge structure (XANES) and Fourier transmission (FT)-IR spectra demonstrated that the number of 4d electrons, energy level of the 4d band, and number of available surface sites of Pd nanoclusters increased with their size, which were unusual compared with previous reports.^[134] Indeed, the catalytic activities of G5-Pd⁰ increased with increasing the size of Pd nanoclusters during the allylic substitution (Scheme 1-9b).

Scheme 1-9. (a) Tailor-Made Synthesis of Pd Clusters in 5th-Generation Poly(Propylene Imine) Dendrimer Functionalized with 3,4,5-Triethoxybenzamide Groups and (b) Effect of Number of Atoms in Pd Nanoclusters on Allylic Substitution

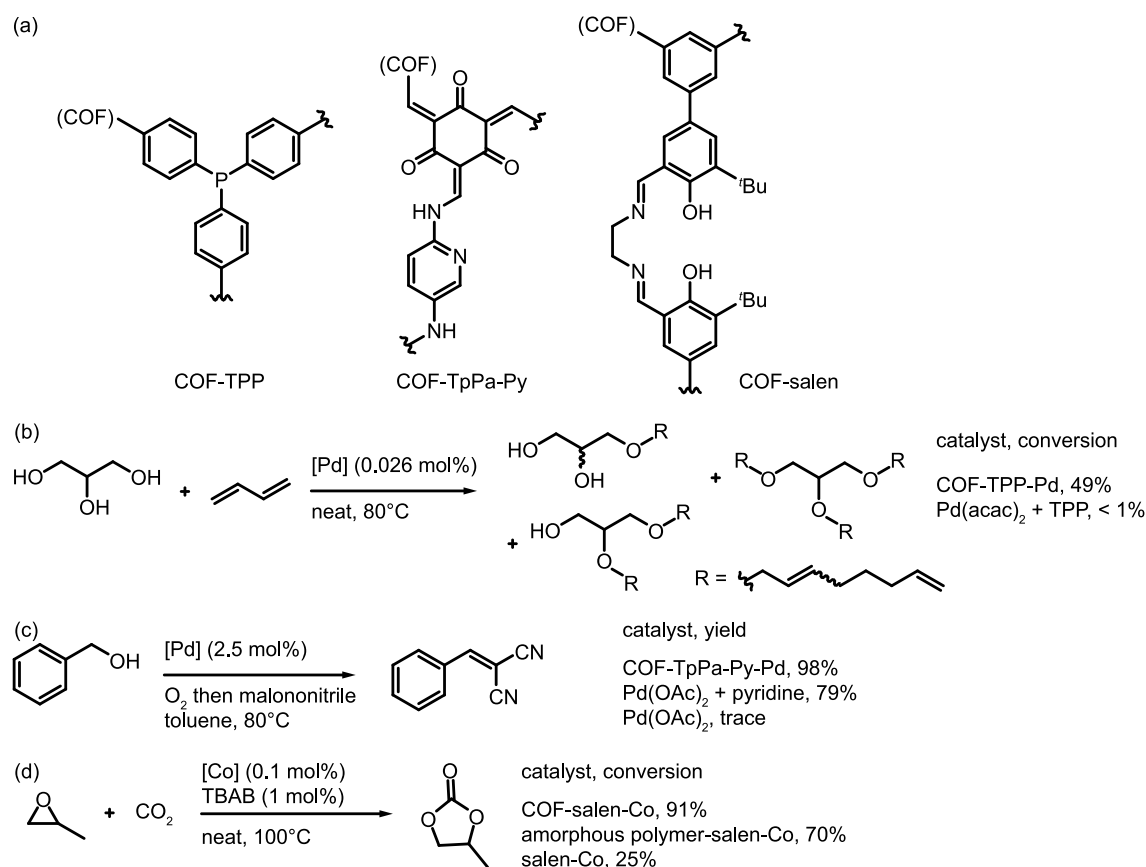


Covalent-organic framework (COF)

Covalent-organic frameworks (COFs) are a class of porous and crystalline materials, with highly ordered organic building blocks and discrete micropores and have attracted much attentions due to their potential applications such as gas storage,^[135] environmental remediation,^[136] catalysis,^[125–127] and so on. A distinct feature of COFs is that their structure and properties can be perfectly tuned by careful selection of building components. This unique feature is very attractive for designing multifunctional catalysts in view of the ability to precisely control the functionality, density, and spatial arrangement of active centers. Due to their crystalline solid architectures, recycling of catalysts can be achieved using simple filtration or decantation.

The representative researches were selected here to show the unique reaction platform of COFs in transition-metal catalyses.^[125–127] The incorporations of ligands into the porous scaffold of COFs were realized mainly by in-situ generation of ligand moieties via substitution or condensation reaction of the building components. The X-ray diffraction (XRD) patterns of the COF-supported ligands showed relatively broad peaks attributable to partly amorphous-ordering. Owing to the presence of microporous network with the size of ~1.9 nm, the COFs had large surface areas of ~1646 m² g⁻¹. These COF-supported ligand shows high selectivity in formation of coordinatively unsaturated metals, which highlighted the site-isolated reaction environment through the well-regulated porous network (Scheme 1-10a). Indeed, the COF-supported ligand-metal systems had significantly higher catalytic activities than those of their homogeneous counterparts and pertaining amorphous polymer (Scheme 1-10b–d).

Scheme 1-10. (a) Ligand-Containing COFs for Transition Metals and Applications to (b) Telomerization,^a (c) Cascade Oxidation-Knoevenagel Reaction, and (d) Cycloaddition of Epoxide and CO₂^b



^aacac = acetylacetonate. ^bTBAB = tetrabutylammonium bromide.

1.3.5. Metal-Organic Hybrid Supports

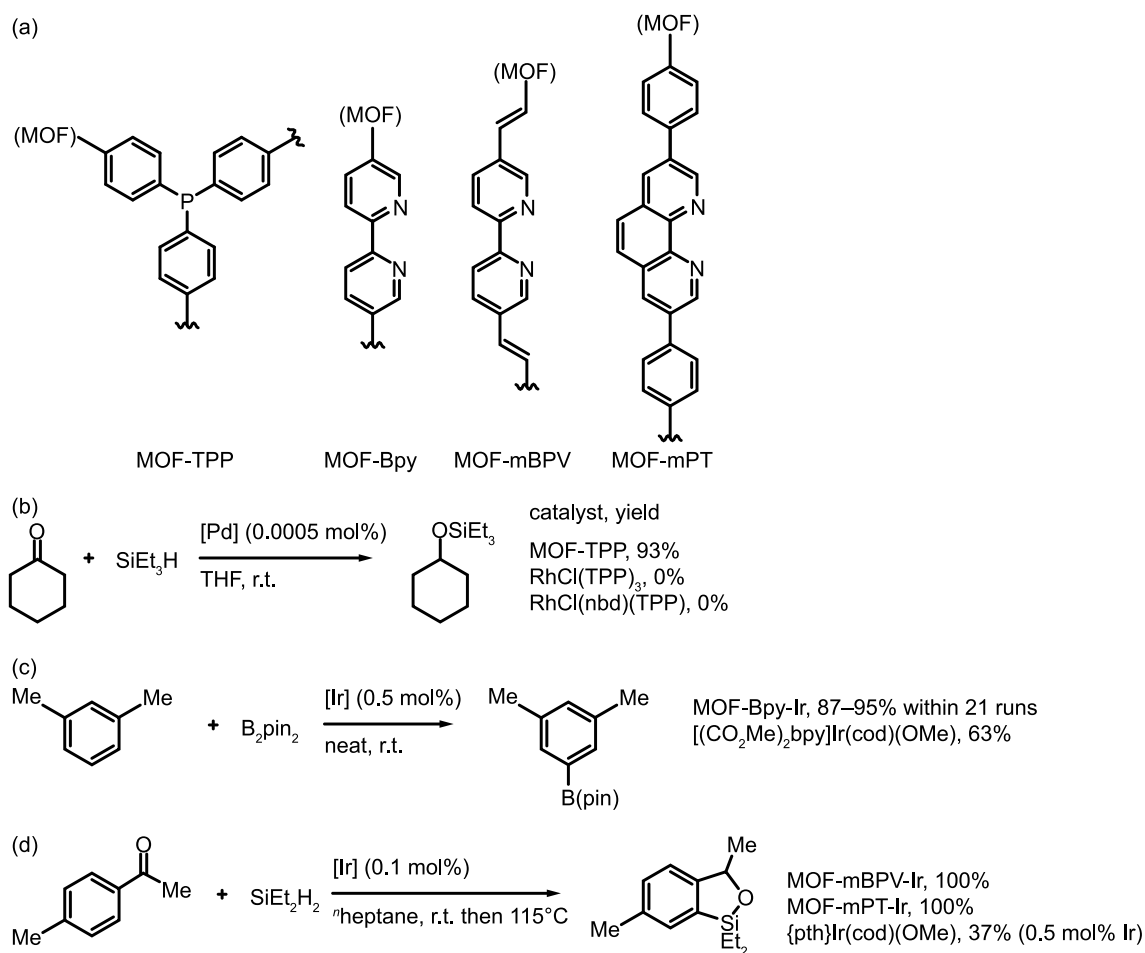
Metal-Organic Framework (MOF)

Consisting of periodically repeating inorganic nodes (i.e. metals) and organic linkers, metal-organic frameworks (MOFs) represent a class of porous molecular solids with well-defined pores and channels. To date, MOFs have demonstrated their applicability to a broad spectrum such as gas storage,^[137] gas separation,^[138] nano medicine,^[139] and catalysis.^[140–143] It should be noted that MOFs provides a unique platform where single-site catalytic centers are effectively formulated through the

intrinsic pores via a limitless combination of metal centers and organic linkers. The uniform distribution of the regulated reaction space also facilitates the identification of catalytic center and reaction mechanisms. Also, catalytically favorable site isolation of metal centers in MOFs can be easily designed compared with homogeneous systems.^[140] Due to their crystalline solid architectures, recycling of catalysts can be achieved using simple filtration or decantation.

Among the MOFs scaffolds, the Zr MOFs with the Zr-oxo secondary building units such as UiO have been most studied due to their structural stability under high temperature ($\sim 350^{\circ}\text{C}$) and a broad range of solvents and reagents.^[144] Sawano and co-workers designed a TPP-based tricarboxylic acid and synthesized a porous TPP-based MOF (MOF-TPP) under solvothermal conditions (Scheme 1-11a).^[141] Metalation of the MOF-TPP with different metal precursors afforded mono-ligated metal-phosphine complexes which facilitates the coordinatively unsaturation of metals. As for N-containing ligand system, Lin and co-workers developed a series of bpy- or phenanthryl-based MOFs (MOF-Bpy, MOF-mBPV, and MOF-mPT) using different length or rigidity of organic linkers (Scheme 1-11a).^[142,143] Mixing spacer linkers in the preparation of the MOFs network (MOF-mBPV and MOF-mPT), much larger open channels were created and these facilitated the mass transport of reactants through the MOF channels with the size of ~ 1.2 nm and surface areas of ~ 3834 m² g⁻¹. In both studies, the MOF-supported ligand system showed significantly high catalytic activities and durabilities compared with homogeneous analogues in hydrosilylation, C-H arylation, and hydrosilylation/intramolecular ortho-silylation (Scheme 1-11b-d). The positive effects of MOF supports were likely due to site isolation of metal centers which prevents any intermolecular deactivation pathways.

Scheme 1-11. (a) Ligand-Containing MOFs for Transition Metals and Applications to (b) Hydrosilylation,^a (c) C–H Borylation, and (d) Tandem Hydrosilylation/Intramolecular *Ortho*-Silylation^b



^anbd = norbornadiene. ^bpth = 3,8- bis(4-methoxycarbonylphenyl)phenanthroline.

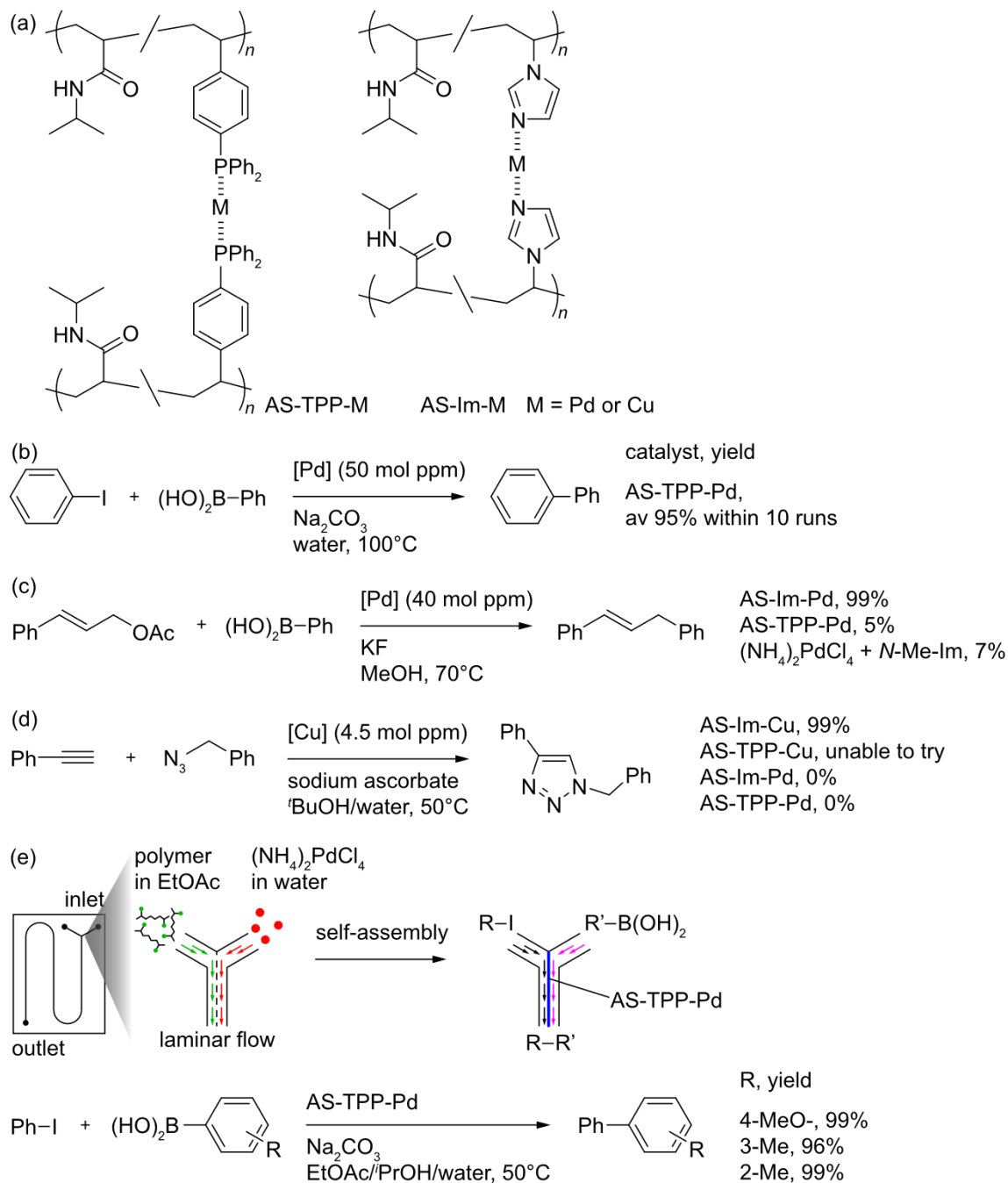
Self-Assembly

Uozumi, Yamada, and co-workers have utilized the metal-directed self-assembly process for networked supramolecular complexes.^[145–148] The amphipathic polyacrylamides bearing TPP or Im moieties were cross-linked via coordination with metal species (M = Pd, Cu) to give insoluble and globular aggregates (AS-TPP-M and AS-Im-M) (Scheme 1-12a). Owing to the amphipathic polymer chain and cross-linking between ligands and metals, the AS-TPP-Pd showed high catalytic efficiencies

in water and organic solvents (THF, toluene, dimethyl sulfoxide (DMF), 1,4-dioxane, 2-butanone, *t*BuOH, and EtOH/Me₂O) probably due to the swelling for acceleration of the molecular diffusion of reactants.^[145] It is noteworthy that the self-assembled polymeric catalysts completed the Pd-catalyzed cross-couplings (Scheme 1-12b,c)^[145,147] and Cu-catalyzed azide-alkyne cycloaddition (Scheme 1-12d)^[148] with low catalyst loading (4.5–50 mol ppm). These amazingly durable activity was highlighted in comparison with the homogeneous catalyst system.

Combining the self-assembling complexation with microfluidic techniques, catalytic membrane reactors were developed for application to continuous-flow cross-coupling reactions (Scheme 1-12e). Co-flowing the polymer-supported TPP in EtOAc and (NH₄)₂PdCl₄ in water under laminar flow condition, self-assembled membrane with thickness of 1.3 μm was in-situ afforded at the interface of the two parallel layers flowing the microchannel. Thanks to the thin catalytic membrane and amphipathic polymer scaffold, the instantaneous transformations via Suzuki-Miyaura cross-coupling reactions were realized under continuous-flow conditions within only 4 sec residence time.

Scheme 1-12. (a) Ligand-Metal Self-Assembled Polymers and Application to (b) Aryl-Aryl Cross-Coupling, (c) Aryl-Allyl Cross-Coupling, and, (d) Azide-Alkyne Cycloaddition, and (e) Formation of AS-TPP-Pd Membrane in a Microchannel for Continuous-Flow Cross-Coupling



1.4 Porous Polymer

1.4.1. Classification of Pores

A porous material is a general term for a solid which has pores with the size from nanometers to micrometers, leading to high porosity and larger specific surface area. According to the International Union of Pure and Applied Chemistry (IUPAC), pore sizes of < 2 nm, 2–50 nm, and > 50 nm are defined as micropore, mesopore, and macropore, respectively (Table 1-8).^[149] In addition to the porous properties, the chemical properties of pore surface are of interest for desired function via synergistic effects. In this sense, porous polymers have been well developed and attracted much attention for their ability to incorporate targeted and/or multiple chemical functionalities into the porous framework by bottom-up or post-synthesis modification approaches as well as high porosity such as zeolites or activated carbon (Table 1-8).^[150,151] Nowadays, the usefulness of the porous polymers can be seen in applications to separation membranes,^[152] batteries,^[153,154] tissue engineering,^[155] and catalysts.^[150] The importance of porous materials is increasing in response to the pursuit of comfort in daily life and the high technology orientation.

Table 1-8. Classification of Pore Size

	micropore	mesopore	macropore
pore size (nm)	< 2	2–50	> 50
representative	COF, porous organic	hyper-cross-linked	macroporous beads,
polymers	polymer	polymer	macroporous monolith

Pores can be also classified based on their accessibility to external fluids. The pores totally isolated from their neighbors are described as “closed pores” (Figure 1-11a), and influence the macroscopic properties such as bulk density, mechanical strength, and thermal conductivity, but are inactive in the surface events. The pores communicating with the external fluids are called “open pores” (Figure

1-11b–f) and provide a route for surrounding molecules and ions to permeate. In some cases, only one end of pore is open (Figure 1-11b and f) which means “dead pores.” while others may be open at two ends, i.e. “through pores” (Figure 1-11e). Pores are also be classified according to their shapes: cylindrical (Figure 1-11c and f), ink-bottle (Figure 1-11b), funnel (Figure 1-11d) or slit.^[156]

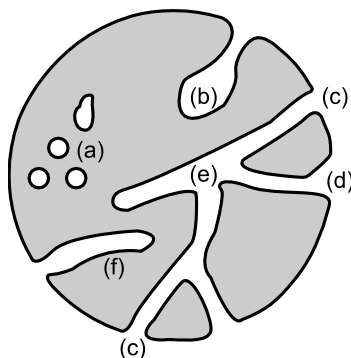


Figure 1-11. Schematic illustration of pores classification according to their availability to surroundings; (a) closed pores, (b), (f) pores open only at one end, (c), (d), (g) open pores, and (e) open at two ends (through) pores.

1.4.2. Measuring Method of Porous Properties

For researchers in materials chemistry, the porous properties such as a (average) pore size and its distribution, porosity, and specific surface area should be key parameters to display the desired performances of porous materials. There exist various approaches to estimate these porous properties of materials. Historically, gas (e.g. He, H₂O, N₂, or CO₂) adsorption^[157] and Hg intrusion porosimetry^[158] have shown potentials in estimation of these porous properties for micro–mesopores and meso–macropores, respectively. The details of these analytical methods will be explained in the later section. Other approaches have also accompanied based on small angle X-ray scattering (SAXS),^[159,160] permporometry,^[161] and laser,^[162] X-ray,^[163] or electron^[164] microtomography to obtain information of pores in accordance with their size scales and conditions (Table 1-9).

Table 1-9. Measuring Methods of Porous Properties

	gas adsorption	Hg intrusion	SAXS	permporometry	micro-tomography
applicable	pore	< 30 ^a	2–300	10 ⁰ –10 ^{3b}	10 ⁰ –10 ^{5c}
size (nm)					
main information	porosity,	porosity,	porosity,	porosity,	porosity,
	surface area,	size distribution	pore structure,	size distribution	pore structure,
	size distribution,		surface area,		surface area,
	pore structure		size distribution		size distribution
condition	dry, high pressure,	dry, high pressure	dry or wet	dry or wet,	dry or wet
	low temperature ^a			high pressure	

^aDependent on the probe molecules and calculation models used. ^bDependent on the fluid used. ^cDependent on the wavelength of probe used.

Hg Intrusion Porosimetry

Hg intrusion into pores requires high pressure to liquid Hg, which is governed by the Young-Laplace and Washburn equations. The mean pore diameter (d) of cylindrical one can be described by

the pressure difference (ΔP) between the pressure in the Hg and in gas phase, surface tension of Hg (γ_{Hg}), and contact angle of Hg on the pore surface (θ_c):

$$d = -\frac{4\gamma_{\text{Hg}}\cos\theta}{\Delta P} \quad (1-15)$$

Thus, the pore volume (V_p) and d can be determined by the degree of Hg penetration as a function of ΔP (applied pressure). In general, assumptions made by Ritter and Drake are used; γ_{Hg} and θ_c are 480 mN m^{-2} and 140° , respectively.^[165] Of course, these physical parameters should depend on the surface state of the porous material and the conditions such as atmosphere, but the estimation by Ritter and Drake is considered reasonable.

In the Hg intrusion experiments, the sample was put in chamber and pressure vessel followed by evacuation and filling with Hg. Under atmospheric pressure, Hg does not enter the pores on the surface of the sample because it hardly wet the most of materials. When pressure is applied to the vessel, Hg starts to intrude into the pores with the size of d which are correlated to the ΔP (Equation 1-15). As the applied pressure increases, the smaller pores become filled with Hg in order from the larger pores. Using penetrometer, the accumulative V_p of the sample can be calculated at each d . The wide range of Hg intrusion porosimetry (typically 3.5–1000 nm or more) in d is useful compared with that of gas adsorption methods applicable to pores with the size of $< 30 \text{ nm}$.^[157]

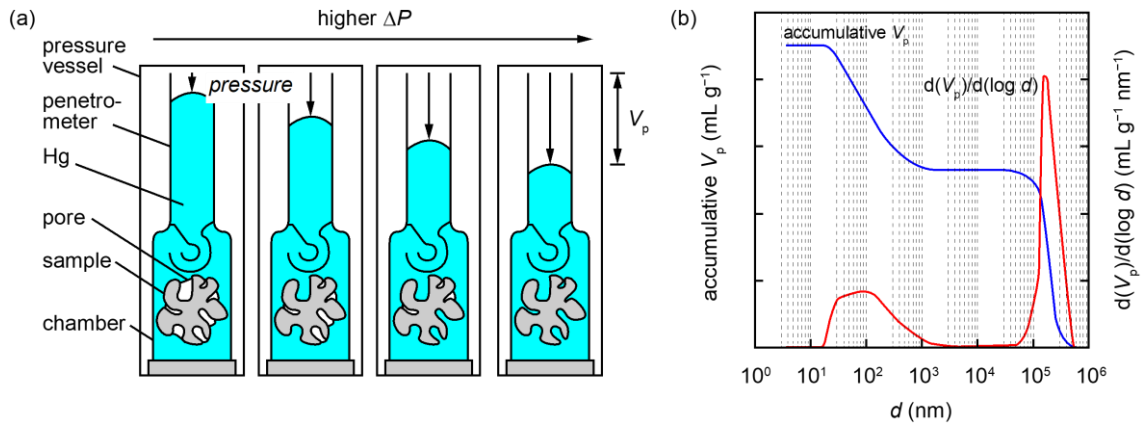


Figure 1-12. (a) Schematic illustration of of Hg intrusion porosimetry and (b) representative pore size distribution.

Gas Adsorption Porosimetry

Molecular adsorption theories have been used to understand the solid surfaces of porous materials. Gas adsorption porosimetry is useful owing to its non-destructive nature for surface chemistry. For example, He, H₂O, N₂, and CO₂ have been properly used as probe molecules for the analysis of micro–mesoporous structure in accordance with the characteristic of samples (Table 1-10).

Table 1-10. Molecular Probe and Adsorption Conditions for Gas Adsorption Porosimetry

	He	H ₂ O	N ₂	CO ₂
projection area (nm ²)	0.117	0.125	0.162	0.142– 0.244
collision diameter (nm)	0.20	0.27	0.41	0.45
diameter in van der Waals constant (nm)	0.42	0.46	0.50	0.51
adsorption temp. (K)	4.2	r.t.	77	r.t.
interaction	weak	dipole	quadrupole	quadrupole
adsorbent	any	hydrophilic	any	any

The typical N₂ physisorption analyzer consists of two main components, which are a deaeration station and an adsorption station (Figure 1-13a). The first step in this process is to calibrate a quartz cell used for gas adsorption: the cell is evacuated under high vacuum at high temperature (e.g. 300 °C) followed by a complete adsorption cycle in the empty cell at 77K. The cell is loaded with sample and connected to a degassing station to remove the physically adsorbed water and volatiles. After degassing, the cell is transferred to the adsorption station and evacuated. The adsorption cycle is performed by incrementally introducing the adsorbed gas using a calibration volume connected to the adsorption station. The difference between the pressure measured and the that in the empty cell correlated with the moles of adsorbed N₂. During the measurement, the cell is maintained at the boiling

point of liquid N₂ in a Dewar flask.

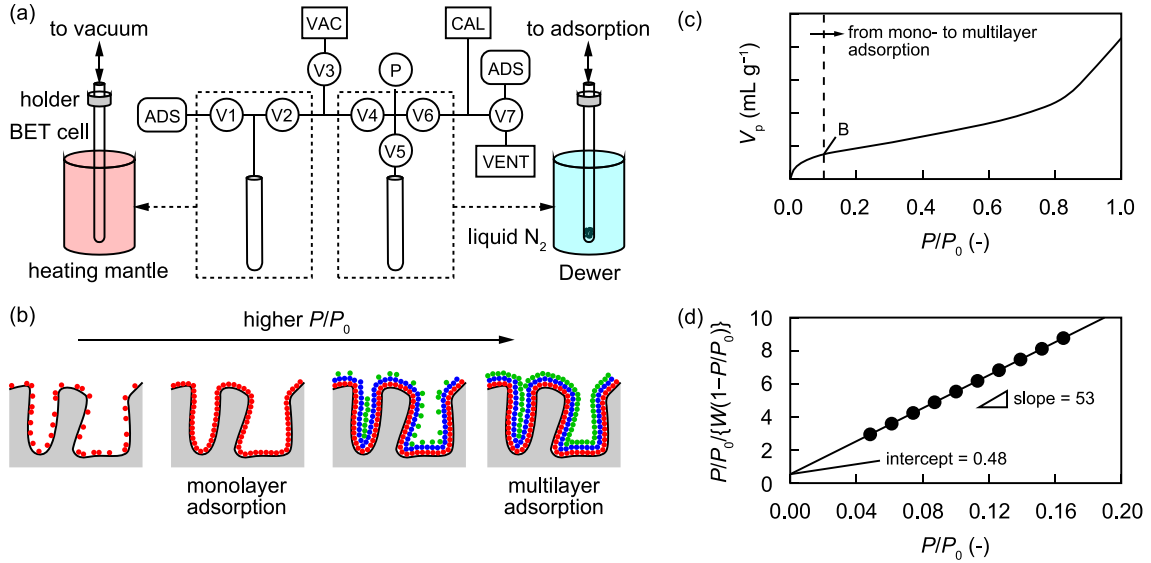


Figure 1-13. (a) Gas physisorption apparatus to obtain adsorption-desorption isotherm. VAC = vacuum, CAL = calibration, ADS = adsorbate, P = pressure gauge, V1–V7 = valves. (b) Transition from mono- to multilayer adsorption depending on P/P_0 . (c) Typical N₂ isotherm for porous materials with macropores, where N₂ molecules are absorbed in mono/multi-layers without restriction and transition from mono- to multilayer adsorption begins at point B. (d) Typical Example of BET plot.

In the N₂ adsorption experiments, different adsorption events occur in accordance with the relative pressure (P/P_0 , where P and P_0 are actual and saturated vapor pressures of adsorbate, respectively) and some theories have been proposed. The determination of S_v of various adsorbents and catalysts is practically nowadays based on the BET theory proposed in 1938 by Brunauer, Emmett and Teller.^[166] The BET theory assumes that the adsorption energy is independent of the adsorption site, where the gas molecules interact only in the vertical direction and the lateral interactions between adjacent molecules are negligible. Physisorption of the first adsorbate layer is as follows:

$$\frac{P/P_0}{W(1-P/P_0)} = \frac{1}{CW_{ml}} + \frac{C-1}{CW_{ml}} \frac{P}{P_0} \quad (1-16)$$

where W and W_{ml} are the mass adsorbed at P/P_0 and the required mass of adsorbate forming a complete

monolayer on a sample. C is a constant corresponding to the difference between the heat of adsorption in the first layers (E_1) and those in the second or higher layers (E_L). For higher layers, E_L equals the latent heat of condensation:

$$C = \exp\left(\frac{E_1 - E_L}{RT}\right) \quad (1-17)$$

where R and T are gas constant and temperature, respectively. According to the Sing,^[167] the transient point from mono- to multilayer adsorption should be included in the estimation of W_{ml} (Figure 1-13b and c). The BET theory can be applied over P/P_0 of 0.05–0.35 in the adsorption branch of isotherm, where monolayer adsorption takes place. Fitting the linear region of BET plot (Figure 1-13d), the W_{ml} can be calculated from its slope and intercept, and S_v is also given using following equation:

$$S_v = \frac{W_{ml}}{M_w m} N_A A \quad (1-18)$$

where M_w , m , a , and N_A are the molecular weight of N_2 , the sample mass, cross sectional area of N_2 (0.162 nm², and N_A is Avogadro's number, respectively.

For pore size distribution of samples, the Barrett-Joyner-Halenda (BJH),^[168] Dollimore-Heal (DH),^[169] or Cranston-Inkley (CI)^[170] methods have been proposed, however, these failed to describe both the micro- and mesopores due to the restrictive hypotheses.

A density functional theory (DFT) is strong method to calculate the pore size distribution of porous materials, which relies on a theoretical description of the experimental adsorption isotherm $N_{exp}(P/P_0)$:

$$N_{exp}\left(\frac{P}{P_0}\right) = \int_{d_{min}}^{d_{max}} N_{DFT}\left(\frac{P}{P_0}, d\right) \times f(d) dd \quad (1-19)$$

where $f(d)$ is unknown pore diameter distribution function, and d_{min} and d_{max} are the minimum and maximum pore sizes in the kernel, respectively. For modeling adsorption and capillary condensation in pores of different geometry and surface chemistry, the non-local (NLDFT) and quench solid (QSDFT) DFT have been.^[171]

Size Exclusion Chromatography (SEC)

Above mentioned Hg intrusion and gas adsorption porosimetry have been well founded to evaluate micro-, meso-, and macroporous materials. However, these methods are unfavorable for wet or swelling materials because of the requirements of drying and degassing before measurements. On the other hand, the porous structures of polymer gels have been evaluated and used in size exclusion chromatography (SEC). In 1953, Wheaton and Bauman first reported a size-based separation of nonionic species such as polyols using cation-exchange resins by a size-based mechanism.^[172] Lindqvist and Storgårds reported the first separation of polypeptides from amino acids or oligopeptides by non-ionic starch-packed column. The applicability of synthetic polymer gel to SEC system was demonstrated in 1959 by Porath and Flodin using cross-linked dextran hydrogel.^[173]

SEC-based porosimetry was originally introduced by Halasz and Martin^[174] and applied to various materials such as hydrophilic gels^[175] and synthetic polymer gels.^[176] The theory and estimation of porosity in SEC lies on the difference of elution behavior of tracers with different M_w , i.e. size. In the packed-bed column, tracers in mobile phase distinguishes two types of liquid phases, which are the path within the gel bed and one surrounding the gel. When a tracer applied to the column, the elution volume of tracer (V_e) can be calculated as follows:

$$V_e = V_0 + KV_p \quad (1-20)$$

where V_p and V_0 are the solvent volume of inner of gel and that of surrounding of gel (void), respectively. K represents the partition coefficient for a tracer which may range from 0 to 1. Complete exclusions from the inner phase of gels for high-molecular weight tracers such as proteins give K of 0, while low-molecular-weight one such as eluent can diffuse freely into the gels and hence give K of ~ 1 (Figure 1-14a).^[177] The relationship between V_e and M_w is normally summarized to give an SEC curve (Figure 1-14b). As M_w is directly related to effective diameter of tracer (d_e) for any polymer in a given solvent, SEC curves can easily be adapted to show the dependence of V_e or K on d_e .^[178] For

example, d_e of polystyrene in THF can be estimated using following formula determined by light-scattering experiment:^[179]

$$d_e \text{ (nm)} = 0.0246 M_w^{0.588} \quad (1-21)$$

The gel porosity (ε_g) can be estimated using V_e and geometrical volume of empty column (V_c) as follows:

$$\varepsilon_g = \frac{V_e}{V_c} \quad (1-22)$$

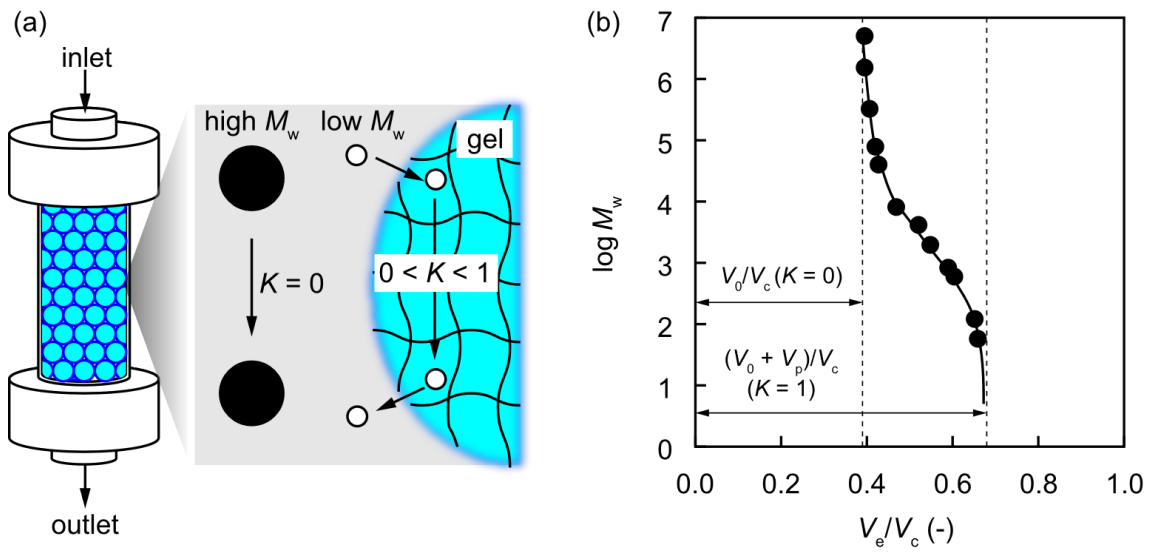


Figure 1-14. (a) Mechanism of SEC using different M_w tracer. (b) typical SEC curves.

1.4.3. Porous Polymer Monolith

Porous Polymer Particles

In applications of porous polymers to continuous-flow applications such as liquid chromatography and catalyses, packed-bed columns have been often used featuring their wide applicability and on-site preparation by users. Nir and Pismen simulated the η in the irreversible first-order reaction and demonstrated a considerable improvement of efficiency by forced convection in intraparticle pores, especially for large-pore catalysts.^[180] Under continuous-flow conditions, the fluid mainly flows

through the interparticle voids whose resistance against the flow is minimum, while the fluid in the intraparticle pores does not move and remains stagnant. To enhance the mass transport into the intraparticle by convective flow, Regnier and co-workers used polymer beads, which had the diameter and “flow-through” pores of 10 and 0.8 μm , respectively, for applications in chromatography, diagnostic, and enzyme immobilizations.^[181] In fact, separation efficiency of packed column was somehow improved, however, convective flow around the porous particles was still favored accounting for > 95% of the total convection flow (Figure 1-15a).^[182] This was presumably attributed to the large inter-particle void size ($d_{\text{inter,void}}$) compared with intra-skeleton pore size ($d_{\text{intra,pore}}$). From Hg intrusion porosimetry, it was proved that the particle-packed column had the $d_{\text{inter,void}}$ /particle diameter size ratio of 0.27–0.37 dependent on the packing manner and shape of particles.^[183–185] Additionally, common porous particles had relatively small $d_{\text{intra,pore}}$ /particle size ratio (~ 0.08).^[181] Thus, particle-packed column had $d_{\text{intra,pore}}/d_{\text{inter,void}}$ of 0.22–0.30, which may leads to broad residence time distributions of solutes. It is highly desired to use the continuous-flow reactor with $d_{\text{intra,pore}}/d_{\text{inter,void}}$ close to 1 to fully benefit from convection effect. This means the demands for the column which has monomodal flow-through pore sizes including intra- and interstitial macropores where convective flow works. From the viewpoint of diffusion length, employing the smaller non-porous particles is also beneficial to exclude the diffusion resistance of solutes toward the active site while maintaining the large S_v . However, the particles are densely packed in the column leading to low interparticle voidage, geometrically calculated to be 36%.^[186] This restriction in tuning the voidage of smaller particle-packed column would suffer from the low permeability in continuous-flow applications.

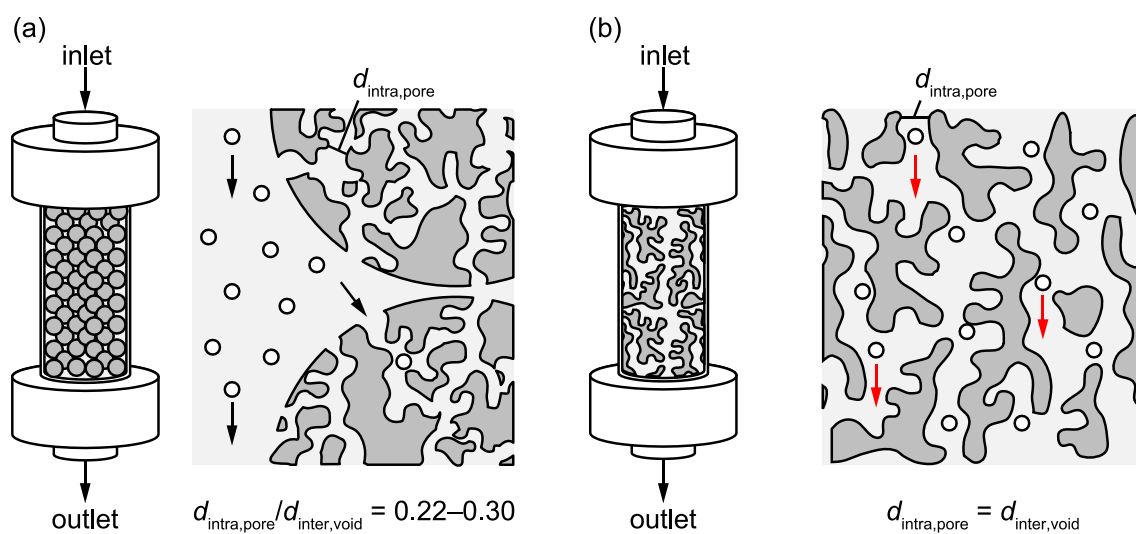


Figure 1-15. Schematic view of continuous-flow fluid in column employing (a) porous polymer particles and (b) porous polymer monolith.

Porous Polymer Monolith

To overcome the limitation of mass transport in packed-bed columns, continuous porous media has been designed, i.e. porous monolith. There exists no clear definition of the porous monoliths, however, they often represent self-standing porous materials with interconnected macropores. As for inorganic scaffold, the rapid growth and installation in practical use of silica-based monolith has been credited to Tanaka and co-workers highlighting the controllability of pore size distribution, thermal and mechanical stability, and surface chemistry.^[187] On the other hand, polymer-based porous monolith have been featured based on their chemical stability and availability of chemical functionalization. From early 1990s, Svec and Fréchet have successfully developed a series of macroporous polymer monoliths for applications in continuous-flow systems.^[188–197] The monoliths contained not only small diffusive pores but also a large number of flow-through pores with diameters of over hundreds nanometers. The wide variety of polymer matrix have been reported such as polymethacrylate,^[189,191,193,195–197] polystyrene,^[190,192] and polyacrylamide^[194] for continuous-flow applications. The detail of the formation mechanism of macropores will be summarized in the later

section. Many of the monoliths have been used in rod shape, but also used in disk format (small length/diameter ratio of < 1).^[198] Focusing on the morphological structure of monolith column, polymer skeletons are arranged in three-dimensionally network with a certain distance from each other to create interconnected pores. Translating this situation to that in packed-bed column, $d_{\text{intra,pore}}$ is considered to be the same as $d_{\text{inter,void}}$, and hence $d_{\text{intra,pore}}/d_{\text{inter,void}}$ of unity would be given (Figure 1-15b). In this situation, all the components in mobile phase is forced to flow through the macropores and the severe diffusion limitations in the macropores could be omitted,^[199] to give narrow residence time distributions. Also, the porosity of typical monolith column reaches as high as over 60%, which is controlled by polymerization conditions independently of the skeleton size of monolith. This is another aspect of interconnected scaffold differing from the particle-packed column, and thus short diffusion length of solutes and high permeability is simultaneously acquired in continuous-flow reactor.

1.4.4. *Formation Mechanism of Pore*

There are vast numbers of approaches to porous monoliths in terms of polymerization mechanisms; chain-growth polymerization such as radical^{[188–197],[200]} and ring-opening metathesis polymerizations,^[201,202] and step-growth polymerization (polycondensation)^[203,204] have been reported. The later sections focus on the formation mechanism of pore in the polymers prepared via the radical polymerizations.

Polymerization-Induced Phase Separation (PIPS)

The generally accepted mechanism of pore formation in porous polymer monoliths via polymerization-induced phase separation (PIPS) in the presence of radical initiator is the following.^[191]

The organic solution includes mono- or multi-vinylated (cross-linking) monomers, radical initiator,

and thermodynamically poor solvent. The radical initiator decomposes at a specific temperature and the polymerization process occurs in the solution (Figure 1-16a). As the polymerization proceeds, insoluble gel-like species (nuclei) are formed and precipitates after becoming insoluble in the reaction medium as a result of both cross-linking and porogen selection (Figure 1-16b). In this process, the monomer is a better thermodynamically solvating agent for the polymer than the porogen. Thus, the nuclei swell with monomers still present in the surrounding liquid phase, while polymerization proceeds both in the solution and in the swollen nuclei. Kinetically, the polymerization process is preferred in the later because the monomer concentration is locally higher than in the surrounding solution. Some branched or cross-linked oligomers soluble in the solution are trapped by the growing nuclei to further increase their size. The nuclei enlarge as they continue to polymerize and are joined by polymer chains that bridge adjacent nuclei to form aggregates. In the later stage of polymerization, the size of the clusters is large enough to allow contact with some of their neighbors, thereby forming a scaffold-like interconnect matrix in the polymerization system (Figure 1-16c). Slight changes of pore size, volume, and surface area were observed even after full consumption of monomers. Owing to the interconnected matrix, the obtained porous polymer is well reinforced by cross-linking each cluster and capturing polymer chains in the solution. Finally, the porous monolith can be obtained which has macroporosity close to the volume fraction of porogenic solvent in the starting monomer solution.

Differing from the suspension polymerizations for porous beads, the bulk polymerization for the monoliths includes the high monomer concentration (~40 vol%) and the absence of surface tension on the polymer surface, which significantly influence the porous structure of the polymers obtained from this molding process.^[191] In the PIPS method, key variables to tune the porous properties of monoliths are polymerization temperature and time, composition of porogenic solvent, content of cross-linking monomer, and so on. Optimizing these parameters, a broad range of pore size from tens to thousands nanometers can be targeted.^[205]

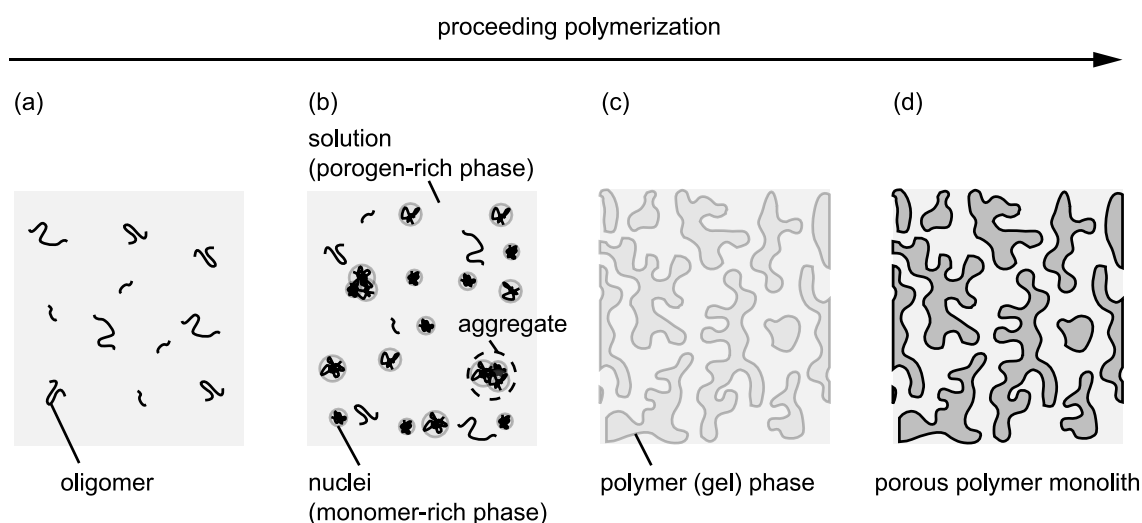


Figure 1-16. Mechanism of pore formation via PIPS mechanism in radical polymerization, where (a) polymerization was first initiated by radical initiator followed by (b) formation of nuclei and their aggregation, (c) full uptake of monomers into the nuclei but still progressive changes of pore structure, and (d) fabrication of porous monolith.

High Internal Phase Emulsions (HIPE)

Based on a high-internal phase emulsion (HIPE) system, Barby and Haq at Unilever first developed a macroporous poly(styrene-divinylbenzene) monolith^[206] and the detailed studies on the HIPE-template polymer were dealt by Sherrington, Cameron, and co-workers.^[207–212] According to the definition by Lissant, a HIPE is a emulsion containing internal phase with fraction of 74.05 vol% or more.^[213] This volume fraction was speculated from that in close packing of equal spheres. For example, water-in-oil HIPE-templated polymer was prepared emulsifying 74–95 vol% aqueous phase containing a radical initiator and electrolyte, in oil phase containing monomers and surfactants (Figure 1-17). Vigorous stirring the mixture, the very viscous mass, HIPE, could be formed. The HIPE is transferred to a mold and polymerized by thermal- or photoinitiation to give the porous monolith, where interconnected spherical voids, which are negative images of the aqueous phase, and the windows between the voids exist. Judicious selection of surfactant and solvent systems allows the use

of oil-in-water,^[214] supercritical CO₂-in-water,^[215] oil-in-oil,^[210] and ionic liquid-in-oil^[216] HIPE templates. Through the emulsion template, the resulting porous structure is significantly influenced by the nature of emulsion itself whose size and stability can be controlled stirring rate, stirring time, types and concentration of electrolytes or surfactants, solvent species, and volume fraction of internal phase. Also, the polymerization locus regulated by types of initiator (water-soluble or oil-soluble) is critical factor to determine the pore interconnectivity.^[217]

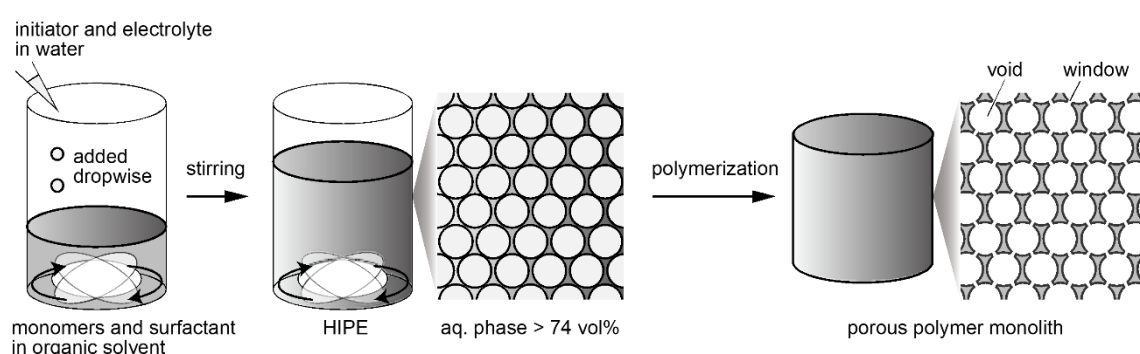


Figure 1-17. Mechanism of pore formation via water-in-oil HIPE template in radical polymerization.

Other Methods

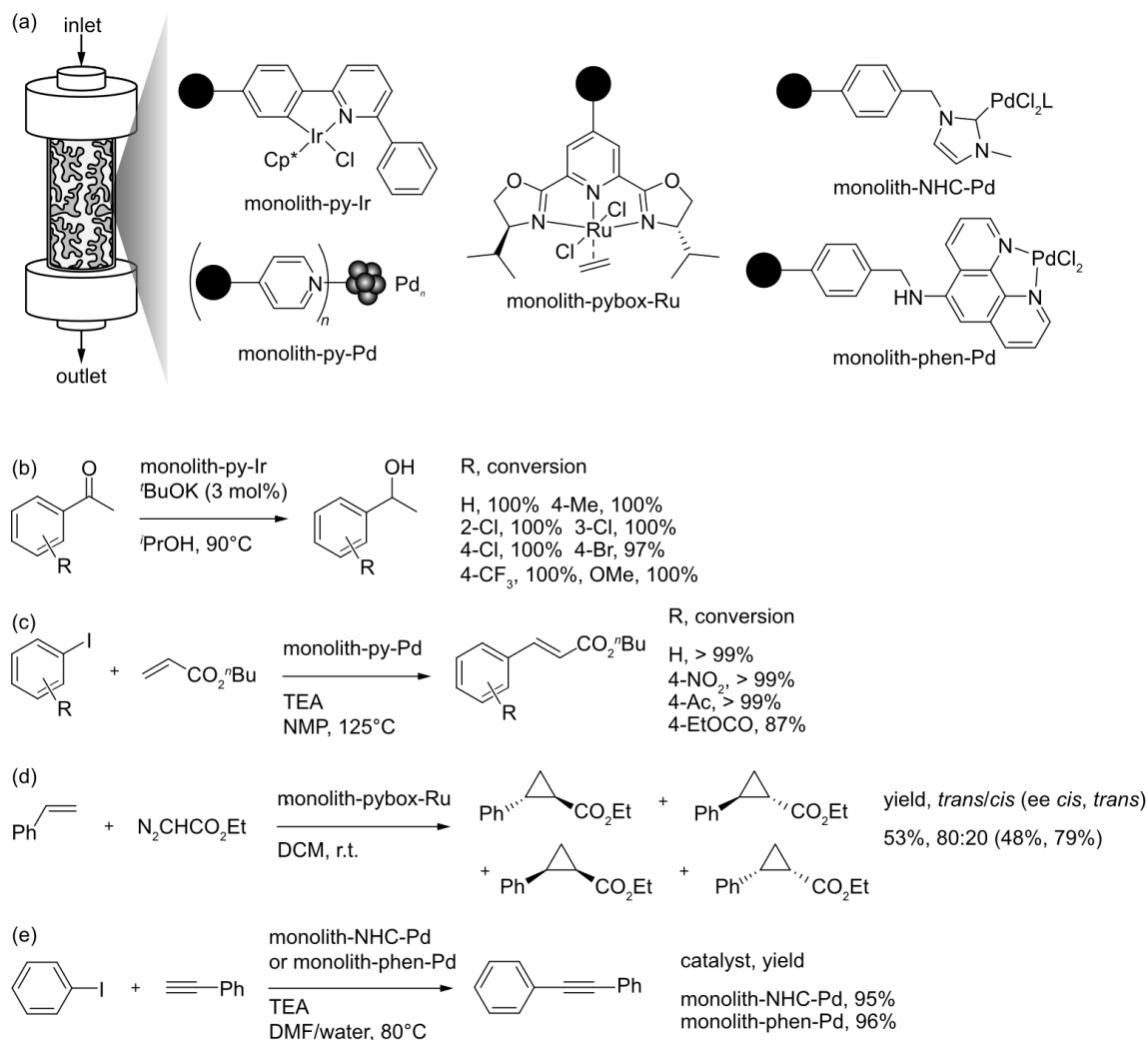
Uyama and co-workers have developed a wide variety of porous polymer monoliths such as polymethyl methacrylate, polyvinylalcohol, polyacrylonitrile, and polyvinylidene difluoride monoliths by thermal-induced phase separation (TIPS).^[218–224] In the TIPS methods, the polymer solution is dissolved in a suitable (mixture) solvent at high temperature followed by cooling to ambient temperature, resulting in a self-standing polymer with interconnected porous structures. The TIPS technique contains only phase separation of polymers in the absence of polymerization process, where polymer concentration, molecular weight, solvent species, and cooling speed significantly influence on the porous properties. The cross-linked polymers can be obtained by in-situ reactions between matrix polymer and cross-linkers.^[220,221] Hierarchically controlled pore could also be obtained by combination of TIPS and thermal treatment.^[219]

The cryotropic gelation technique, implying synthesis at sub-zero temperature, has been employed to prepare the hydrophilic and highly porous polymer monoliths, which are known as cryogels.^[225,226] Two methods are adopted to form the porous monolith via cryogelation: (i) crosslinking of polymers such as polyvinylalcohol dissolved in water and (ii) polymerization of monomers dissolved in water. The reaction mixture contains monomers or polymer, initiator, and cross-linkers and are filled in an appropriate mold. Rapid cooling to a subzero temperature and addition of reaction accelerator, the polymerization proceeds. During the cooling, the water crystals grow and aggregate each other to form a continuous frozen network as porogen, while monomer-rich phase also forms continuous liquid. After polymerization, the remaining ices in the polymer mass melt at ambient temperature to give a self-standing porous monolith.^[227] Careful control the temperature and choice of solvent allows the highly porous structures in the monoliths which typically have 1–200 μm pores^[225] and 74–94% porosity.^[226]

1.4.5. *Application to Immobilized Catalyst*

Thanks to the tunable pore sizes and porosity, monolith configuration has been adopted in continuous-flow production of fine chemicals in an academic research field. The broad scope of immobilized ligands could be seen in the recent porous polymer monolith reactors (Scheme 1-13a). Indeed, these monolith reactors have demonstrated their feasibilities in continuous-flow transition-metal catalyses including Ir-catalyzed hydrogen transfer (Scheme 1-13b),^[228] Pd-catalyzed C–C cross-couplings (Scheme 1-13c and e),^[229–234] and Ru-catalyzed cyclopropanation (Scheme 1-13d).^[235]

Scheme 1-13. (a) Porous Polymer Monolith Reactors and Application to (b) Ir-Catalyzed Hydrogen Transfer, (c) Pd-Catalyzed Heck Reactions,^a (d) Ru-Catalyzed Cyclopropanation,^b and (e) Pd-Catalyzed Sonogashira Reaction



^aTEA = triethylamine, NMP = *N*-methylpyrrolidone. ^bDCM = dichloromethane.

Not only the supported ligand nature but also interconnected macroporous structures of the monoliths were highlighted for improved productivities. Sans and co-workers investigated the column configuration effect on the Pd-catalyzed Heck reactions under continuous-flow condition.^[233] The excellent performance of poly(styrene-divinylbenzene-NHC) monoliths as a support was highlighted compared with packed-bed column system employing macroporous polymer beads, owing to the size-

controlled interconnected macropores of the monolith reactors for narrow residence time distribution.

1.5 Aim of This Study

For over half a century, fine chemical industries have relied on batch systems because the synthetic routes for the compounds are complicated and difficult to achieve with continuous-flow systems. Particularly, increasing demand for energy-saving, waste-reducing, and cost-effective chemical manufacturing has motivated the employment of immobilized catalysts in the continuous-flow syntheses. Very general issue in the continuous-flow reactors using immobilized catalysts are the mass transport of reactants due to the large diffusion resistance toward the catalysts. Even when the macroporous particle-packed columns are employed, the large difference between pore sizes of intra- and interparticles causes the insufficient mass transport toward the catalyst leading to low catalytic efficiency. Additionally, decreasing the particle size leads to the decrease in interparticle pore sizes, which are geometrically restricted, and hence suffers from the increased pressure losses. These problems should be mitigated via material designs while maintaining or going even further beyond the intrinsic catalyst performance.

In this thesis, the author describes the porous monoliths based on polymer gels, which is one of the cross-linked polymers swelling in the specific solvent, as supports for transition-metal catalysts and their application to continuous-flow synthesis of fine chemicals. For the application to continuous-flow syntheses of fine chemicals, a polymer-gel-based porous monolith has never been fully discussed. Featuring the flexible nature of gel and interconnected macropores, the presented continuous-flow system using porous gel monolith showed the fully accelerated mass transport of reactants and high permeability compared with the conventional supports. Careful selection and tuning of the polymer compositions enabled to install this concept into hydrogel- and organogel-based monolith reactors while maintaining or overcoming the intrinsic performance of catalysts immobilized. The author

believes that the present studies in this thesis would give a fundamental insight into design of supports for efficient and practical transition-metal catalyses for fine chemicals.

In chapter 2, hydrogel-based monolith reactors for continuous-flow cross-coupling reactions in aqueous media were discussed. The macroporous structure of the hydrogel was obtained via PIPS technique in water and high permeability of the resulting monolith column was highlighted. Considering the mass transport issue in the gel network, the catalytic efficiency under continuous-flow conditions was fully improved by tuning the hydrogel compositions, which were very efficient compared with those of non-swelling inorganic supports.

In chapter 3, the formation of coordinatively unsaturated and hence highly active metal species in organogel-based monolith was discussed. Cross-linking effect on the site-isolation of ligand in three-dimensionally connected gel network was confirmed by detailed analyses. In fact, selective formation of highly active mono-ligated Pd in the organogel showed significantly high activity toward unactivated aryl chloride cross-couplings in batch systems.

In chapter 4, the application of organogel-based monolith to Pd-catalyzed cross-coupling reactions under continuous-flow conditions was discussed. Not only the immobilized ligand design but also hydrodynamic parameters of the monoliths were fully investigated in continuous-flow conditions, and significantly high catalytic efficiency was confirmed compared with those of batch conditions. The effects of cross-linking density of the organogel was confirmed in terms of site-isolation of ligands, size exclusion behavior, and interaction between metals and polymer scaffold.

1.6 References

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Chapter 2

Development of Macroporous Hydrogel Monolith for Continuous-Flow Cross-Coupling in Aqueous Media

Chapter 2 Development of Macroporous Hydrogel Monolith for Continuous-Flow Cross-Coupling in Aqueous Media

Abstract

A living system adopts target molecules permeation through capillary and cells for chemical transformation in the limited reaction space. Inspired by this concept, A monolithic porous gel (**MPG**) was easily prepared by copolymerization of gel matrix, tertiary amine, and crosslinking monomer in one step synthesis (Figure 2-1). Interconnected capillaries existed in the **MPG**, enabling continuous-flow application with high permeability. Because the capillaries were constituted of polymer gel, Pd(0)-loaded **MPG** provided another permeable pathway to substrates in a gel network, contributing to its much high turnover number after 30 days of use, compared with those of Pd(0)-loaded inorganic supports. Interestingly, the gel network size of the **MPG** influenced the catalytic frequency. Diffusivities of the substrates and product in the gel networks increased with increasing network sizes in relation to catalytic activities. The **MPG** strategy provides a universal reactor design in conjunction with a practical process and precisely controlled reaction platform.

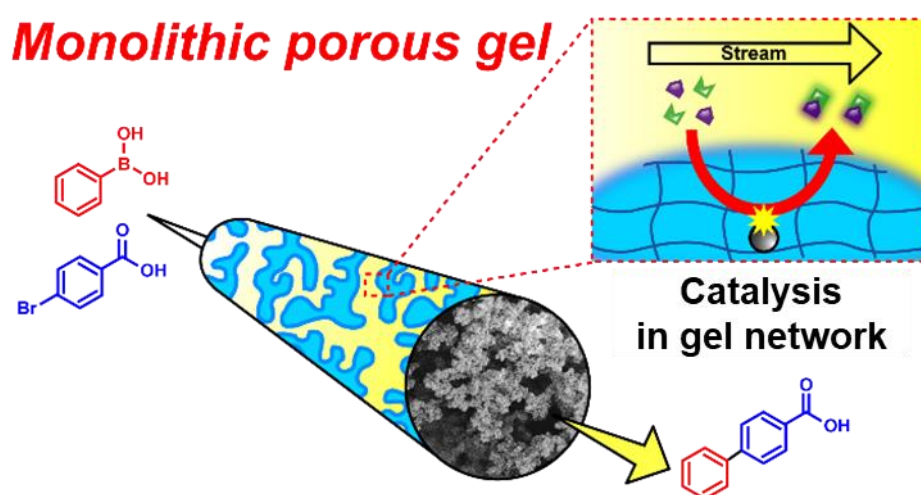


Figure 2-1. Schematic illustration of hydrogel-based **MPG** reactor for Pd(0)-catalyzed Suzuki-Miyaura cross-coupling reaction under continuous-flow conditions.

2.1 Introduction

Process innovations for chemical syntheses impact growth in chemical industries. Highly efficient chemical manufacture has motivated the development of batch and continuous-flow systems. Continuous-flow syntheses have several advantages over batch syntheses, in terms of productivity, heat and mixing efficiency, reproducibility, and operability.^[1-4] Moreover, large-scale production is easily achieved by increasing the size or number of continuous-flow reactors.^[5,6] Chemical manufacture requires a high quality synthesis with excellent system operability. In this regard, the development of highly efficient continuous-flow reactors with a sophisticated synthetic design is desirable. Designs for chemical syntheses and practical devices could result in advanced continuous-flow reactors. Taking inspiration from an evolved, natural, and efficient continuous-flow reactor, a living system where continuous-flow syntheses is processed smoothly through capillaries, is mimicked.^[7] Nowadays, many continuous-flow reactors that possess capillary arrangements have been proposed for chemical syntheses.^[8-12] Although this approach has succeeded and attracted inquisitive attention in the industrial field, the fabrication of integrated capillaries requires complicated and cost-consuming micromachining techniques. A monolithic porous material, in which capillaries are integrated three-dimensionally, has been proposed.^[13] A single piece of porous material can be prepared in any desired shape in a one-step synthesis, and easily scaled up. Additionally, its porous property and chemical functionality are also precisely controllable.^[14] Frechet and Svec have developed many monolithic porous polymers and demonstrated their feasibilities in continuous-flow applications.^[15-32] In the living system, substrates can be transported through not only the capillaries but also cells comprising the wall of the capillaries. The cells provide a reaction platform in their internal space. Thus, in the living system, the substrates can fully permeate throughout a body. If the wall of capillary in the monolithic porous polymer is also permeable to target molecules, its internal space could be provided as a reaction platform in a fashion similar to that of the living system. Such a

hierarchical permeability (through capillaries and cells)^[33] facilitates continuous-flow operation and enlarges a space available to a chemical transformation within the limited volume of the continuous-flow reactor. However, the hierarchical permeability of the target molecules has not been considered in a continuous-flow synthesis yet.

Herein, a poly(*N*-isopropylacrylamide) (PNIPAm)-based monolithic porous gel (**MPG**) was developed as a continuous-flow reactor for a Pd(0)-catalyzed Suzuki coupling reaction. Capillaries existed in the **MPG** as interspatial pores, contributing to successful application in the continuous-flow system. A reaction platform was provided in the gel network by the loading of Pd(0), affording a Pd(0)-loaded **MPG** (Pd/**MPG**). The Pd/**MPG** should contain two different pathway scales for the substrates and product (Figure 2-2). First, the feed solution containing the substrates flows continuously through capillaries in the Pd/**MPG**. Next, the substrates easily diffuse into the walls of the capillaries that are composed of a gel. Molecular diffusivities into a gel network are well maintained owing to the flexibility of the polymer chain. Therefore, if catalysts are immobilized in the gel network, the substrates can easily access the catalysts and are transformed smoothly, giving a desired product. Finally, the product diffuses out of the gel network. This **MPG** strategy would be a key to fabricate the hierarchically permeable structure in a catalytic continuous-flow reactor. A set of Pd/**MPGs** with different gel network sizes was also prepared and demonstrate their advantages over other types of inorganic supports (porous glass membrane, silica particles, or carbon) in the continuous-flow cross-coupling reaction. The influence of the size of gel network on molecular transport under continuous-flow conditions was suggested.

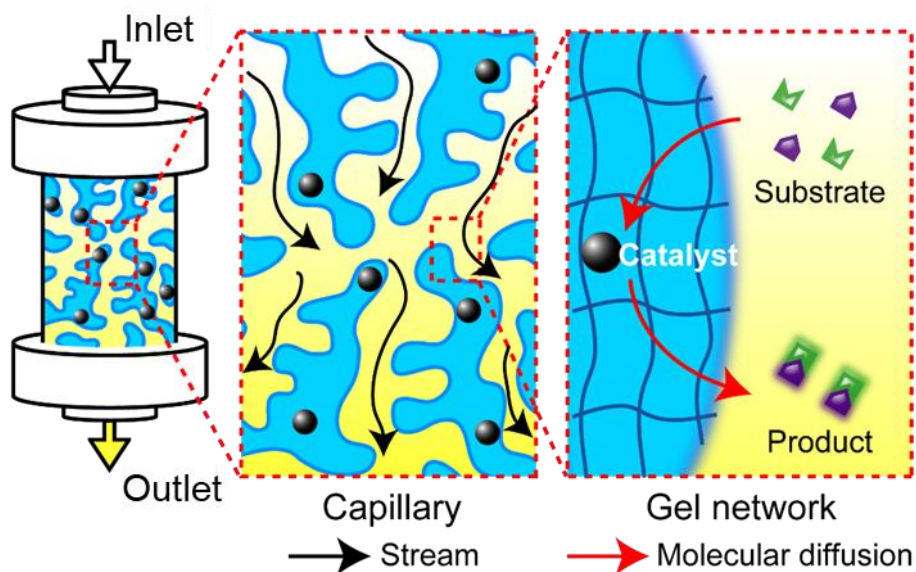


Figure 2-2. Conceptual illustration of a continuous-flow reactor using **MPG** for the catalytic reaction.

2.2 Experimental Section

2.2.1. Reagents

Water with a conductivity of 18.2 MΩ cm (Milli-Q, Millipore Co., Bedford, MA, USA) was used in all experiments. NIPAm (Wako Pure Chemical Industries Ltd., Osaka, Japan), *N*-(3-dimethylaminopropyl)methacrylamide (DMAPM, Tokyo Chemical Industry Co., Ltd., Tokyo, Japan), *N,N'*-methylenebisacrylamide (BIS, Tokyo Chemical Industry Co., Ltd.), and 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPD, Wako Pure Chemical Industries Ltd.) were used as the gel matrix, tertiary amine ligand, crosslinker, and radical initiator, respectively. NIPAm was purified by recrystallization from benzene/*n*-hexane and dried *in vacuo* at room temperature. The polymerization inhibitor in DMAPM was removed using an activated alumina column. The porous glass membrane (mean pore size: 2010 nm, surface area: 12 m² g⁻¹, porosity: 61%, 20 mmφ, SPG Technology Co. Ltd., Miyazaki, Japan) and silica particles (particle size: 40–63 μm, BET surface are: 443 m² g⁻¹, Merck Co., Darmstadt, Germany) were tertiary-aminated using a procedure similar to that previously

reported.^[34] K₂PdCl₄ (Sigma-Aldrich Co., St. Louis, MO, USA) and NaBH₄ (Tokyo Chemical Industry Co. Ltd.) were used to prepare Pd(0)-loaded supports. Pd(0)-loaded carbon (Pd/C, 5 wt% Pd, BET surface area: 946 m² g⁻¹, Wako Pure Chemical Industries Ltd.) was purchased and used as a referential Pd catalyst. Phenylboronic acid (**1**, Tokyo Chemical Industry Co., Ltd.), aryl halide (**2**, Tokyo Chemical Industry Co., Ltd.), and Na₂CO₃ (Wako Pure Chemical Industries Ltd.) were used to prepare the substrate stock solution. 4-Phenylbenzoic acid (**3**, Tokyo Chemical Industry Co., Ltd.) was used to prepare a standard solution of the Suzuki coupling product for calibration.

2.2.2. Preparation of Pd/**MPGs**

MPGs were prepared by the copolymerization of NIPAm, DMAPM, and cross-linking monomer BIS in water (Scheme 2-1a and Table 2-1).^[35] NIPAm (100-*X*-*Y* mol%), DMAPM (*X* mol%), and BIS (*Y* mol%) were dissolved in water with a total monomer concentration of 1.5 mol L⁻¹ followed by degassing with N₂ gas for more than 30 min. 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPD) as a radical initiator (1 mol% of total monomers) was added to the monomer solution. The mixed solutions (3.14 mL) were poured into glass vials with inner diameters of 20 mm, which were then incubated at 70°C for 3 h. The cylindrical **MPGs** were removed from the vials and washed with a sufficient volume of water for more than 1 day. From H⁺ adsorption experiments, amine densities in the **MPG1**, **MPG2**, and **MPG3** were estimated to be 707, 740, 650, and 1680 μmol g⁻¹, respectively.^[35] After washing with sufficient water and lyophilizing, the yields of the dried **MPGs** were >92%. Differences among gel network sizes for **MPG1–3** were confirmed by evaluating the swelling properties of the **MPGs** in water.

Pd/**MPGs** were prepared by Pd(II)-ion adsorption and subsequent reduction into Pd(0) using K₂PdCl₄ and NaBH₄ (Scheme 2-1b). Differences among gel network sizes for Pd/**MPG1–3** were also confirmed in the same manner as mentioned above. The Pd/**MPGs** were lyophilized and their internal

structures were observed using field emission scanning electron microscopy (FE-SEM, SU8000, Hitachi High-Technologies Corporation, Tokyo, Japan). Before observation, the **MPG** surfaces were coated with platinum (thickness: approx. 4 nm) using an auto fine coater (JFC-1600, JEOL Ltd., Tokyo, Japan). The porous properties of the Pd/**MPGs** were also evaluated using mercury intrusion porosimetry (AutoPoreIV9520, Micromeritics Instrument Co., Norcross, GA). Pd(0) loaded in the **MPGs** was observed using transmission electron microscopy (TEM, TECNAI 20, Philips FEI, Netherlands). The Pd/**MPGs** were then immersed in aqua regia for 24 h, and the eluent was analyzed using inductively coupled plasma atomic emission spectroscopy (ICP-AES, ICPS-8100, Shimadzu Corporation, Kyoto, Japan) to estimate the amount of Pd loaded per bulk volume (q_{Pd}), which was defined as follows:

$$q_{\text{Pd}} = \frac{[\text{Pd}]_{\text{E}}}{V_{\text{M}}} v_{\text{E}} \quad (2-1)$$

where V_{M} and v_{E} are the bulk volume of the **MPGs** determined by their diameter and thickness, and the volume of solution, respectively, and the subscript E indicates elution.

Table 2-1. Bulk Volumes, Pd Amount, Gel Network Size, and Pd(0) Average Size in Pd/MPG

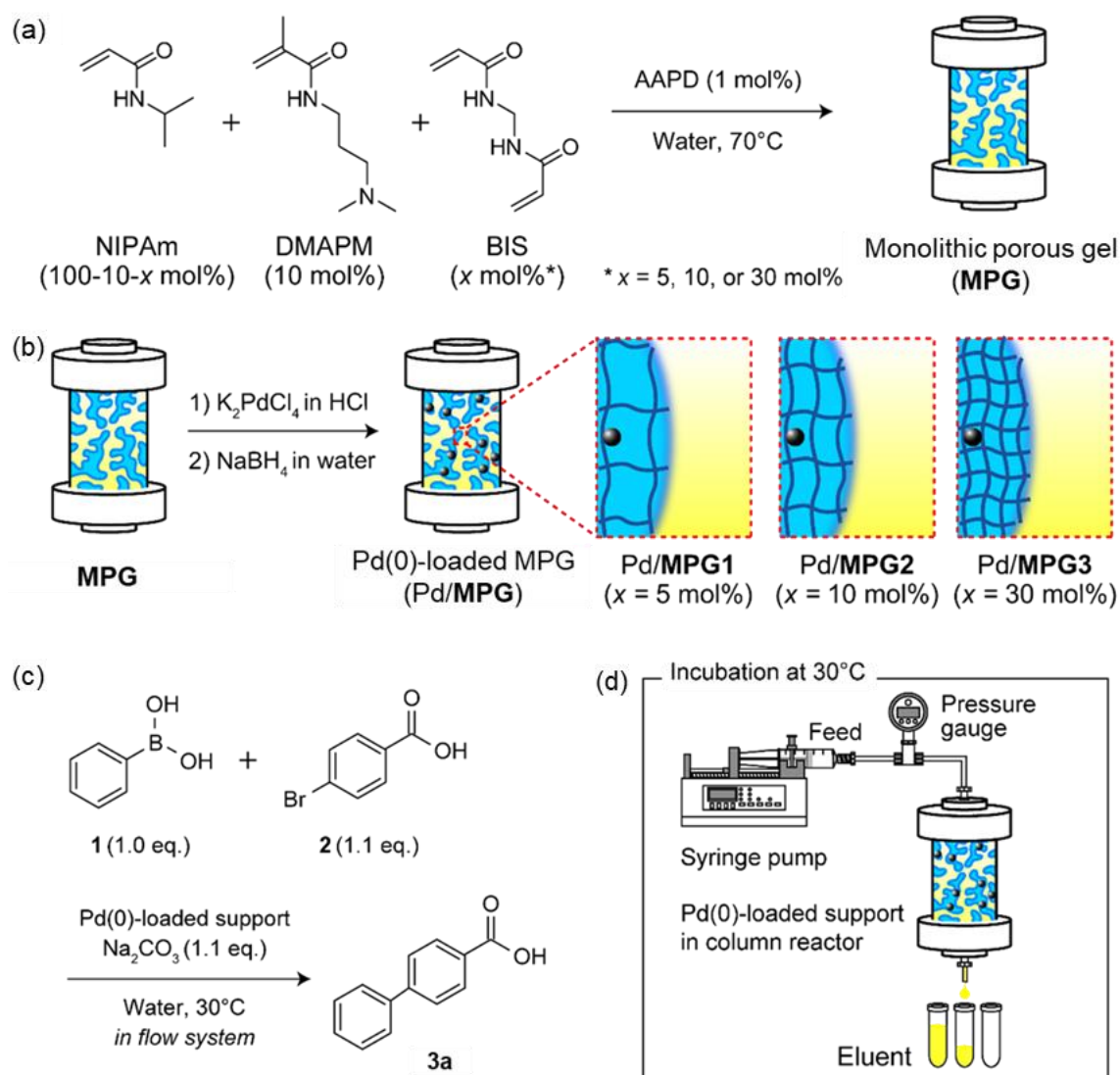
Catalyst	Feed ratio (mol%) ^a		V_{M}	q_{Pd}	Network size	Pd(0) size
	X	Y	(cm ³ g ⁻¹) ^b	(μmol cm ⁻³) ^c	(nm) ^d	(nm) ^e
Pd/ MPG1	10	5	10.4	1.3	7.0	2.4 ± 0.7
Pd/ MPG2	10	10	7.9	1.4	5.2	2.2 ± 0.7
Pd/ MPG3	10	30	5.3	1.5	2.8	2.1 ± 0.7
Pd/ MPG4	30	30	7.7	2.1	2.8	2.8 ± 0.9

^aConditions; NIPAm (100- X - Y mol%), DMAPM (X mol%), BIS (Y mol%), AAPD (1 mol% with respect to monomers),

1.5 mol L⁻¹, water, 70°C, 3 h. ^bCalculated in water at 30°C. ^cEstimated by immersion in aqua regia followed by ICP-

AES measurement. ^dCited from the literature.^[37] ^eMeasured from TEM images of Pd/**MPGs**.

Scheme 2-1. (a) Chemical Reaction^a, (b) Loading of Pd(0)^b, (c) Suzuki Coupling Reaction^c, and (d) Continuous-Flow Reactor^d



^aChemical reaction for synthesis of **MPG** with tertiary amine. ^bLoading of Pd(0) on the tertiary amine in the **MPG**.

^cSuzuki coupling reaction between **1** and **2** to give 4-phenylbenzoic acid (**3a**) under continuous-flow condition.

^dContinuous-flow reactor using Pd(0)-loaded support for the Suzuki coupling reaction.

2.2.3. Preparation of Pd(0)-Loaded Nonporous Gel (Pd/NG)

Nonporous gels (**NG**) were prepared by the copolymerization of NIPAm with tertiary-aminated

2.2.4. Preparation of Pd(0)-Loaded Porous Glass Membrane (Pd/Porous Glass Membrane) and Pd(0)-Loaded Silica Particles (Pd/Silica Particles)

Tertiary-aminated porous glass membrane and silica particles were synthesized using silane-coupling reaction similar to that of the previous report.^[34] Porous glass membrane (mean pore size: 2000 nm, 20 mm ϕ , 90 g L⁻¹) or silica particles (particle size: 40-63 μ m, 200 g L⁻¹), and *N,N*-(dimethylaminopropyl)trimethoxysilane (DMAPTMS, 9 or 100 mmol L⁻¹, Sigma-Aldrich Co.) were added to toluene, and stirred at 110°C for 3 h. After washing with toluene and acetone, the resulting supports were dried in vacuo at room temperature. From H⁺ adsorption experiments, amine densities on the porous glass membrane and silica particles were determined to be 57.6 and 780 μ mol g⁻¹, respectively.

Pd(0)-loaded porous glass membrane (Pd/porous glass membrane) and silica particles (Pd/silica particles) were prepared by the adsorption of Pd(II) ions and subsequent reduction. The tertiary-aminated porous glass membrane and silica particles were immersed in K₂PdCl₄ (0.1 mmol L⁻¹) solution dissolved in 10 mmol L⁻¹ aqueous HCl solution, then incubated at 30°C for 72 h. After washing the Pd(II)-adsorbed supports in water, the Pd(II) ions were reduced into Pd(0) by immersion in aqueous NaBH₄ solution (pH 8) at 30°C for 72 h. The solid/liquid ratio was 180 mg of the dry inorganic support for 90 mL of the solution. After washing the Pd/porous glass membrane and Pd/silica particles in water, they were lyophilized before or after catalytic reactions. Pd loaded on the supports and Pd/C were observed using TEM. To estimate the amounts of the Pd loaded, Pd/porous glass membrane, Pd/silica particles, and Pd/C were immersed in aqua regia for 24 h. The eluent was analyzed using inductively coupled plasma-atomic emission spectroscopy (ICP-AES, ICPS-8100, Shimadzu Corporation, Kyoto, Japan). The q_{Pd} on the porous glass membrane, silica particles, and carbon were estimated to be 1.6, 6.3, and 131 μ mol cm⁻³, respectively.

2.2.5. Permeability of Continuous-Flow Reactor

The continuous-flow reactor was constructed packing the supports in a homemade stainless column with a support screen (0.45 μm Omnipore, Millipore Co., Billerica, MA), then attached to a syringe pump (YSP-101, YMC Co., Ltd., Kyoto, Japan) and pressure gauge (KDM-30, Krone Co., Tokyo, Japan) in a thermo-controlled incubator at 30 $^{\circ}\text{C}$ (Scheme 2-1d). The water permeabilities of the columns were preliminarily examined to obtain permeation coefficients using Darcy's law (k_D) as follows:

$$\frac{\Delta P A}{\mu L} = \frac{1}{k_D} Q \quad (2-2)$$

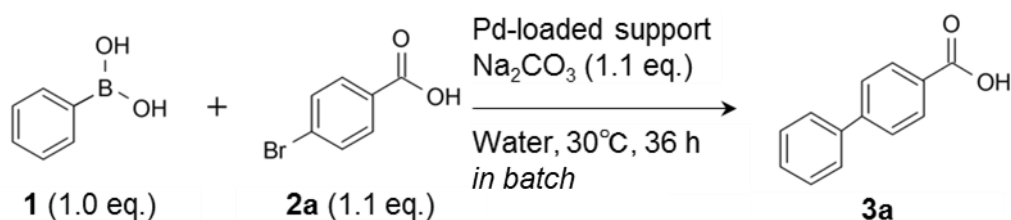
where ΔP , μ , L , A , and Q are the pressure loss, water viscosity, thickness, base area, and flow rate of elution, respectively. The permeabilities of Pd(0)-loaded supports were also determined in the same condition.

2.2.6. Suzuki Coupling Reactions in Batch System

Suzuki coupling between **1** and **2** to give **3** in aqueous Na_2CO_3 solution were conducted using Pd(0)-loaded supports in batch system (Scheme 2-3). The reactions were initiated by addition of the catalysts to solutions of **1** (0.010 mol L^{-1} , 1.0 eq.) and **2** (0.011 mol L^{-1} , 1.1 eq.) in aqueous Na_2CO_3 (0.011 mol L^{-1} , 1.1 eq.). The solutions were shaken at 30 $^{\circ}\text{C}$ for 36 h. The solid/liquid ratio was set to 5 mg of dry gel for every 5 mL of solution. Small aliquots from the reaction mixture were analyzed using a high-performance liquid chromatography (HPLC, LC-2000Plus, JASCO CO., Tokyo, Japan) system with a reverse phase column (Mightysil RP-18 GP 250-4.6, Kanto Chemical Co., Tokyo, Japan) and an ultraviolet detector. Acetonitrile and water (50:50) containing 0.1 vol% trifluoroacetic acid was employed as a mobile phase. After reactions, the catalysts were immersed in aqua regia for 24 h. Using ICP-AES, the eluent was analyzed to estimate the amount of Pd added to the system. The initial molar

ratio of **1** to Pd in the reaction mixture was around 500–1000. Percentage conversions into **3** and turnover numbers (TONs) of the Pd(0)-loaded supports were estimated.

Scheme 2-3. Pd(0)-Catalyzed Suzuki Coupling between Phenylboronic Acid (1**) and 4-Benzoic Acid (**2a**), to Give Biphenyl-4-Carboxylic Acid (**3a**)**



2.2.7. Suzuki Coupling Reactions in Continuous-Flow System

Suzuki coupling reactions of **1** and 4-bromobenzoic acid (**2a**) (Scheme 2-1c) were conducted using Pd(0)-loaded supports in continuous-flow system. All continuous-flow operations were carried out in an incubator at 30°C. The Pd(0)-loaded supports were packed into the homemade column with a support screen, then attached to a syringe pump and pressure gauge in a thermo-controlled incubator at 30°C (Scheme 2-1d). After conditioning the reactor using aqueous Na₂CO₃ solution, **1** (0.010 mol L⁻¹, 1.0 eq.) and **2** (0.011 mol L⁻¹, 1.1 eq.) in aqueous Na₂CO₃ (0.011 mol L⁻¹, 1.1 eq.) solution were permeated through the reactor at a fixed *Q* for 30 days. The residence time (τ) of the substrates was around 0.5 h, which was calculated as follows:

$$\tau = \frac{Q}{V_M} \quad (2-3)$$

The eluent was continuously collected and analyzed using the HPLC system. Based on the amount of biphenyl-4-carboxylic acid (**3a**) produced, turnover numbers (TONs) of catalysts in the continuous-flow system were estimated using the following equation:

$$\text{TON} = \int_0^{v_E} \frac{[\mathbf{3a}]_E}{q_{\text{Pd}} V_M} dv_E \quad (2-4)$$

During the substrate permeation, the cumulative Pd leaching into the eluent was also confirmed using ICP-AES.

2.2.8. *Kinetics Study of the Suzuki Coupling Reaction Using Pd/MPGs in Continuous-Flow System*

Pd/MPG and a support screen were packed into the homemade column, then attached to the continuous-flow apparatus. After conditioning of the reactor using aqueous Na₂CO₃ solution, the substrate was pumped into the reactor at various τ . In the period with the short residence time ($\tau = 0.1$ h), turnover frequencies (TOFs) of Pd catalysts in the continuous-flow system were estimated from the apparent reaction rate per amount of Pd catalysts.

2.2.9. *Diffusion Experiment of Substrates and Product in Gel Network*

The diffusion coefficients (D) of substrates and product in Suzuki coupling reaction in a gel network were evaluated (Figure 2-3). NG1–3 were prepared by polymerization in a cylindrical mold with a diameter of 1.5 mm. The resulting NGs were cut into 25 mm-long cylinders. Each gel was added to the solutions of **1** (0.010 mol L⁻¹), **2a** (0.011 mol L⁻¹), or **3a** (0.010 mol L⁻¹) in aqueous Na₂CO₃ solution (0.011 mol L⁻¹, 10 mL) at 30°C for over 5 days. The equilibrium concentration of **1**, **2a**, and **3a** in the outer solution were determined using ultraviolet and visible (UV-Vis) spectroscopy (Agilent 8453, Agilent technologies Inc., Santa Clara, CA, USA) at wavelength of 270, 285, and 309 nm, respectively. After imbibing the diffusing species, the dimensions of the gels were measured with calipers. Each gel was suspended in a glass cuvette employing a wire basket and containing aqueous Na₂CO₃ solution (0.011 mol L⁻¹, 3.5 mL) and stirrer (350 rpm). The concentration changes of **1**, **2a**, or **3a** in the solution were measured periodically at sampling intervals of 1 min.

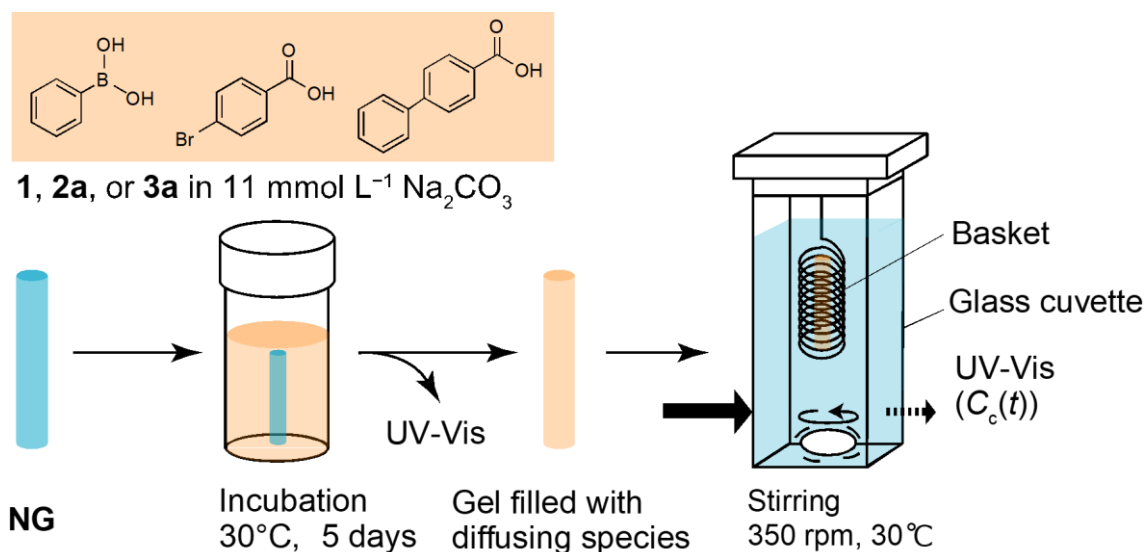


Figure 2-3. Diffusion experiment in **NG** using substrates (**1** and **2a**) and product (**3a**) in Suzuki coupling.

2.3 Results and Discussion

2.3.1. Properties of Pd/MPGs

A white and monolithic structure was obtained from all monomer compositions to prepare **MPGs**. The bulk volumes of the **MPGs** changed with temperature, and the thermo-responsiveness was suppressed by increasing BIS content (Figure 2-4a). Pd/**MPGs** was obtained by Pd(II)-ion adsorption and subsequent reduction into Pd(0). The Pd/**MPGs** were slightly brown (Figure 2-5, inset). The bulk volumes and thermo-responsiveness of the Pd/**MPGs** were almost identical to those of the original **MPGs** (Figure 2-4b). The internal morphologies of the Pd/**MPGs** were observed using FE-SEM (Figure 2-5). The pore sizes in the Pd/**MPGs** were in the order of several hundred nanometers and several micrometers (Figure 2-6 and Table 2-2). The q_{Pd} in the **MPGs** were around 1.3–2.1 $\mu\text{mol cm}^{-3}$ (Table 2-1). Pd(0) loaded on the **MPGs** were observed using TEM, with average Pd(0) sizes of 2.0–2.8 nm in all of the Pd/**MPGs** (Table 2-1 and Figure 2-7). In a similar manner, the Pd/porous glass membrane, Pd/ silica particles, and Pd/C were also evaluated (Figure 2-8).

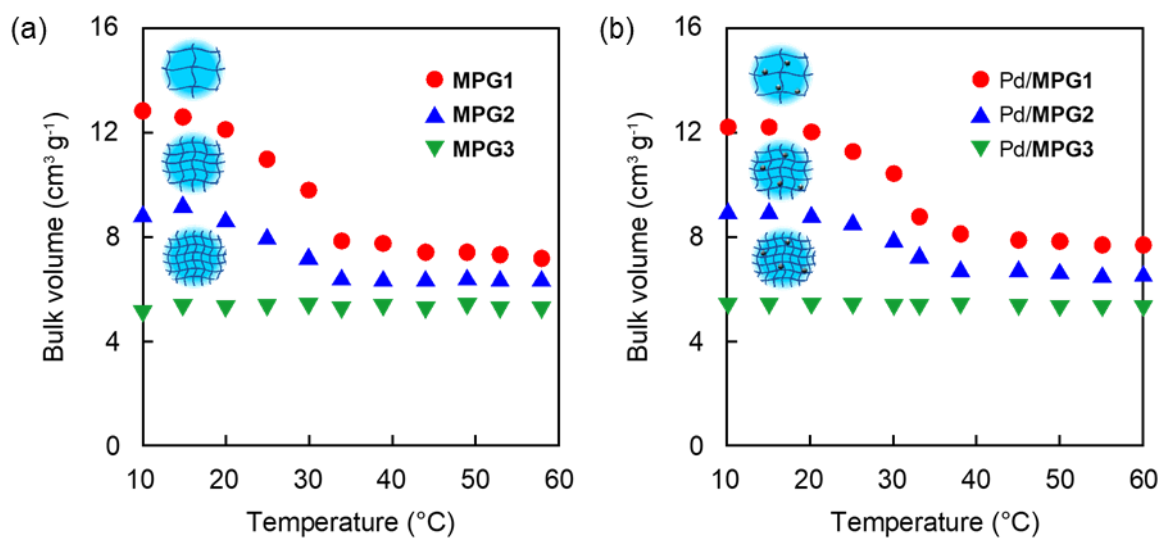


Figure 2-4. Bulk volumes changes of **MPG1**, **MPG2**, and **MPG3** with temperature swing in water (a) before and (b) after loading of Pd(0).

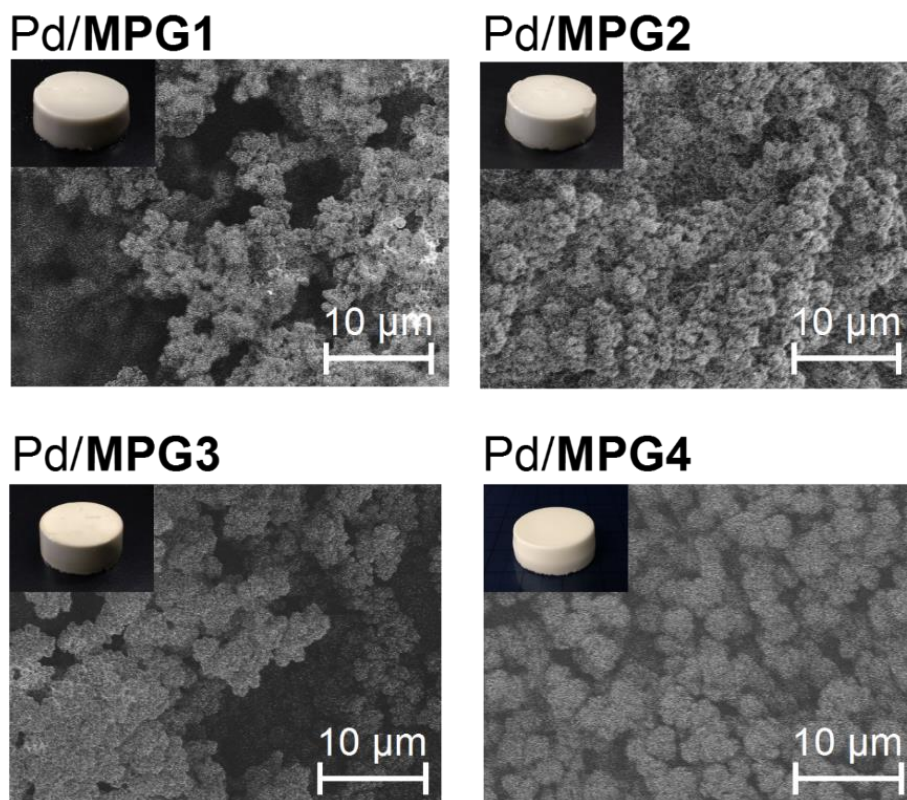


Figure 2-5. Photographic (inset) and FE-SEM images of Pd/MPG1, Pd/MPG2, Pd/MPG3, and Pd/MPG4.

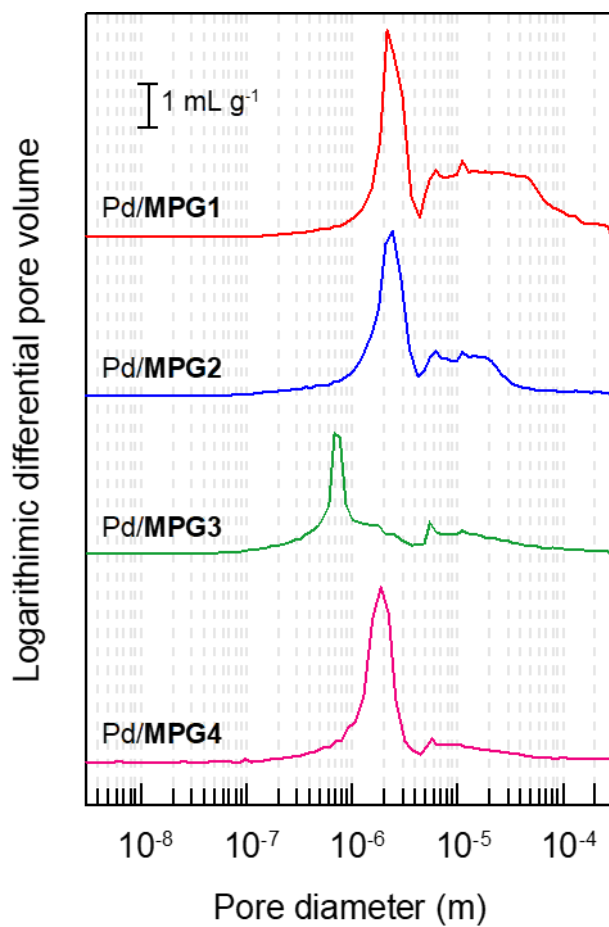


Figure 2-6. Pore size distributions of Pd/MPG1, Pd/MPG2, Pd/MPG3, and Pd/MPG4 determined using Hg porosimetry.

Table 2-2. Median Pore Sizes and Surface Areas of Pd/MPG1, Pd/MPG2, Pd/MPG3, and Pd/MPG4^a

Catalyst	Median pore size (nm)	Surface area (m ² g ⁻¹)	Porosity (-)
Pd/MPG1	8500	6	0.81
Pd/MPG2	3310	8	0.72
Pd/MPG3	810	13	0.67
Pd/MPG4	2220	5	0.59

^aMeasured using Hg porosimetry.

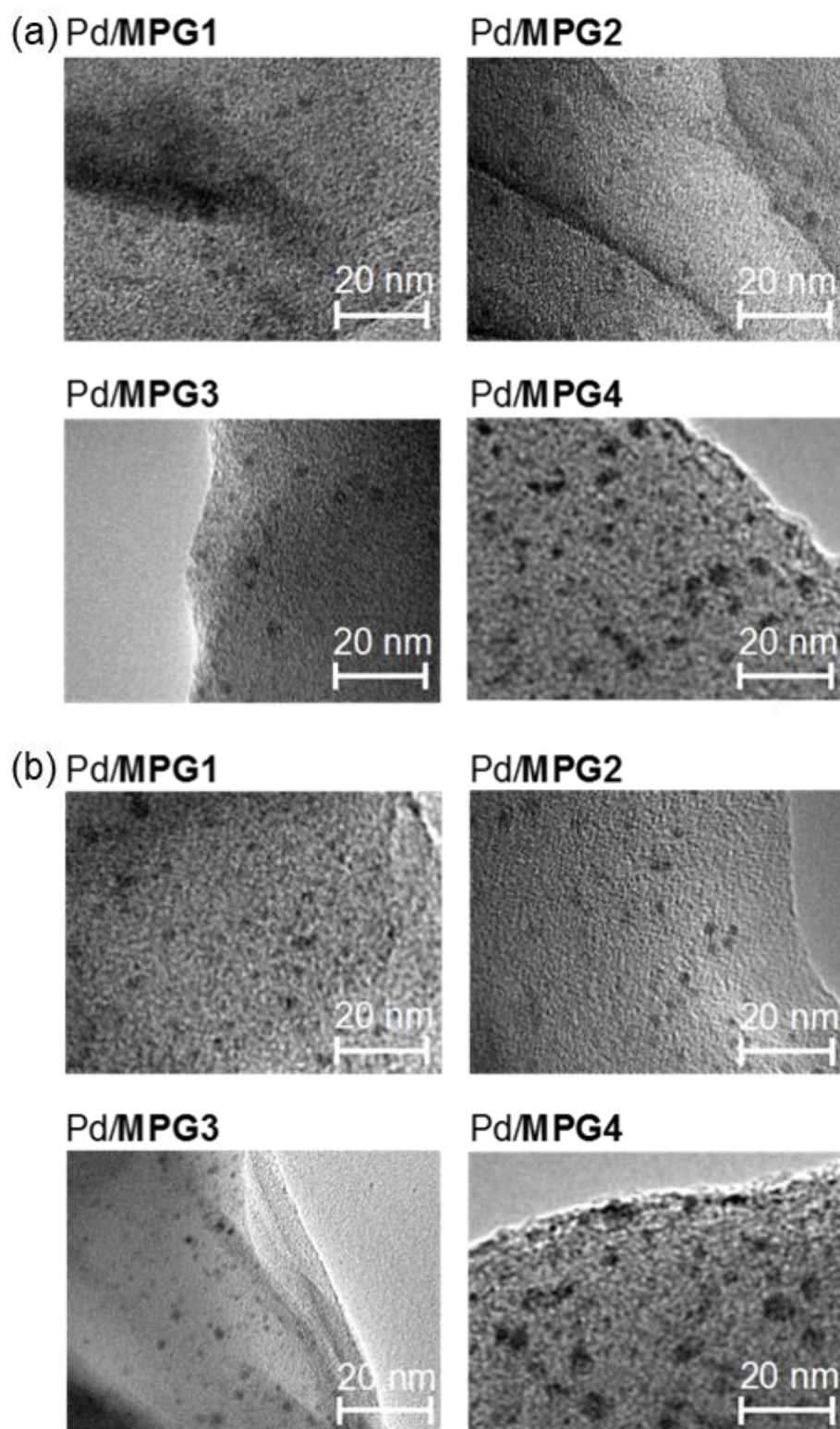


Figure 2-7. TEM images of Pd/MPG1, Pd/MPG2, Pd/MPG3, and Pd/MPG4 (a) before and (b) after 30-days uses in Suzuki coupling.

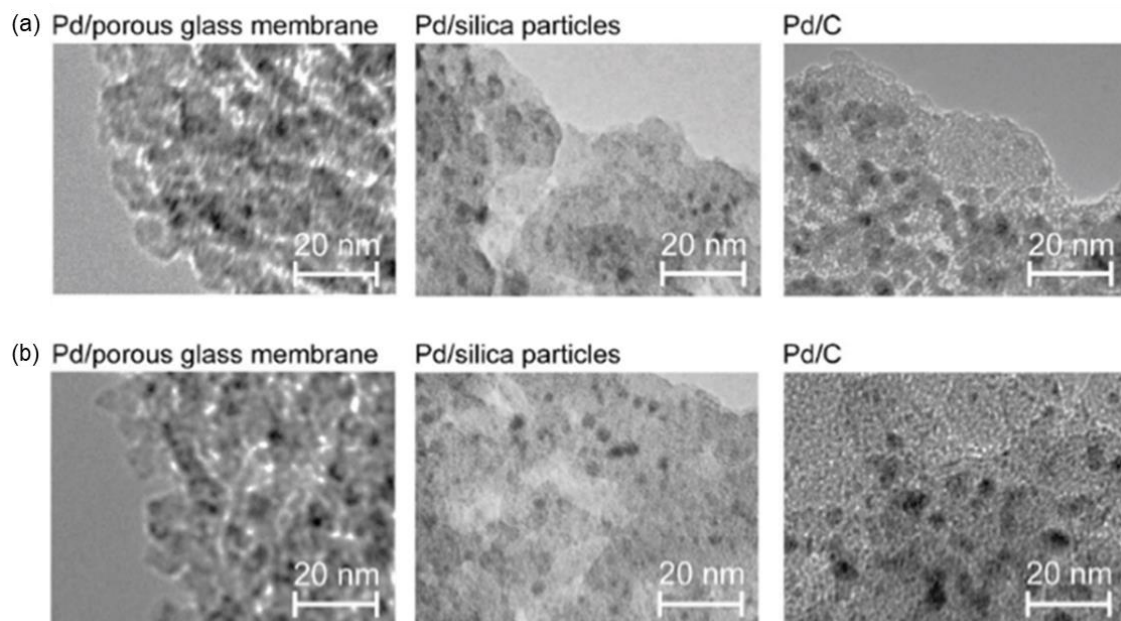


Figure 2-8. TEM images of Pd/porous glass membrane, Pd/silica particles, and Pd/C (a) before and (b) after 30-days uses in Suzuki coupling.

The bulk volumes of the **MPG1–3** were dependent on temperature, which was attributed to the phase transition of PNIPAm as a gel matrix (Figure 2-4a). The volume-change responsiveness to temperature was suppressed by increasing the BIS content. The increase in the cross-linker content in the PNIPAm gel could be regarded as parallel to the decrease in the gel network size.^[36] The network sizes of PNIPAm gels with BIS contents of 5, 10, and 30 mol % were calculated to be 7.9, 5.2, and 2.8 nm, respectively.^[37] The gel network sizes of the **MPGs** were indicated to be controlled by their BIS contents. The loading of Pd(0) did not affect the bulk volumes of the Pd/**MPGs** (Figure 2-4b), suggesting that the gel network sizes were conserved. The FE-SEM images showed that the Pd/**MPGs** had capillaries as interspatial pores (Figure 2-5), which would facilitate the continuous-flow system using the Pd/**MPGs**. As the average sizes of Pd(0) in the **MPGs** were smaller or almost equal to the gel network sizes (Table 2-1), reaction platforms were expected to be provided within the gel networks.

2.3.2. Permeabilities of Continuous-Flow Reactors

Before application in the continuous-flow system, the water permeabilities of support materials were evaluated. When water permeated through **NG1** at Q of 100 mL h^{-1} , the ΔP was tremendously high and never reached a steady state (Figure 2-9a). However, water permeation through **MPG1** gave moderate ΔP under the same conditions. The ΔP at the steady state proportionally increased with increasing Q (Figure 2-9b). The k_D of **MPGs**, porous glass membrane, and silica particles were estimated to be around 10^{-14} – 10^{-13} m^2 (Figure 2-10), which were comparable to those of commercially available membrane filters with pore sizes ranging from 10^3 to 10^4 nm .^[38] The k_D of **MPGs** were slightly decreased with increasing their BIS contents. After loading of Pd(0), the k_D was in almost of the same order as that of the original supports (Figure 2-9c and 2-10). Pd/C also showed almost the same k_D ($2.4 \times 10^{-14} \text{ m}^2$) as those of porous glass membrane and silica particles.

The **MPGs** exhibited their excellent permeabilities, which were attributed to the capillaries (Figure 2-9b). However, water could not permeate through the **NG1** (Figure 2-9a). Therefore, it was difficult to apply the **NG** to a continuous-flow process. The permeabilities of Pd/**MPGs** slight decreased with decreasing their pore size (Figure 2-6 and Table 2-2). As the water permeabilities of the Pd(0)-loaded supports were acceptable (Figure 2-9c and 2-10), it was expected that Suzuki coupling reactions could be achieved in the continuous-flow system with moderate ΔP .

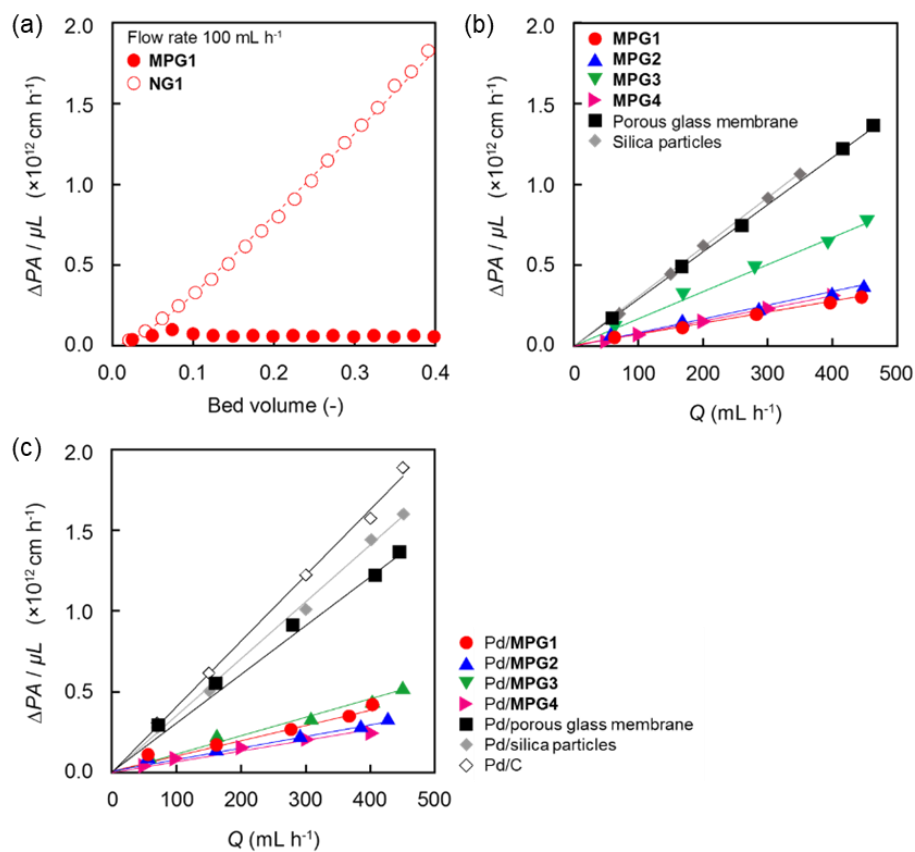


Figure 2-9. Water permeation properties of continuous-flow reactors at 30°C. (a) ΔP changes along with water permeating through **MPG1** and **NG1**. (b) ΔP v.s. Q of water diagram using support materials before loading of Pd(0). (c) ΔP v.s. Q of water diagram using Pd(0)-loaded supports.

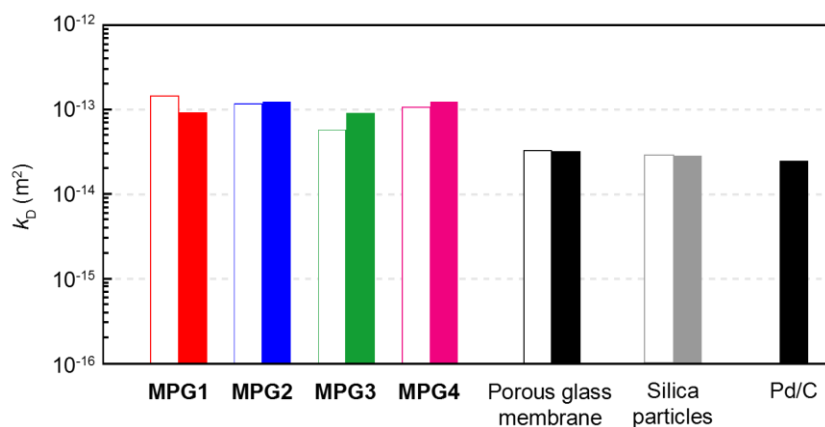


Figure 2-10. Permeation coefficients of support materials before (open rectangle) and after (filled rectangle) loading of Pd(0).

2.3.3. Suzuki Coupling Reaction in Batch System

Pd(0)-loaded supports were applied to batch Suzuki coupling between **1** and **2a** (Scheme 2-3). In all Pd-supported catalysts, the formation of **3a** was confirmed by HPLC measurements and the conversion of **1** increased with increasing reaction time (Figure 2-11). Pd/**MPG1-3** converted > 85% of **1** within 36 h of reaction time (Table 2-3). Pd/**NG1-3** also showed > 55% conversion at 36 h. Furthermore, the TOFs of all the Pd/**MPGs** were more than twice as large as those of all the Pd/**NGs**. On the other hand, the Pd/porous glass membrane and Pd/C were only 41 and 36% conversions, respectively. Pd/silica particles showed > 99% conversion.

Pd/**MPG** and Pd/**NG** converted substrate **1** very quickly compared to that supported on porous glass membrane and carbon (Figure 2-11). The reaction platform in **MPGs** and **NGs** was considered to be the inside of gel network. The swelling polymer chains in the **MPGs** and **NGs** have relatively high mobility and large space for molecular diffusion. Even when Pd(0) was immobilized within the gel network via tertiary amine ligands, the substrate and product could access the Pd(0) catalyst with a relatively high diffusivity. On the other hand, when Pd/porous glass membrane and Pd/C were used as catalysts, it was expected that Pd(0) on the support surface was mainly involved in the catalytic cycle since the molecular diffusion into Pd(0) in the micropores of the non-swelling inorganic supports might be severely limited. The TOF ($> 23 \text{ h}^{-1}$) of Pd/**NG** with no macropores was larger than those of Pd/porous glass membrane and Pd/C (20 and 12 h^{-1}), suggesting that molecular diffusion of the reactants into the material support was the rate-determining step in the present batch Suzuki coupling (Table 2-3). Owing to the presence of silanol groups on the support surface, Pd/SiO₂ had somehow hydrophilic environment around the immobilized Pd catalyst and show the fastest conversion of reactants on their large surface of particles. From these experiments, the catalytic efficiency of the hydrogel-supported Pd(0) was considered to be larger than that of the inorganic support. The usefulness of the gel network as a reaction platform is further enhanced by the formation of macropores

in the **MPG**. The macropores and gel network of Pd/**MPG** are ideal for catalytic cycles, maximizing accessibility of reactants to the catalyst.

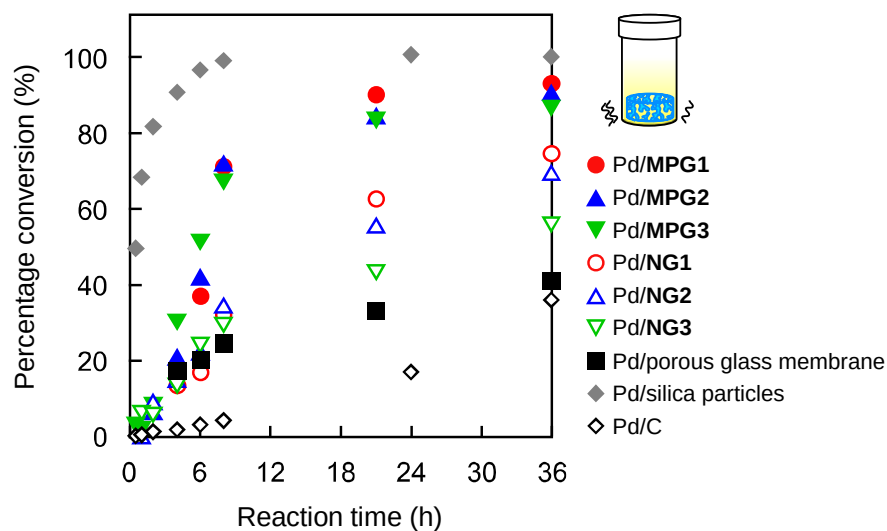


Figure 2-11. Time course of conv. for batch Suzuki coupling using Pd(0)-loaded supports.

Conditions: **1** (0.010 mol L⁻¹, 1.0 eq.), **2a** (0.011 mol L⁻¹, 1.1 eq.), Na₂CO₃ (0.011 mol L⁻¹, 1.1 eq.),

Pd catalyst (0.09–0.17 mol%), water, 30°C, 36 h.

Table 2-3. Conversion Percentage, TON, and TOF for Batch Suzuki Coupling Using Pd(0)-Loaded Supports^a

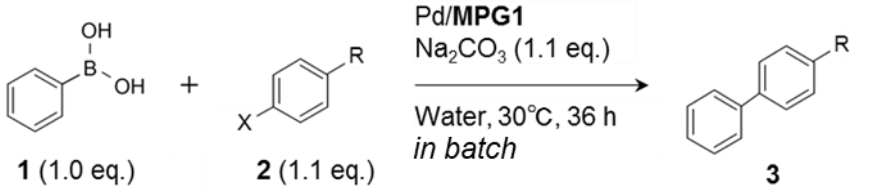
Catalyst	Reaction platform	Conv. of 1 (%) ^b	TON (-)	TOF (h ⁻¹) ^c
Pd/MPG1	gel network	92	987	75
Pd/MPG2	gel network	90	833	70
Pd/MPG3	gel network	86	506	47
Pd/NG1	gel network	74	520	24
Pd/NG2	gel network	69	537	41
Pd/NG3	gel network	55	322	31
Pd/porous glass membrane	support surface	41	248	20
Pd/silica particles	support surface	> 99	1004	490
Pd/C	support surface	36	359	12

^aConditions: **1** (0.010 mol L⁻¹), **2a** (0.011 mol L⁻¹), Na₂CO₃ (0.011 mol L⁻¹), Pd-loaded support (0.09–0.17 mol%), water, 30°C, 36 h. ^bMeasured from concentration of **1** after reaction using HPLC. ^cDetermined within the reaction period, when the reaction proceeded proportionally to the time.

Batch Suzuki coupling of **1** with other aryl halides (**2**) was also performed using Pd/MPG1 (Table 2-4). Almost all substrates were successfully converted to biaryl when either aryl iodides (**2b–2f**) or aryl bromides (**2g** and **2h**) were used. However, Pd/MPG1 could not induce Suzuki coupling with aryl

chlorides (**2i–k**).

Table 2-4. Pd-Catalyzed Suzuki Coupling Between **1 and Various Aryl Halides (**2**) Using Pd/MPG1^a**

		
Entry	Aryl halide	Conv. into 3 (%) ^b
1	2b (X = I, R = H)	98
2	2c (X = I, R = OH)	92
3	2d (X = I, R = OMe)	96
4	2e (X = I, R = CHO)	> 99
5	2f (X = I, R = COOH)	> 99
6	2g (X = Br, R = OMe)	95
7	2h (X = Br, R = COMe)	97
8	2i (X = Cl, R = Me)	0
9	2j (X = Cl, R = SO ₃ H)	0
10	2k (X = Cl, R = COOH)	0

^aConditions: **1** (0.010 mol L⁻¹), **2** (0.011 mol L⁻¹), Na₂CO₃ (0.011 mol L⁻¹), Pd/MPG1 (0.1 mol%), water, 30°C, 36 h.

^bMeasured from concentration of **1** after reaction using HPLC.

2.3.4. Suzuki Coupling Reaction in Continuous-Flow System

Pd(0)-loaded supports were applied to the Suzuki coupling reaction between **1** and **2a** under continuous-flow condition (Scheme 2-1c). The TONs of Pd(0)-loaded supports were estimated along

with permeation of the substrate at a fixed Q ($\tau = 0.5$ h) for 30 days (Figure 2-12). In all of the catalysts, there were no aggregations of Pd(0) observed from TEM images after the Suzuki coupling reaction (Figure 2-7b and 2-8b). Remarkably, the TONs of Pd/**MPG1**, Pd/**MPG2**, Pd/**MPG3**, and Pd/**MPG4** were 2631, 2290, 1333, and 1369, respectively, which were considerably higher than those of the Pd/porous glass membrane, Pd/silica particles, and Pd/C (65, 144, and 26) (Table 2-5). In addition, Pd leaching from the Pd/**MPGs** were below the detection limit of ICP-AES (< 10 ppb). However, Pd leaching from the Pd/porous glass membrane, Pd/silica particles, and Pd/C were detected to be 5.0, 2.9, and 1.6% in total (with respect to Pd loading in the column), respectively.

Surprisingly, the productivities of Pd/**MPG1–3** were well maintained without any Pd leaching, whereas those of the Pd/porous glass membrane and Pd/silica particles were lost during 30 days of use due to Pd leaching (Figure 2-12). It should be noted that the TONs of the Pd/porous glass membrane, Pd/silica particles, and Pd/C under batch condition were much higher (248, 1004, and 720, Table 2-3) than of those under continuous-flow condition (65, 144, and 26). Using the porous glass membrane, silica particles, and carbon as support materials, active Pd(0) were localized on the surface accounting for 1.6–5.0% of total Pd loadings and the rest should present in their interior (micro–meso pores). The Pd(0) on the surface were only accessible by reactants due to the severe diffusion limitation in the micro–meso pores and eluted easily under continuous-flow conditions. The solid-liquid contacting efficiency on the Pd/porous glass membrane was expected to be higher than that on the Pd/silica particles.^[39] However, the improved efficiency resulted in a larger leaching percentage from the Pd/porous glass membrane (5.0%) than that from the Pd/silica particles (2.9%). Using the **MPGs** as support materials, Pd(0) was fully taken up into the gel networks. A moderate steric hindrance by polymer chain and/or weak coordination of amide groups,^[40] and multi-point interaction by tertiary-amine ligands in the hydrogel network allowed effective retention of Pd(0) while fast molecular transport in the gel network (Figure 2-13).

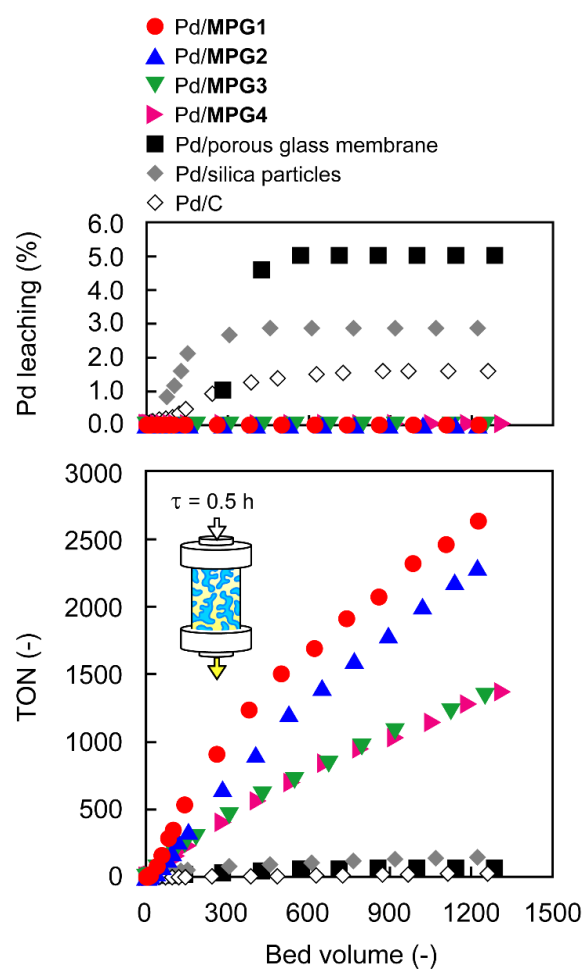


Figure 2-12. TONs of Pd(0)-loaded supports and Pd leaching study for the continuous-flow Suzuki coupling. Conditions: **1** (0.010 mol L^{-1}) and **2a** (0.011 mol L^{-1}) in aqueous Na_2CO_3 solutions (0.011 mol L^{-1}), 30°C , $\tau = 0.5 \text{ h}$, 30 days.

Table 2-5. TONs of Pd-Loaded Supports and Pd Leaching Study for the Continuous-Flow Suzuki Coupling^a

Catalyst	Reaction platform	Surface area (m ² g ⁻¹) ^b	TON (-) ^c	Pd leaching (%) ^d
Pd/MPG1	gel network	6	2631 (1228)	n.d. ^e
Pd/MPG2	gel network	8	2290 (1222)	n.d.
Pd/MPG3	gel network	13	1333 (1251)	n.d.
Pd/MPG4	gel network	5	1369 (1314)	n.d.
Pd/porous glass membrane	support surface	12	65 (1286)	5.0
Pd/silica particles	support surface	443	144 (1222)	2.9
Pd/C	support surface	946	26 (1260)	1.6

^aConditions: **1** (0.010 mol L⁻¹) and **2a** (0.011 mol L⁻¹) in aqueous Na₂CO₃ solutions (0.011 mol L⁻¹), 30 °C, τ = 0.5 h, 30 days. ^bDetermined by Hg intrusion or N₂ adsorption for **MPGs** or inorganic supports, respectively. ^cBed volume was shown in the parenthesis. ^dDetermined using ICP-AES. ^eNot detected.

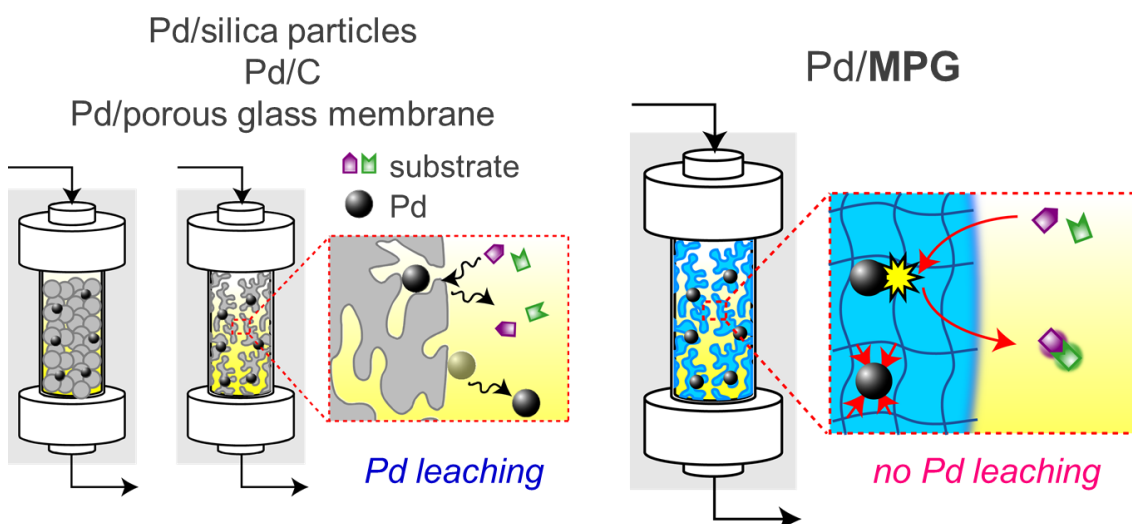


Figure 2-13. Conceptual illustration of Pd(0)-loaded supports for Pd-catalyzed Suzuki coupling in continuous-flow system.

The TOFs of the Pd(0)-loaded supports were calculated using the TONs and time on stream (Figure 2-14). Pd/**MPGs** clearly showed the burst phase of products at the early stage in the reaction, and provided the TOFs at steady state, which were considerably higher than those of Pd(0)-loaded inorganic supports. Considering the large surface area of inorganic supports, the TOFs of Pd on the inorganic supports were too low to compare with those of Pd/**MPGs** in the early period of the reaction, when the Pd leaching could be neglected. Some reports demonstrated that the positive effect of polymer gel supports on the uptake of both of the hydrophilic and hydrophobic reactants in the supports to accelerate the molecular conversions.^[41] As for the “true” catalytic activity of the immobilized Pd center, the coordination state of Pd might be different in **MPGs** from those on inorganic supports since the Pd catalyst should be surrounded three-dimensionally by amide groups and tertiary amine ligands in the PNIPAm gel network. Kaneda and co-workers performed the Pd K-edge X-ray absorption fine structure (XAFS) and Pd L₃-edge X-ray absorption near edge structure (XANES) analyses and revealed that the amine-rich reaction platform in the dendrimer provided the Pd sub-nanoclusters, which were highly active in phosphine-free allylic substitution reaction.^[42,43] In the present system, increasing the amine ligand density did not influence on the TOFs of Pd/**MPGs** (Pd/**MPG3** and Pd/**MPG4**) and further increase in amine density failed due to lack of macroporous structure of the resulting gel.^[35] The coordination of amide groups^[40] in the PNIPAm gel might work to formulate the Pd sub-nanoclusters and boost their TOFs in Pd/**MPGs**.

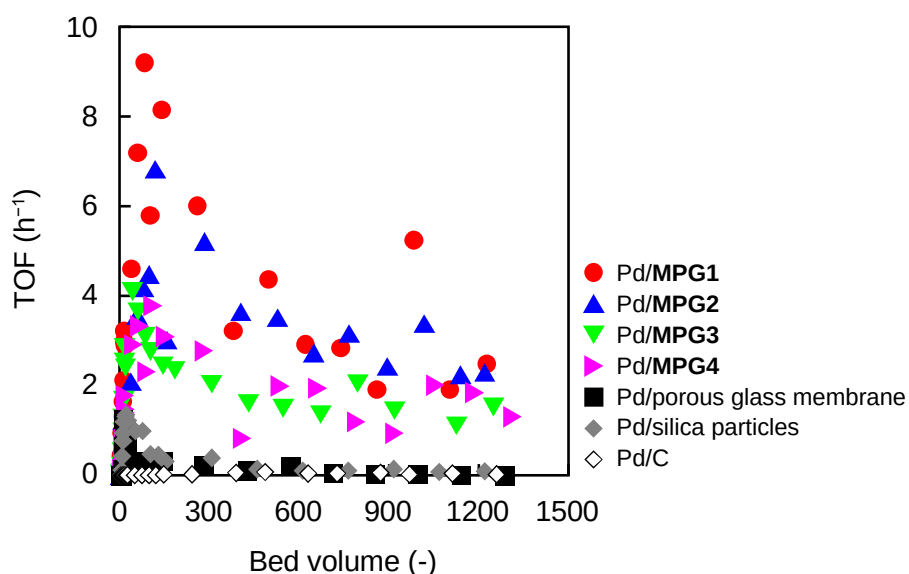


Figure 2-14. Changes in TOFs of Pd(0)-loaded supports in the continuous-flow Suzuki coupling. Conditions: **1** (0.010 mol L⁻¹) and **2a** (0.011 mol L⁻¹) in aqueous Na₂CO₃ solutions (0.011 mol L⁻¹), 30 °C, τ = 0.5 h, 30 days.

2.3.5. Effect of Gel Network Size on Catalytic Activity of Pd(0) in Continuous-Flow System

Kinetics studies of the Suzuki coupling reaction under continuous-flow conditions were conducted using Pd/ **MPGs** with different BIS contents (Figure 2-15). The percentage conversion into **3a** increased with increasing τ of the substrates. The TOFs of the Pd/**MPG1**, Pd/**MPG2**, Pd/**MPG3**, and Pd/**MPG4** were 27.4, 16.1, 7.8, and 6.4 h⁻¹, respectively (Table 2-6). Interestingly, the Pd/**MPG1** exhibited a 3.5-fold higher TOF than that of Pd/ **MPG3**.

Using Pd/**MPG1**, the highest TOF was achieved for the Suzuki coupling reaction in the continuous-flow system (Table 2-6). The surface areas of capillaries in the **MPGs** increased with increasing BIS contents (Table 2-2), supporting that molecular transport on the surface of the capillaries was not rate-limiting. The TOFs of the Pd/**MPGs** were likely to be dependent on the size of the gel network provided as a reaction platform. In fact, the TOFs of Pd/**MPG3** and Pd/**MPG4** were almost the same (7.8 and 6.4 h⁻¹), and the density of tertiary amines used as ligands to Pd(0) did not

significantly affect the catalytic efficiency of Pd. This suggested that the molecular diffusion of reactants was dominant in determining the reaction kinetics.

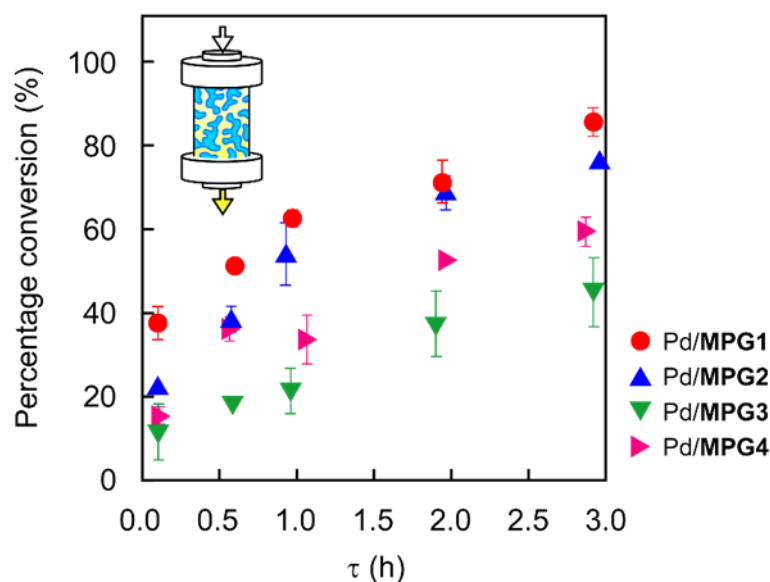


Figure 2-15. Kinetics study on the Suzuki coupling reaction using Pd/MPGs in the continuous-flow system. Conditions: **1** (0.010 mol L⁻¹) and **2a** (0.011 mol L⁻¹) in aqueous Na₂CO₃ solutions (0.011 mol L⁻¹), 30 °C.

Table 2-6. TOFs for the Continuous-Flow Suzuki Coupling Using Pd/MPGs^a and Diffusion Coefficients of the Substrates and Product in the Gel Network

Catalyst	<i>D</i> in gel network ($\times 10^{-10}$ m ² s ⁻¹) ^b			TOF (h ⁻¹)
	1	2a	3a	
Pd/MPG1	5.8	8.0	3.5	27.4
Pd/MPG2	4.9	3.9	2.1	16.1
Pd/MPG3	1.2	3.2	1.2	7.8

^aConditions: **1** (0.010 mol L⁻¹) and **2a** (0.011 mol L⁻¹) in aqueous Na₂CO₃ solutions (0.011 mol L⁻¹), 30 °C. ^bEstimated using **NGs** with the same monomer composition as **MPGs**.

NGs with different BIS contents (**NG1**, **NG2**, and **NG3** with BIS contents of 5, 10, and 30 mol%) were prepared and tested for diffusion experiments of **1**, **2a**, and **3a** in the **NGs** (Figure 2-16a). The diffusion of a solute from an infinite circular cylinder to a well stirred solution of limited volume was dealt by Carman and Haul^[44] as follows:

$$\frac{C(t)}{C_{\infty}} = 1 - \sum_{n=1}^{\infty} \frac{4\alpha(1+\alpha)}{4+4\alpha+\alpha^2 q_n^2} \exp\left(-\frac{Dtq_n^2}{a^2}\right) \quad (2-4)$$

where t , a , $C(t)$, and C_{∞} are the time, radius of cylindrical gel, solute concentration at $t = t$, and solute concentration at $t = \infty$ (equilibrium state), respectively. α and q_n satisfy following equations:

$$\alpha = \frac{\text{Solution volume}}{\text{gel volume}} \times K \quad (2-5)$$

$$2J_1(q_n) + \alpha q J_0(q_n) = 0 \quad (2-6)$$

where K and $J_m(q_n)$ are the equilibrium partition coefficient and Bessel's function of the m -th order. The diffusivities of solutes in gel networks were estimated by iteration with those to minimize the root-mean-square errors between experimental data and simulated data. It was found that the D of **1**, **2a**, and **3a** in the **NGs** were comparable to those of small molecules in bulk liquid.^[45] Interestingly, the D increased with decreasing the BIS contents of the **NGs** (Table 2-6). Furthermore, molecular diffusion within **MPG** was faster than all the **NGs** (Figure 2-16b).

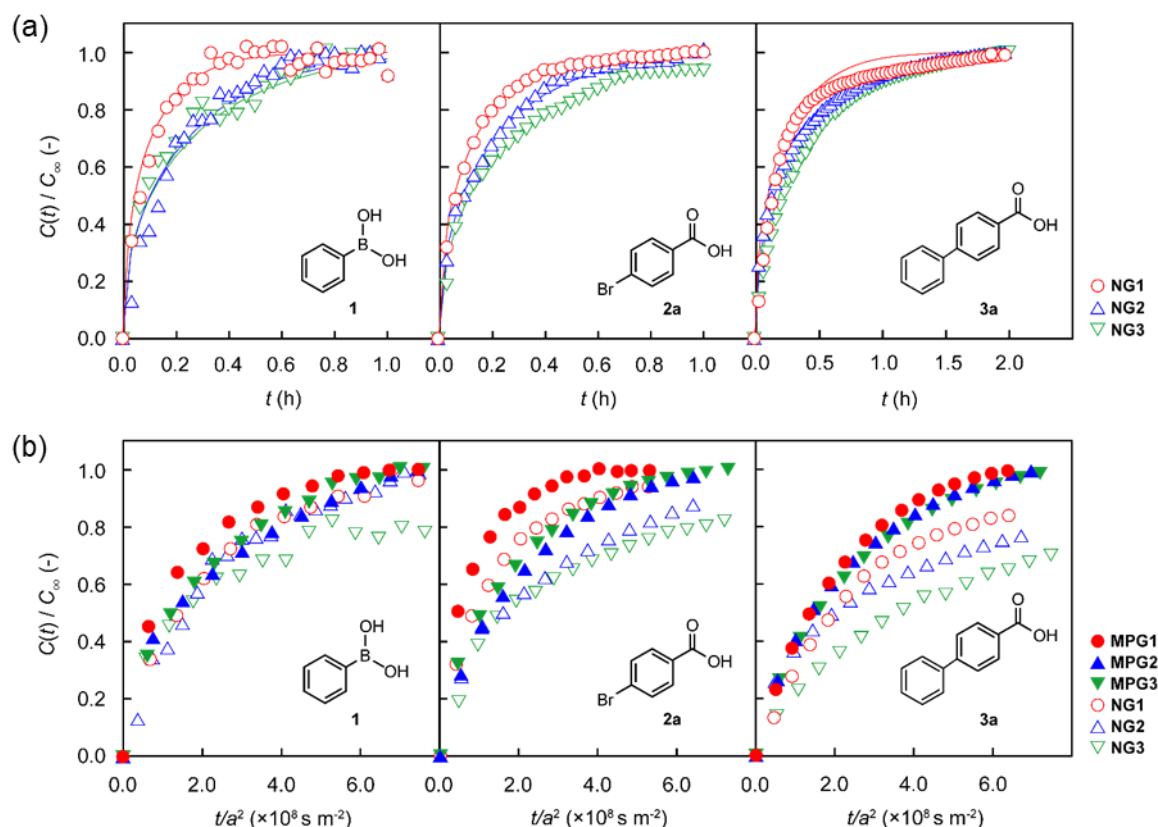


Figure 2-16. (a) Diffusion curves for **1**, **2a**, and **3a** from cylindrical **NGs**. (b) Diffusion curves of **1**, **2a**, and **3a** from cylindrical **MPGs** and **NGs**.

In the gel network, diffusivities of substrates and product were well maintained because of the flexible polymer chain of PNIPAm gel. The D values increased with increasing gel network size (Table 2-6) and were similar to those previously reported.^[46–49] If the molecular diffusions in the gel network were rate-limiting steps in the Suzuki coupling reaction, the D values would strongly influence catalytic activities, as demonstrated (Figure 2-15 and Table 2-6). The **MPG** with macropores showed faster substrate and product release than **NG** (Figure 2-16b). The molecular diffusion was accelerated by macroporous architectures of **MPGs** as well as the highly retained D in the gel network, which were strongly supported by the results of batch Suzuki couplings (Figure 2-11 and Table 2-3). Therefore, the design of hierarchical permeabilities in a capillary and gel network were key factors in

constructing a highly efficient continuous-flow reactor for chemical synthesis.

2.4 Conclusions

A continuous-flow reactor using the monolithic porous gel, **MPG**, for chemical synthesis was proposed. The **MPGs** had capillaries as interspatial pores, and the **MPG** gel network sizes were controlled by tuning a feed ratio of the cross-linking monomer. The capillaries in the **MPG** allowed continuous-flow application. The **MPGs** showed excellent permeabilities comparable with those of commercially available membrane filters with pore sizes in the range 10^3 – 10^4 nm. Owing to the moderate steric hindrance of the gel network, Pd/**MPG** showed significant stability and catalytic activity in a Suzuki coupling reaction under continuous-flow conditions. However, little performance was observed in the inorganic supports. The catalytic activities of the Pd/**MPGs** were dependent on the gel network size, which corresponded to the diffusivities of the substrates and product. The **MPG** provides an easy and sophisticated strategy for preparing and functionalizing a continuous-flow reactor for chemical synthesis. In conjunction with a practical process, the **MPG** would have a significant impact on the field of current continuous-flow reactors. The conceptual design of a hydrogel network can be extended to a reactor design for chemical synthesis in a continuous-flow system under aqueous media. The concept should be further extended to other types of continuous-flow catalytic reactions using transition-metal catalysts.

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Chapter 3

Investigation of Cross-Linking Effect on Site-Isolation of Ligand for Mono-Ligated Metal in Organogel-Based Monolith

Chapter 3 Investigation of Cross-Linking Effect on Site-Isolation of Ligand for Mono-Ligated Metal in Organogel-Based Monolith

Abstract

Hybridization of porous synthetic polymer and sophisticated ligands play an important role in transition-metal catalysis for chemical transformations at laboratory and industrial levels. A monolithic porous polymer, which is a single piece with continuous macropores, is desired for high permeability, fast mass transfer properties, high stability, and easy modification. Herein, a monolithic porous polystyrene containing three-fold cross-linking PPh_3 (TPP) was first developed, which were called **M-PS-TPP**, for transition-metal catalysis. The monolithic and macroporous structure of **M-PS-TPP** was fabricated via polymerization-induced phase separation using porogenic solvent. Moreover, the **M-PS-TPP** was synthesized using different feed ratios of divinylbenzene (DVB) for site-isolation and mono-P-ligating behavior of TPP ^{31}P CP/MAS NMR analysis revealed that the different selectivity of **M-PS-TPPs** was obtained in formation of mono-P-ligation toward Pd^{II} . The macroporous properties and controlled mono-P-ligating behavior of **M-PS-TPP** facilitated the challenging Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl chlorides (**Figure 3-1**).

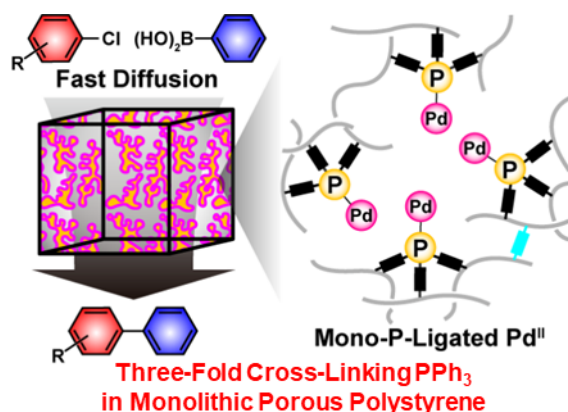


Figure 3-1. Schematic illustration of **M-PS-TPP** for site-isolation of TPP and Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl chlorides.

3.1 Introduction

Porous materials have received much attention for their potential in applications such as catalysts and gas separation and storage because of their controllable pore size and large surface area.^[1] In particular, porous synthetic polymers have straight-forward preparation, flexible chemical modification, high stability, and insolubility. This makes porous synthetic polymers attractive for energy efficient, cost-effective, and recyclable systems in laboratory and industrial processes.^[2] During the past few decades, increasing demand for porous synthetic polymers have motivated the development of micro-,^[3] meso-,^[4] and macroporous^[5] organic polymers. Among them, monolithic porous polymers, which consist of a single piece containing continuous macropores, have attracted much attention because of their high permeability, fast mass transfer properties, high stability, and ease of modification.^[6,7] Monolithic porous polymers containing NHC,^[8,10b] pyridine,^[9] bipyridine,^[10] pybox,^[11] and phosphine^[12] moieties have all been applied in transition-metal catalysis.

The combination of materials science and organic chemistry has led to innovative chemical transformations in science and industry. Recently, Sawamura and co-workers developed a cross-linked polystyrene (PS)-phosphine hybrid, where three-fold vinylated PPh₃ (TPP) was copolymerized (**PS-TPP**).^[13] In the beaded **PS-TPP**, the TPP unit was site-isolated and favored mono-P-ligation towards Pd^{II}. This resulted in excellent activity for Suzuki-Miyaura cross-coupling reactions of unactivated aryl chlorides, which are typically challenging.^[14] Further to the molecular design of the ligand, modulating the design of **PS-TPP** while maintaining the coordination behavior of the TPP unit is essential. In this context, the monolithic and macroporous structure in **PS-TPP** could provide a catalytic system with fast mass transfer. For efficient and practical chemical transformations, the **PS-TPP** system has three requirements: 1) selective mono-P-ligation, 2) monolithic and macroporous structure, and 3) fast mass transfer. This has not yet been achieved experimentally. Here, a monolithic porous **PS-TPP (M-PS-TPP)** where the TPP unit is arranged for site-isolation and mono-P-ligation

toward Pd^{II} (Figure 3-2) is reported. The monolithic and macroporous structure of **M-PS-TPP** was achieved via polymerization-induced phase separation using a porogenic solvent.^[7] The TPP unit was carefully arranged in **M-PS-TPP** by varying the feed ratio of divinylbenzene (DVB) as a cross-linker to favor mono-P-ligation, while maintaining the macroporous structure. Measurement of physical properties (macroporous structure or diffusivity of reactants) and ³¹P CP/MAS NMR spectra were used to evaluate the molecular diffusion in the **M-PS-TPPs** and their mono-P-ligating behavior. The Pd-loaded **M-PS-TPP** (**M-PS-TPP-Pd**) was applied to Suzuki-Miyaura cross-coupling reactions of unactivated aryl chlorides. The **M-PS-TPP-Pd** showed excellent catalytic efficacy regulated by the macroporous structure and spatial density of TPP.

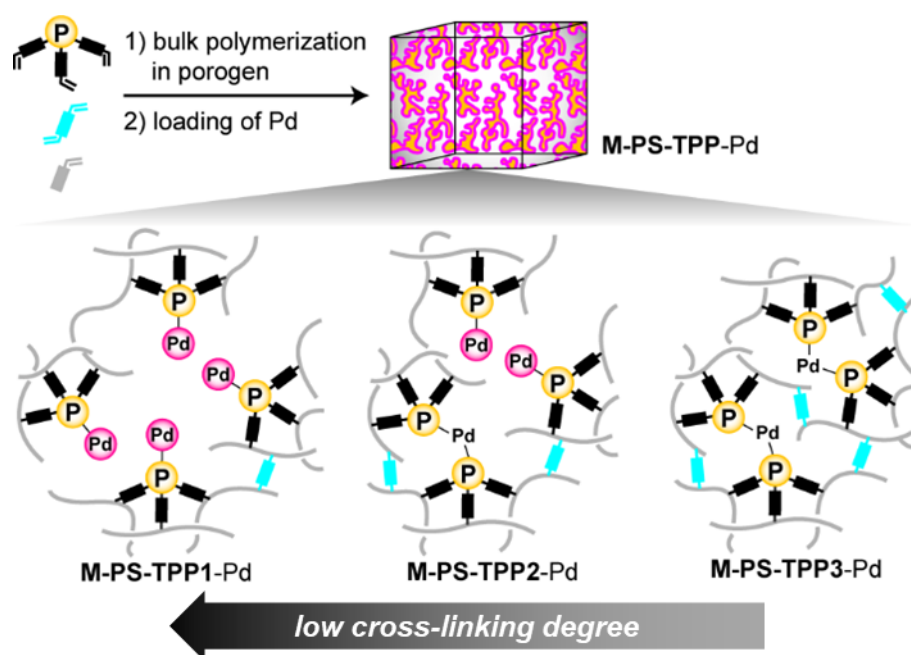


Figure 3-2. Schematic representation of the preparation of monolithic porous PS-threefold vinylated TPP hybrids (**M-PS-TPP1-3**) and controlled formation of mono-P-ligated Pd^{II} complex by divinylbenzene (DVB) contents. TPP units (set of yellow ball and three black nodes), mono-P- ligated Pd^{II} center (pink balls), DVB units (blue nodes), and PS chains (gray lines) are shown.

3.2 Experimental Section

3.2.1. *Generals*

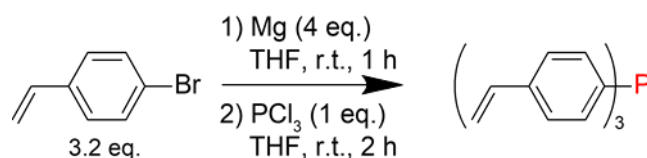
The samples for field emission scanning electron microscopy (FE-SEM) analysis were coated with platinum (thickness: approx. 4 nm) using an JEOL JFC-1600 auto fine coater (JEOL Ltd., Tokyo, Japan). FE-SEM analysis was performed on a Hitachi SU8000 microscopy (Hitachi High-Technologies Corporation, Tokyo, Japan). Hg intrusion porosimetry analysis was performed on a Micromeritics AutoPoreIV9520 (Micromeritics Instrument Co., Norcross, GA, USA). Fourier transform-infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectroscopy (PerkinElmer Inc., Waltham, MA, USA) at room temperature in air with 2 cm^{-1} spectral resolution and 100 scans. Compressive stress-strain measurements were performed on a MinebeaMitsumi LTS-50N-S100 tester (MinebeaMitsumi Inc., Nagano, Japan). The samples for transmission electron microscopy (TEM) analysis were prepared by placing a drop of THF suspension of monoliths onto a carbon-coated copper grid and allowing THF to be evaporated under air. TEM analysis was performed on a Philips FEI Tecnai 20 (Philips FEI, Hillsboro, OR, USA) with accelerating voltage of 200 kV. Ultraviolet-visible (UV-Vis) spectra were recorded on an Agilent 8453 spectroscopy (Agilent technologies Inc., Santa Clara, CA USA). Solution nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECZ400S spectroscopy, operating at 400, 101, and 162 MHz for ^1H , ^{13}C , and ^{31}P NMR, respectively. Chemical shifts values for ^1H , ^{13}C , and ^{31}P NMR spectra were referenced to Me_4Si , the residual solvent, and 85% H_3PO_4 , respectively. Cross polarized/magic angle spinning (CP/MAS) NMR spectra were recorded on a Bruker AVANCE III 500 spectroscopy (Bruker Co., Billerica, MA, USA), operating at 203 MHz for ^{31}P NMR. Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis was performed on a Seiko Instruments SPS-1700 HVR spectroscopy (Seiko Instruments Inc., Chiba, Japan). High-performance liquid chromatography (HPLC) analyses were

performed on a JASCO LC-2000Plus system equipped with a JASCO DG-980-50 degasser, a JASCO PU-980 pump, a Kanto Chemical Mightysil RP-18 GP 250-4.6 column (Kanto Chemical Co., Tokyo, Japan), a JASCO UV-2077Plus UV detector, and a JASCO CO-2065Plus column oven (JASCO Co., Tokyo, Japan). Acetonitrile/water (80:20 v/v) containing trifluoroacetic acid (0.1 vol%) was employed as a mobile phase in the HPLC measurements. Thin-layer chromatography analyses were performed on aluminum sheers bearing 0.17–0.22 mm layer of Merck Silica gel 60F₂₅₄. Merck silica gel 60 (40–63 μ m, neutral, Merck Co., Darmstadt, Germany) was used for column chromatography.

All catalytic reactions were carried out under N₂ atmosphere. Materials were obtained from commercial suppliers unless otherwise noted. Styrene (>99% GC purity, stabilized with 4-*t*-butylcatechol, Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) and divinylbenzene (DVB, 3- and 4- mixture, contains ethylvinylbenzene and ethylbenzene, >80% GC purity, stabilized with 4-*t*-butylcatechol, Sigma-Aldrich Co., St. Louis, MO, USA) were purified using basic alumina column. 2,2'-Azobis(isobutyronitrile) (AIBN) was purified by recrystallization from MeOH. PCl₃ was purified by distillation under N₂ atmosphere before use.

3.2.2. Synthesis of TPP Monomers

Scheme 3-1. Synthesis of Threefold Vinylated TPP (TPP Monomer)



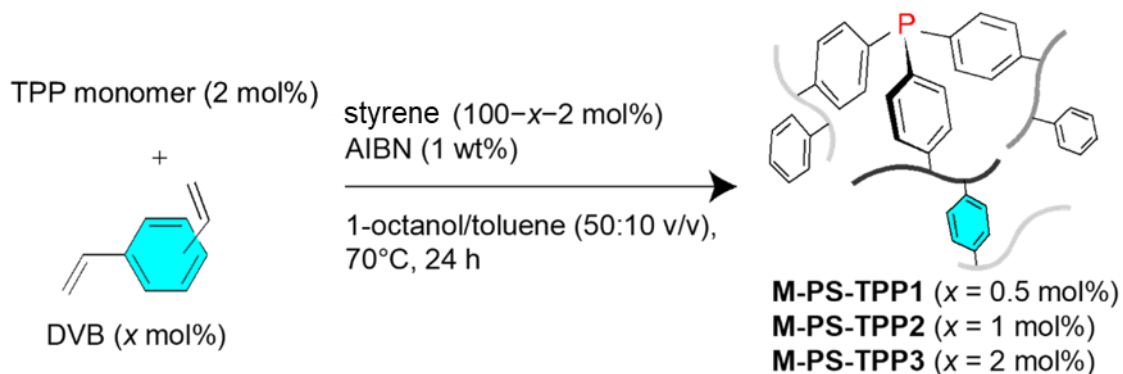
The threefold vinylated TPP (TPP monomer) was synthesized according to the previous reports (Scheme 3-1).^[13a,15] Mg turnings (2.40 g, 100 mmol, 4 eq) were placed in a 300-mL round-bottom flask equipped with a magnetic stirring bar. After addition of anhydrous THF, 80 mL) under N₂, 4-bromostyrene (14.64 g, 80 mmol, 3.2 eq) was slowly added to the flask followed by stirring at room

temperature for 1 h. PCl_3 (3.43 g, 25 mmol, 1 eq) was added to the solution in ice water bath over 0.5 h followed by stirring at room temperature for 4 h. Quenching with aq. NH_4Cl , the mixture was extracted with Et_2O . The organic layer was washed with water, dried over MgSO_4 , filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/ EtOAc 97:3 v/v) to give TPP as white solids (4.82 g, 57% yield).

^1H NMR (CDCl_3): δ 5.27 (d, J = 11.0 Hz, 3H), 5.77 (d, J = 17.4 Hz, 3H), 6.70 (dd, J = 17.4, 11.0 Hz, 3H), 7.23–7.38 (m, 12H). ^{13}C NMR (CDCl_3): δ 114.85 (3C), 126.44 (d, $J_{\text{C-P}}$ = 7.1 Hz, 6C), 134.00 (d, $J_{\text{C-P}}$ = 19.2 Hz, 6C), 136.45 (3C), 136.72 (d, $J_{\text{C-P}}$ = 10.1 Hz, 3C), 138.07 (3C). ^{31}P NMR (CDCl_3): δ –6.21.

3.2.3. Preparation of **M-PS-TPP**

Scheme 3-2. Synthesis of M-PS-TPP



The monolithic porous polystyrene (PS)-TPP (**M-PS-TPP**) was prepared by the bulk copolymerization of TPP (2 mol%), DVB (x mol%), and styrene ($100-x-2$ mol%) in a porogenic solvent (Scheme 3-2).^[7,13] The feed ratio of DVB was tuned to be $x = 0.5$, 1, and 2 mol% for preparation of **M-PS-TPP1**, **M-PS-TPP2**, and **M-PS-TPP3**, respectively. Monomers were dissolved in 1-octanol/toluene (50:10 v/v) followed by addition of AIBN (1 wt% with respect to monomers), to

give a monomer solution (1 mL, 3.5 mol L⁻¹). After degassing via three freeze-pump-thaw cycles, the monomer solution was poured into a glass vial (16 mm i.d.) in a glove box. The vial was sealed with a screw cap and removed from the glove box. The monomer solution was incubated at 70°C for 24 h. Carefully crushing the vial, the resulting polymer was washed by immersion in anhydrous THF for more than 1 day. The diameter and thickness of the THF-swollen **M-PS-TPP** was measured using calipers to give swelling volumes. The THF-swollen **M-PS-TPP** was cut into ~5 mm small blocks and dried in vacuo at room temperature overnight, to give a white solid polymer (0.32–0.33 g, 83–86% yield). The amount of TPP incorporated was 0.18 mmol g⁻¹ on the basis of feed ratio of TPP monomer (Table 3-1). The internal structure of the dried **M-PS-TPPs** were observed using FE-SEM. The porous properties of **M-PS-TPPs** were evaluated using Hg intrusion porosimetry. FT-IR studies of the **M-PS-TPPs** were conducted using FT-IR spectroscopy. For comparison, a cross-linked PS was also prepared using DVB (0.5 mol%) and styrene (99.5 mol%) in 1-octanol/toluene (50:10 v/v) using the same method as the **M-PS-TPPs**.

Table 3-1. Yields and Swelling Volume of M-PS-TPPs^a

M-PS-TPP	DVB (mol%)	Yield (%)	Swelling volume ^b (mL g ⁻¹)	Amount of TPP incorporated (mmol g ⁻¹) ^c
M-PS-TPP1	0.5	83	4.3	0.18
M-PS-TPP2	1	86	3.7	0.18
M-PS-TPP3	2	85	3.6	0.18

^aConditions; TPP monomer (2 mol%), DVB ($x = 0.5, 1, 2$ mol%), styrene (100– x –2 mol%), AIBN (1 wt% with respect to monomers), 3.5 mol L⁻¹, 1-octanol/toluene (50:10 v/v), 1 mL of monomer solution in total, 70°C, 24 h. ^bMeasured after immersion in anhydrous THF for more than 1 day. ^cEstimated on the basis of feed ratio of TPP monomer.

3.2.4. Preparation of **M-PS-TPP**

The compression tests were performed on THF-swollen **M-PS-TPP** using a tensile-compressive tester. The cylindrical **M-PS-TPP** with diameter of 16 mm and thickness of 5 mm was set on a lower plate and compressed by an upper plate, which was connected to a loadcell, at a strain rate of 10 mm min⁻¹. Stress and strain were defined as follows:

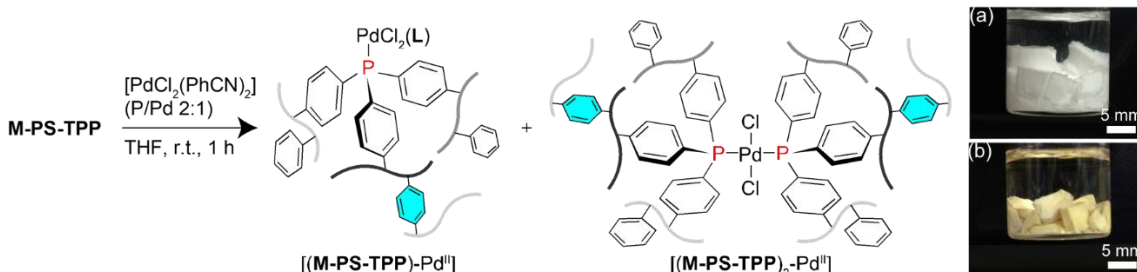
$$\text{Stress} = \frac{\text{Uniaxially exerted force}}{\text{Cross-sectional area of the } \mathbf{M-PS-TPP}} \quad (3-1)$$

$$\text{Strain} = \frac{\Delta(\text{Thickness})}{\text{Free-standing thickness}} \quad (3-2)$$

The compressive stress-strain curves were obtained for **M-PS-TPP1–3**. For **M-PS-TPPs** after reaction with [PdCl₂(PhCN)₂] (P/Pd 2:1) (experimental details will be explained in the later section), compressive stress-strain curves were also measured. The compressive tests were performed in triplicate for each composition using three separate lots of **M-PS-TPPs** to give average fracture stresses.

3.2.5. ³¹P CP/MAS NMR Studies for Reactions of **M-PS-TPP** and [PdCl₂(PhCN)₂]

Scheme 3-3. Ligand Exchange Reaction of [PdCl₂(PhCN)₂] using M-PS-TPP (P/Pd 2:1; L = PhCN or solvent), Photographic Images of (a) M-PS-TPP1, and (b) M-PS-TPP1-Pd



In a glove box, the dried **M-PS-TPP** (51.1 mg, 0.092 mmol P) and [PdCl₂(PhCN)₂] (17.6 mg, 0.046 mmol, P/Pd 2:1) were placed in a glass vial. Anhydrous and degassed THF (9.2 mL) was added

to the vial, and the mixture was stirred at room temperature for over 1 h. This caused the coloring of the THF-swollen **M-PS-TPP** to yellow (Scheme 3-3a and b). Removed from the glove box, the suspension was filtered, washed with anhydrous THF, and dried in vacuo at room temperature overnight. Using the ICP-AES analyses for the filtrate, the abundance of TPP-Pd complex to amount of TPP incorporated (0.18 mmol g^{-1} on the basis of feed ratio of TPP monomer, Table 3-1) were estimated. The obtained orange solid was analyzed using ^{31}P CP/MAS NMR spectroscopy.

3.2.6. Loading Experiment of Pd to **M-PS-TPP**

In a glove box, the **M-PS-TPP** (4.0 mg, 0.00072 mmol) were placed in a glass vial. A solution of $[\text{PdCl}_2(\text{PhCN})_2]$ ($0.0125\text{--}1 \text{ mmol L}^{-1}$, P/Pd 29:1–1:3) in anhydrous and degassed THF (2 mL) was added to the vial, and the mixture was stirred at room temperature for over 1 h. Removed from the glove box, the suspension was filtered and washed with anhydrous THF. The obtained organic phase was recovered, and the residual solvent was removed under reduced pressure at 70°C overnight. The remaining Pd salt was dissolved in aq. HCl (1 mol L^{-1} , 2 mL) and analyzed using ICP-AES. The amount of Pd loaded to the **M-PS-TPP** (q_{Pd}) was estimated as follows:

$$q_{\text{Pd}} = \frac{(C_i - C_e)V}{W} \quad (3-3)$$

where C , V , and W represent the concentration of Pd, volume of Pd solution, and weight of the **M-PS-TPP**, respectively. The subscripts i and e indicate the initial and equilibrium conditions, respectively.

3.2.7. Preparation of Nonporous **PS-TPP**

Nonporous **PS-TPP** was prepared by the bulk copolymerization of TPP monomer (2 mol%), DVB (0.5 mol%), and styrene (97.5 mol%) in toluene. Monomers were dissolved in toluene followed by addition of AIBN (1 wt% with respect to monomers), to give a monomer solution (1 mL , 3.5 mol L^{-1}).

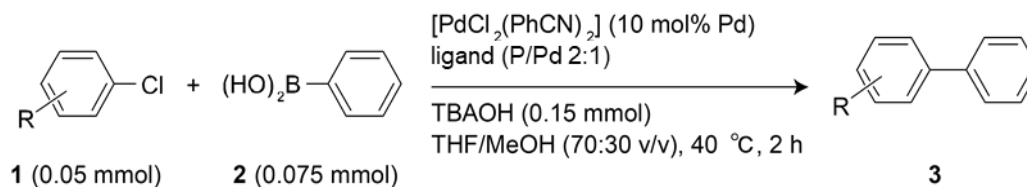
After degassing via three freeze-pump-thaw cycles, the monomer solution was poured into a glass vial (16 mm i.d.) in a glove box. The vial was sealed with a screw cap and removed from the glove box. The monomer solution was incubated at 70°C for 24 h. Carefully crushing the vial, the resulting polymer was washed by immersion in anhydrous THF for more than 1 day. The diameter and thickness of the THF-swollen **PS-TPP** was measured using calipers to calculate the swelling volume of 4.3 mL g⁻¹. The THF-swollen **PS-TPP** was cut into ~5 mm small blocks and dried in vacuo at room temperature overnight, to give a white solid polymer (0.36 g, 95% yield). The amount of TPP incorporated was 0.18 mmol g⁻¹ on the basis of feed ratio of TPP monomer. The internal structure of the dried nonporous **PS-TPP** was observed using FE-SEM.

3.2.8. Preparation of Beaded **PS-TPP**

Beaded **PS-TPP** was prepared by suspension copolymerization of TPP (2 mol%), DVB (0.5 mol%), and styrene (97.5 mol%) in chlorotoluene/water.^[13] A solution of acacia gum (1.2 g) and NaCl (0.75 g) in water (30 mL) was placed in a 50-mL test tube equipped with a magnetic stirring bar and was degassed purging with N₂. On the other hand, monomers were dissolved in chlorotoluene followed by addition of and AIBN (1 wt% with respect to monomers), to give monomer solution (9.5 mL, 3.5 mol L⁻¹). After degassing via three freeze-pump-thaw cycles, the monomer solution was injected into the rapidly stirred aqueous solution. The mixture was stirred at 70°C for 24 h. After cooling to room temperature, the mixture was filtered and washed successively with water, MeOH, THF, toluene, and THF. Drying in vacuo at room temperature overnight, polymer as white beads were obtained (2.55 g, 70%). The amount of TPP incorporated was 0.18 mmol g⁻¹ on the basis of feed ratio of TPP monomer. The surface morphology of the beaded **PS-TPP** in dry state was observed using FE-SEM.

3.2.9. Typical Procedure for Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction

Scheme 3-4. Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions



In a glove box, **M-PS-TPP** (0.01 mmol, 20 mol% P) was placed in a glass vial. A solution of $[\text{PdCl}_2(\text{PhCN})_2]$ (1.9 mg, 0.005 mmol, 10 mol% Pd) in anhydrous and degassed THF (1 mL) was added to the vial. After stirring for over 1 h, 4-chlorotoluene (**1a**, 6.3 mg, 0.05 mmol), phenylboronic acid (**2**, 9.1 mg, 0.075 mmol), and a solution of tetrabutylammonium hydroxide (TBAOH, 0.33 mol L^{-1} in MeOH, 0.15 mmol) were added successively. Removed from the glove box, the reaction mixture was shaken at 40°C for 2 h. A small aliquot was taken out from the reaction mixture, then analyzed using HPLC to determine a yield of 4-methylbiphenyl (**3a**). The **M-PS-TPP1-3-Pd** were observed using TEM before and after reaction (Scheme 3-4).

3.2.10. Diffusion Experiment of Solutes in **M-PS-TPP**

The apparent diffusion coefficients (D) of solutes in the **M-PS-TPP** were evaluated.^[16] The **M-PS-TPP** was polymerized in a cylindrical glass mold with inner diameter of 1.5 mm and length of 15 mm. The resulting **M-PS-TPP** was immersed in THF/MeOH (70:30 v/v, 4 mL) containing solutes, **1a** (34.4 mmol L^{-1}), **2** (51.6 mmol L^{-1}), or **3a** (34.4 mmol L^{-1}), for 5 days. The equilibrium concentration of **1a**, **2**, or **3a** in outer solution were determined using UV-Vis spectroscopy at wavelength of 269, 267, and 280 nm, respectively. After imbibing the solute, the dimension of the **M-PS-TPP** was measured using calipers. The solute-containing **M-PS-TPP** was suspended in a glass cuvette employing a wire basket and containing THF/MeOH (70:30 v/v, 3.5 mL) and magnetic stirrer. Under

stirring (350 rpm), the concentration change of solute in outer solution was measured periodically at sampling intervals of 10 sec. The diffusion of a solute from an infinite circular cylinder to a well stirred solution of limited volume was analyzed using following equation:^[16b]

$$\frac{C(t)}{C_{\infty}} = 1 - \sum_{n=1}^{\infty} \frac{4\alpha(1+\alpha)}{4(1+\alpha)+\alpha^2 q_n^2} \exp\left(-\frac{Dtq_n^2}{a^2}\right) \quad (3-4)$$

where t , a , $C(t)$, and C_{∞} are the time, radius of cylindrical **M-PS-TPP**, solute concentration at $t = t$, and solute concentration at $t = \infty$ (equilibrium state), respectively. The α and q_n satisfy following equations:

$$\alpha = \frac{\text{Solution volume in glass cuvette}}{\text{M-PS-TPP volume}} \times K \quad (3-5)$$

$$2J_1(q_n) + \alpha q_n J_0(q_n) = 0 \quad (3-6)$$

where K and $J_m(q_n)$ are the equilibrium partition coefficient (ratio of concentration in **M-PS-TPP** to that in outer solution) and Bessel's function of the m -th order. The time-course of concentration of the solutes in the outer solution was fitted by iteration with those to minimize the root-mean-square errors between experimental data and simulated data, to give D .

3.2.11. Hot Filtration Test for Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction

In a glove box, **M-PS-TPP1** (0.01 mmol, 20 mol% P) was placed in a glass vial. A solution of $[\text{PdCl}_2(\text{PhCN})_2]$ (1.9 mg, 0.005 mmol, 10 mol% Pd) in anhydrous and degassed THF (1 mL) was added to the vial. After stirring for over 1 h, **1a** (6.3 mg, 0.05 mmol), **2** (9.1 mg, 0.075 mmol), and a solution of TBAOH (0.33 mol L⁻¹ in MeOH, 0.45 mL, 0.15 mmol) were added successively. Removed from the glove box, the reaction mixture was shaken at 40 °C for 2 h. During the catalytic reaction, a small aliquot was periodically taken from the reaction mixture, followed by HPLC measurement to determine the yield of **3a**. In an independent experiment, the **M-PS-TPP1**-Pd was filtered at reaction time of 0.25 h, while the reaction was still monitored.^[17]

3.3 Results and Discussion

3.3.1. Characterization of *M-PS-TPPs*

TPP (2 mol%), DVB (x mol%), and styrene ($100-x-2$ mol%) were copolymerized in 1-octanol/toluene (50:10 v/v) using 2,2'-azobis(isobutyronitrile) (AIBN, 1 wt.% with respect to total monomer) to give **M-PS-TPPs**.^[7,13] The feed ratio of DVB was tuned to be $x = 0.5, 1$, and 2 mol% for preparing **M-PS-TPP1**, **M-PS-TPP2**, and **M-PS-TPP3**, respectively. The monomer solution was incubated in a glass vial at 70 °C for 24 h. The resulting solid was removed from the vial and washed with anhydrous THF to give a white and self-standing **M-PS-TPP** (Figure 3-3, inset). The **M-PS-TPPs** were dried in vacuo at room temperature overnight, to give **M-PS-TPP1–3** as a white solid (83–86% dry yield, Table 3-1). FE-SEM observations revealed that dried **M-PS-TPPs** consisted of an agglomerate of globules which formed interstitial macropores (Figure 3-3). The pore size distributions of the dried **M-PS-TPPs** were evaluated, and the median pore diameter ranged from 242 to 627 nm (Figure 3-4 and Table 3-2). Increasing the DVB content of the **M-PS-TPPs** decreased the median pore diameter and increased the surface area. FT-IR (Figure 3-5) and ³¹P CP/MAS NMR (Figure 3-6a–3-8a) spectra of the **M-PS-TPPs** confirmed the formation of the PS backbone (FT-IR peaks at 1600–1450, 1200–950, and 900–650 cm⁻¹) and coordinatively active TPP (NMR peak at –6 ppm) in the cross-linked network, respectively.

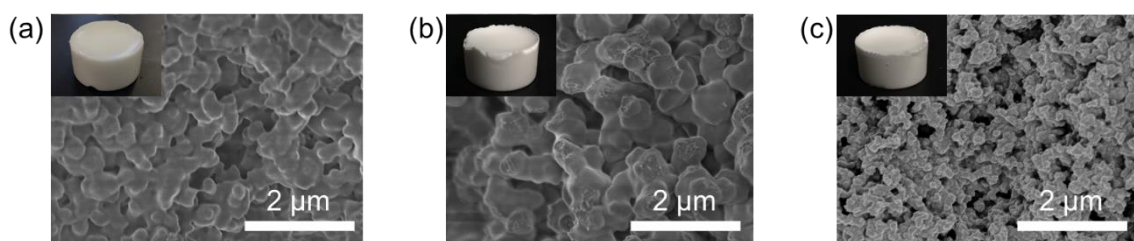


Figure 3-3. Photographic (inset, THF-swollen) and FE-SEM images of (a) **M-PS-TPP1**, (b) **M-PS-TPP2**, and (c) **M-PS-TPP3**.

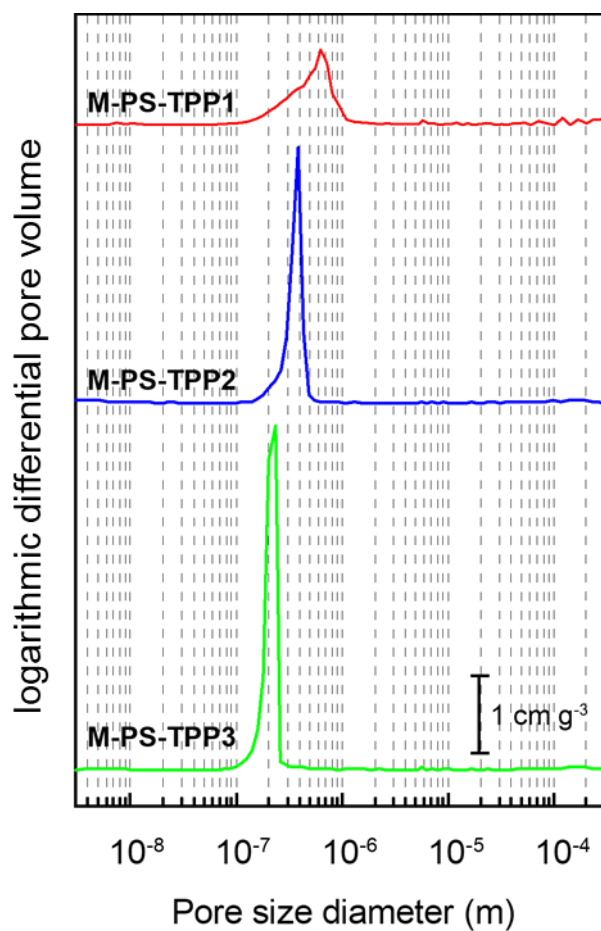


Figure 3-4. Pore size distributions of dried **M-PS-TPPs**.

Table 3-2. Median Pore Sizes, Specific Surface Areas, and Porosities of **M-PS-TPPs**

Ligand	DVB (mol%)	Median pore size (nm)	Specific surface area (m ² g ⁻¹)	Porosity (-)
M-PS-TPP1	0.5	630	5	0.31
M-PS-TPP2	1	410	31	0.50
M-PS-TPP3	2	240	28	0.51

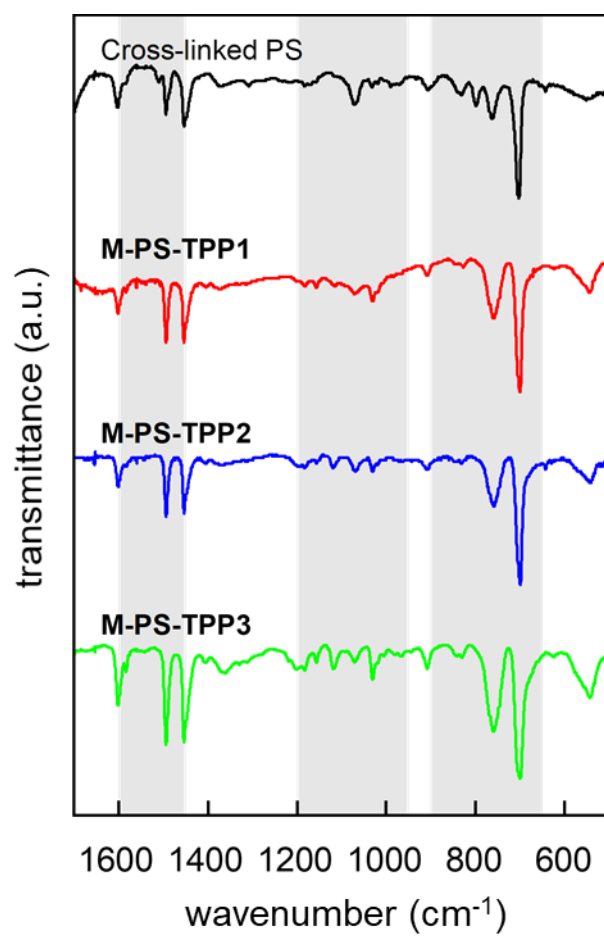


Figure 3-5. FT-IR spectra of cross-linked PS and **M-PS-TPP**.

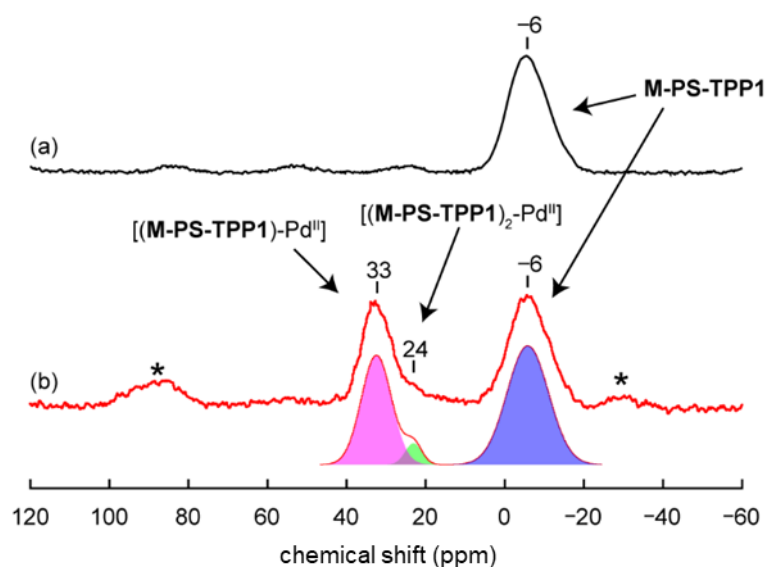


Figure 3-6. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP1** (a) before and (b) after reaction with $[\text{PdCl}_2(\text{PhCN})_2]$ (P/Pd 2:1). The relative peak intensities of free **M-PS-TPP1**, mono-P-ligated Pd^{II} complex $[(\text{M-PS-TPP1})\text{-Pd}^{\text{II}}]$, and bis-P-ligated Pd^{II} complex $[(\text{M-PS-TPP1})_2\text{-Pd}^{\text{II}}]$ were estimated using Gaussian peak fitting method. Asterisks (*) indicate spinning side bands.

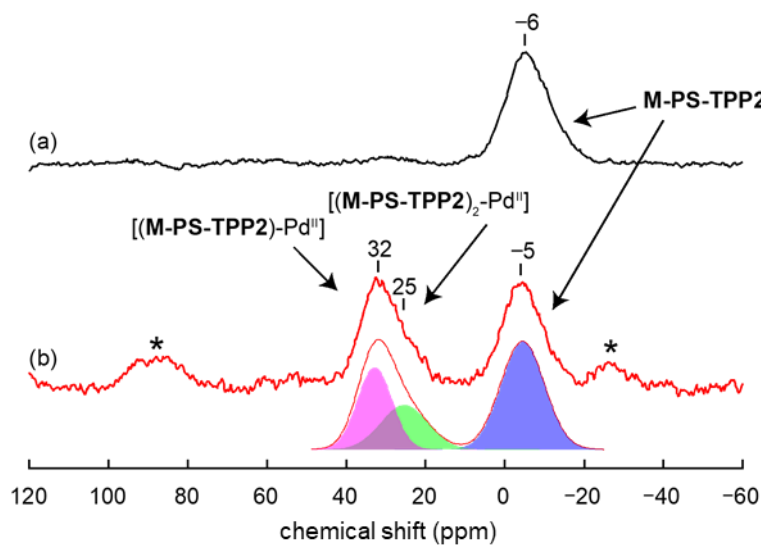


Figure 3-7. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP2** before (a) and after (b) reactions with $[\text{PdCl}_2(\text{PhCN})_2]$ (P/Pd 2:1). The relative peak intensities of free **M-PS-TPP2**, mono-P-ligated Pd^{II} complex $[(\text{M-PS-TPP2})\text{-Pd}^{\text{II}}]$, and bis-P-ligated Pd^{II} complex $[(\text{M-PS-TPP2})_2\text{-Pd}^{\text{II}}]$ were estimated using Gaussian peak fitting method. Asterisks (*) indicate spinning side bands.

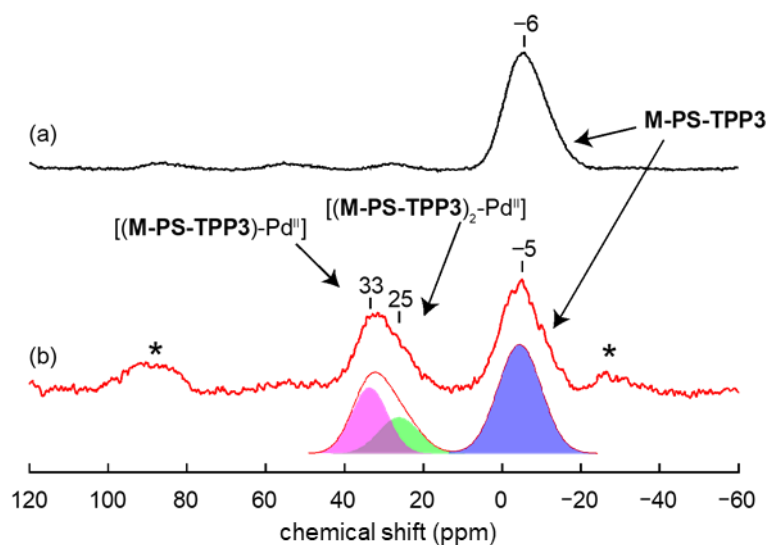


Figure 3-8. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP3** before (a) and after (b) reactions with $[\text{PdCl}_2(\text{PhCN})_2]$ (P/Pd 2:1). The relative peak intensities of free **M-PS-TPP3**, mono-P-ligated Pd^{II} complex $[(\text{M-PS-TPP3})\text{-Pd}^{\text{II}}]$, and bis-P-ligated Pd^{II} complex $[(\text{M-PS-TPP3})_2\text{-Pd}^{\text{II}}]$ were estimated using Gaussian peak fitting method. Asterisks (*) indicate spinning side bands.

In anhydrous THF, **M-PS-TPP1**, **M-PS-TPP2**, and **M-PS-TPP3** had swelling volumes of 4.3, 3.7, and 3.6 mL g^{-1} , respectively (Table 3-1). From compression tests, the fracture stresses of THF-swollen **M-PS-TPP1**, **M-PS-TPP2**, and **M-PS-TPP3** were 0.29 ± 0.01 , 0.37 ± 0.03 , and 0.40 ± 0.01 MPa, respectively (Figure 3-9a and 3-10, open rectangles). The increasing DVB content of the **M-PS-TPPs** was reflected in the decreasing swelling volume and increasing compressive strength in THF.^[18]

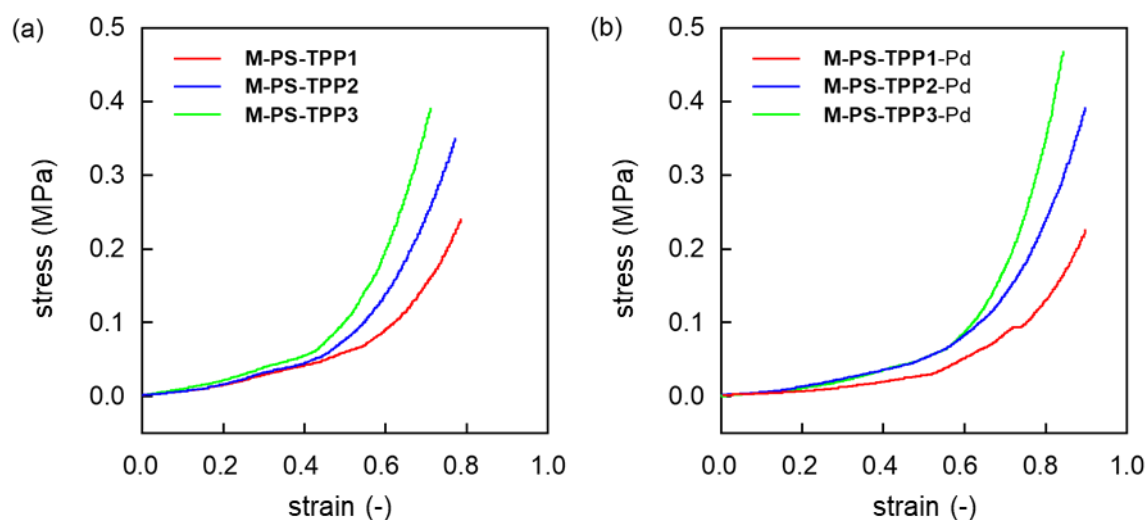


Figure 3-9. Stress-strain curves for THF-swollen **M-PS-TPPs** under uniaxial compression (a) before and (b) after reaction with $[\text{PdCl}_2(\text{PhCN})_2]$ (P/Pd 2:1). The tests were performed in triplicate for each composition using three separate lots of **M-PS-TPPs** to give average fracture stresses.

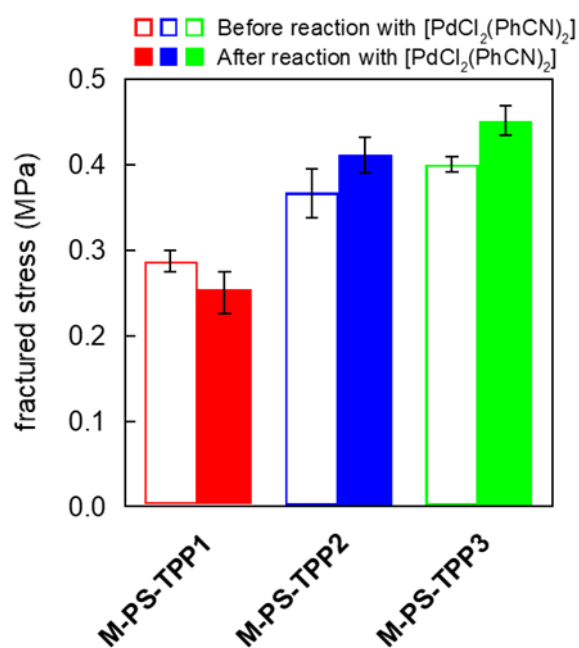


Figure 3-10. Compressive strengths of the **M-PS-TPPs** before (open rectangles) and after (filled rectangles) reaction with $[\text{PdCl}_2(\text{PhCN})_2]$ (P/Pd 2:1). The tests were performed in triplicate for each composition using three separate lots of **M-PS-TPPs** to give average fracture stresses.

3.3.2. Coordination of **M-PS-TPPs** to Pd^{II}

The loading of Pd was performed by the reaction of **M-PS-TPP** with $[\text{PdCl}_2(\text{PhCN})_2]$ (P/Pd 2:1) (Scheme 3-3). First, the maximum loading of Pd on **M-PS-TPPs** were tested at various feed concentration of $[\text{PdCl}_2(\text{PhCN})_2]$ in THF (P/Pd 29:1–1:3). The q_{Pd} increased with increasing the feed concentration of Pd and saturated to be 0.17–0.18 mmol g^{-1} (Figure 3-11). The saturated q_{Pd} was comparable with the amount of TPP incorporated (0.18 mmol g^{-1}), which was assumed based on the feed ratio of TPP monomer. These suggested that all the TPP unit in **M-PS-TPPs** participated in coordination toward Pd^{II} with excess $[\text{PdCl}_2(\text{PhCN})_2]$.

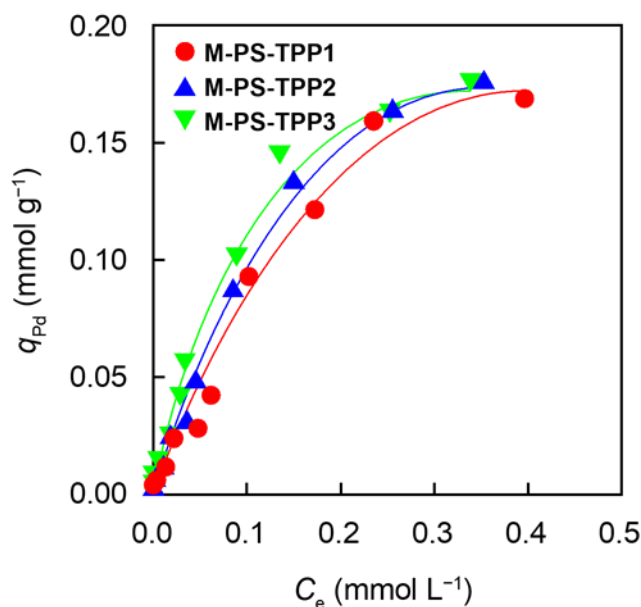


Figure 3-11. Loading of Pd to **M-PS-TPP**. Conditions: $[\text{PdCl}_2(\text{PhCN})_2]$ (0.0125–1 mmol L^{-1} , P/Pd 29:1–1:3), THF (2 mL), **M-PS-TPP** (4.0 mg, 0.00072 mmol P), r.t., 1 h.

Further detailed studies on the coordination of **M-PS-TPPs** to Pd^{II} were conducted based on the ^{31}P CP/MAS NMR analyses. Under the loading condition of P/Pd 2:1, the amount of TPP-Pd complex in **M-PS-TPP**-Pd was 0.08 mmol g^{-1} as determined using ICP-AES (Table 3-3). In the ^{31}P CP/MAS NMR spectra of the **M-PS-TPP**-Pd, new peaks attributable to the mono-P-ligated Pd^{II} complex [(**M**-

PS-TPP)-Pd^{II}] (32–33 ppm) and bis-P-ligated Pd^{II} complex **[(M-PS-TPP)₂-Pd^{II}]** (24–25 ppm) were observed (Figure 3-6b–3-8b).^[13a] Using the Gaussian peak fitting method, relative peak intensities were calculated to determine the selectivity of mono-P-ligation. **M-PS-TPP1-Pd** showed the highest relative peak intensity of the mono-P-ligated Pd^{II} complex (95%). Increasing the DVB content of **M-PS-TPP** decreased the relative peak intensities of the mono-P-ligated Pd^{II} complex (79 and 76% for **M-PS-TPP2-Pd** and **M-PS-TPP3-Pd**, respectively) (Table 3-3). The ³¹P CP/MAS NMR analysis clearly indicated the formation of mono-P-ligated Pd^{II} complex regulated by the DVB content of **M-PS-TPPs**.

Table 3-3. Pd Content and Relative Peak Intensity of ³¹P CP/MAS NMR Spectra

Ligand	Pd content	Relative peak intensity
	(mmol g ⁻¹) ^{a,b}	[(M-PS-TPP)-Pd^{II}]/[(M-PS-TPP)₂-Pd^{II}]^{c,d}
M-PS-TPP1	0.08	95:5
M-PS-TPP2	0.08	79:21
M-PS-TPP3	0.08	76:24

^aMolar ratio to total TPP of **M-PS-TPP** (0.18 mmol g⁻¹). ^bDetermined using ICP-AES. ^cThe peak intensity of bis-P-ligated Pd^{II} was divided by two. ^dDetermined using ³¹P CP/MAS NMR spectra.

The microenvironment of **M-PS-TPP1** favored mono-P-ligation toward Pd^{II} rather than bis-P-ligation. The molecular design of the incorporated TPP was the same in all the **M-PS-TPPs**, so the mono-P-ligating behavior should be affected by different DVB contents of the **M-PS-TPPs**. In the present system, increasing the DVB content induced an increasing number of cross-linking points in the PS network, resulting in the **M-PS-TPPs** shrinking and stiffening (Table 3-1 and Figure 3-10). It has been reported that bis-P-ligation toward metal leads to additional cross-linking between polymer

chains.^[19] The cross-linking effect via bis-P-ligation on the swelling volume of **M-PS-TPP**-Pd was confirmed, however, no significant change was observed ($\pm 3\%$ change). **M-PS-TPP2**-Pd and **M-PS-TPP3**-Pd formed a certain amount of bis-P-ligated Pd^{II} complex (Table 3-3) and showed slightly higher compressive strengths (Figure 3-9b and 3-10, filled rectangles). One explanation to the cross-linking via bis-P-ligation in the **M-PS-TPPs** is that the bis-P-ligated Pd^{II} complex formed in TPP-rich domains of the macroporous PS.^[20,21] The formation of the cross-linking complex (bis-P-ligated Pd^{II} complex) hardened the **M-PS-TPPs** without causing them to shrink. In the **M-PS-TPP** system, tuning the DVB content controlled the **M-PS-TPPs** swelling and hence the spatial density of TPP for selective mono-P-ligation toward Pd^{II}. This should lead to enhanced catalytic activity.

3.3.3. Catalytic Activities of **M-PS-TPP**-Pd

To assess the potential application of the **M-PS-TPP** system, [PdCl₂(PhCN)₂] (10 mol% Pd) and ligand (20 mol% P, P/Pd 2:1) complexes were employed for batch Suzuki-Miyaura cross-coupling reactions between 4-chlorotoluene (**1a**, 0.05 mmol) and phenylboronic acid (**2**, 0.075 mmol) in the presence of tetrabutylammonium hydroxide (TBAOH, 0.150 mmol) (Table 3-4).^[22] Using **M-PS-TPP1**, **M-PS-TPP2**, and **M-PS-TPP3**, the yields of **3a** were 87, 68, and 56%, respectively (Table 3-4, entries 1, 2, and 3). The catalytic efficacy of the **M-PS-TPPs**-Pd could therefore be enhanced tuning the DVB content. Focusing on the morphological structure of **PS-TPP**, nonporous or beaded **PS-TPP**^[13a] were also employed for cross-coupling reactions (Figure 3-12), which gave yields of 56 and 90%, respectively (entries 4 and 5). Using homogeneous TPP solution or a ligand-free system, the production of **3a** was not observed (entries 6 and 7). Importantly, ICP-AES measurement confirmed that Pd species did not dissolve into a reaction media (<10 ppb). The time-yield profile for the catalytic reactions using **M-PS-TPP1**-Pd, **M-PS-TPP2**-Pd, and **M-PS-TPP3**-Pd provided turnover frequencies (TOFs) of 26, 17, and 7 h⁻¹ (Figure 3-13). The catalytic performance of **M-PS-TPP1**-Pd was

comparable with that of beaded **PS-TPP**-Pd (90%) which had smaller diameter (several hundred micrometer), while the catalytic performance of nonporous **PS-TPP**-Pd was poor (56%). Obviously, **M-PS-TPP1**-Pd showed macroporous properties and selective mono-P-ligation and exhibited excellent activity (87%) in the batch Suzuki-Miyaura cross-coupling reaction.

The TPP-Pd complex in the porous organogel showed the high TOF in the cross-coupling of aryl chloride, which depended on the cross-linking degree of the gel network. The hot filtration test using **M-PS-TPP1**-Pd revealed that the true “immobilized catalyst” system in the cross-coupling of aryl chloride (Figure 3-13). A moderate steric hindrance from the PS chain and/or the donation of π electrons from the styrene pendant to Pd^[23] in the gel network suppressed the leakage of Pd into the reaction media. The TOFs based on the existence ratio of mono-P-ligated Pd complex (Table 3-3) also decreased with increasing cross-linking degree (27, 21, and 9 h⁻¹ for **M-PS-TPP1**-Pd, **M-PS-TPP2**-Pd, and **M-PS-TPP3**-Pd, respectively), while TONs (~11) of the mono-P-ligated Pd were almost identical (Figure 3-13). This comparison indicated that the other factors influenced on the TOFs of immobilized TPP-Pd complex, except for the mono-P-ligation behavior. In terms of interaction between PS pendant and Pd, high cross-linking degree might deteriorate the catalytic cycles of Pd center via excessive coordination. Unfortunately, those PS-Pd interactions failed to prevent the Pd catalyst from the aggregation which led to less activity, confirmed by TEM observations of the **M-PS-TPP**-Pd (Figure 3-14). In fact, the spent **M-PS-TPP1**-Pd was recovered by filtration after reaction in 1st run, and recycled in 2nd run, showing decreased catalytic efficiency (27% yield of **3a**).

Table 3-4. Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions^a

Entry	Chloroareene 1	Ligand	Product 3	Yield (%)
1	1a (R = 4-Me)	M-PS-TPP1	3a	87
2	1a	M-PS-TPP2	3a	68
3	1a	M-PS-TPP3	3a	56
4	1a	Nonporous PS-TPP	3a	56
5	1a	Beaded PS-TPP	3a	90
6	1a	TPP	3a	0
7	1a	none	3a	0
8	1b (R = 2-NO ₂)	M-PS-TPP1	3b	85
9	1c (R = 3-NO ₂)	M-PS-TPP1	3c	87
10	1d (R = 4-NO ₂)	M-PS-TPP1	3d	89
11	1e (R = 4-COMe)	M-PS-TPP1	3e	82
12	1f (R = 4-OMe)	M-PS-TPP1	3f	61

^aConditions: **1** (0.050 mmol), **2** (0.075 mmol), TBAOH (0.150 mmol), [PdCl₂(PhCN)₂] (0.005 mmol, 10 mol% Pd), ligand (0.01 mmol, 20 mol% P), THF/MeOH (70:30 v/v, 1.45 mL), 40°C, 2 h.

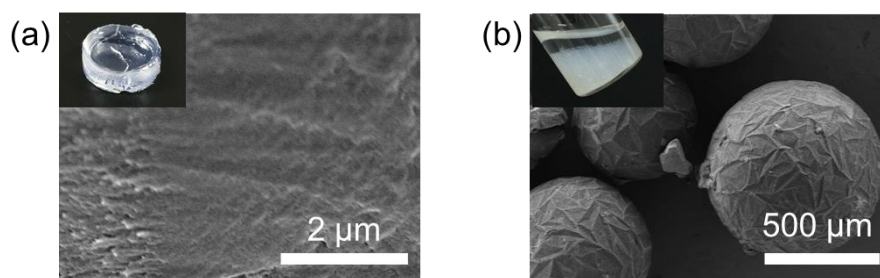


Figure 3-12. Photographic (inset, THF-swollen) and FE-SEM images of (a) nonporous **PS-TPP** and (b) beaded **PS-TPP**.

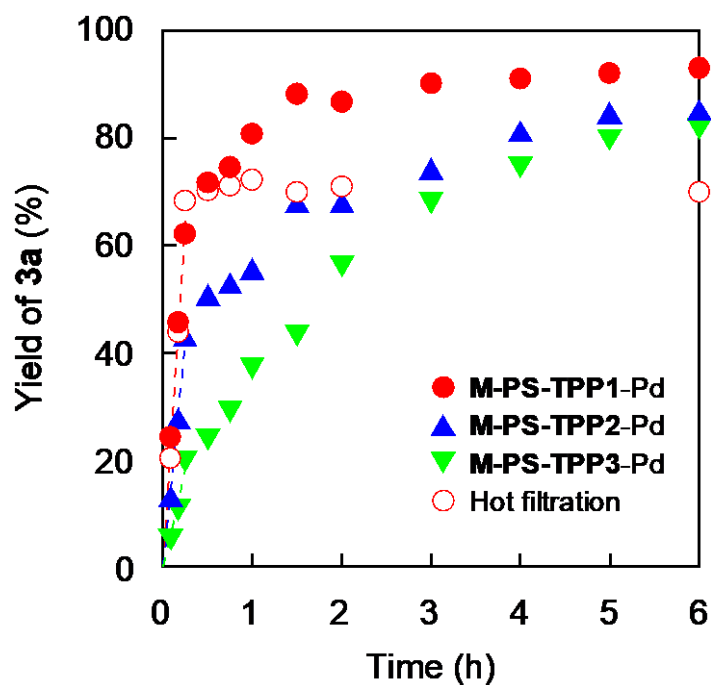


Figure 3-13. Time-yield profile and hot filtration test for Suzuki-Miyaura cross-coupling reaction using **M-PS-TPP**-Pd to give **3a**. Conditions: **1a** (0.050 mmol), **2** (0.075 mmol), TBAOH (0.150 mmol), [PdCl₂(PhCN)₂] (0.005 mmol, 10 mol% Pd), **M-PS-TPP1** (0.01 mmol, 20 mol% P), THF/MeOH (70:30 v/v, 1.45 mL), 40°C, 2 h. The TOF of **M-PS-TPP**-Pd was estimated within period where yield increased linearly with increase in time (dashed line). In the hot filtration test, **M-PS-TPP1**-Pd was removed at reaction time of 0.25 h, while the reaction was still monitored.

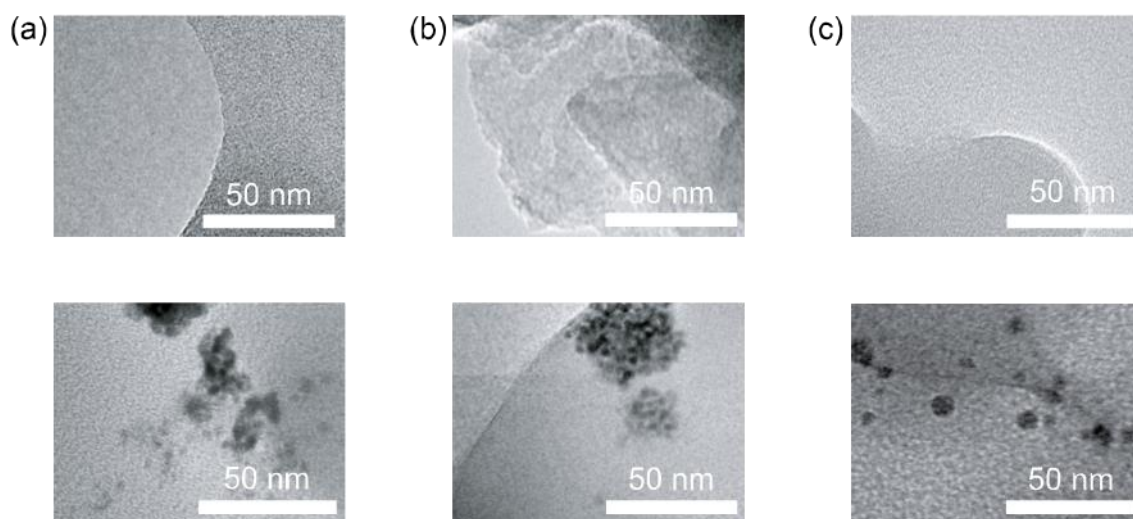


Figure 3-14. TEM images of (a) **M-PS-TPP1-Pd**, (b) **M-PS-TPP2-Pd**, and (c) **M-PS-TPP3-Pd** before (upper) and after (bottom) reaction.

M-PS-TPP1-Pd was further examined in batch Suzuki-Miyaura cross-coupling reactions of various aryl chlorides (Table 3-4). The **M-PS-TPP1-Pd** complex induced conversions for aryl chlorides bearing electron-withdrawing groups, such as 2, 3, or 4-substituted $-\text{NO}_2$ (85, 87, and 89% yields, entries 8, 9, and 10, respectively), and 4-substituted $-\text{COMe}$ (82% yield, entry 11). Moderate conversion of chloroarene bearing an electron-donating group, 4-substituted $-\text{OMe}$ (61% yield, entry 12), was observed. These results demonstrated the broad applicability of the **M-PS-TPP1** system for Pd-catalyzed Suzuki-Miyaura cross-coupling reactions.

3.3.4. Diffusion of Solutes in **M-PS-TPP**

Diffusion experiments in cylindrical **M-PS-TPPs** were performed to estimate the D of solutes. It was demonstrated that the D of **1a**, **2**, and **3a** were higher in all the **M-PS-TPPs** than in nonporous **PS-TPP** (Table 3-5). The macroporous structure of the **M-PS-TPPs** clearly enhanced the molecular diffusion of reactants in the catalytic system. The diffusivities in the **M-PS-TPPs** were not

significantly different, despite the **M-PS-TPPs-Pd** showing different catalytic efficacies (Table 3-4, entries 1, 2, and 3). When using the **M-PS-TPPs-Pd** in the Suzuki-Miyaura cross-coupling reaction, the diffusivities of reactants were sufficiently fast, and selective mono-P-ligation was a more important factor affecting the catalytic efficacy. From these results, both the macroporous structure (Figure 3-3) and selective mono-P-ligation (Table 3-3) of **M-PS-TPP** were essential to efficiently facilitate this challenging chemical transformation via cross-coupling reaction.

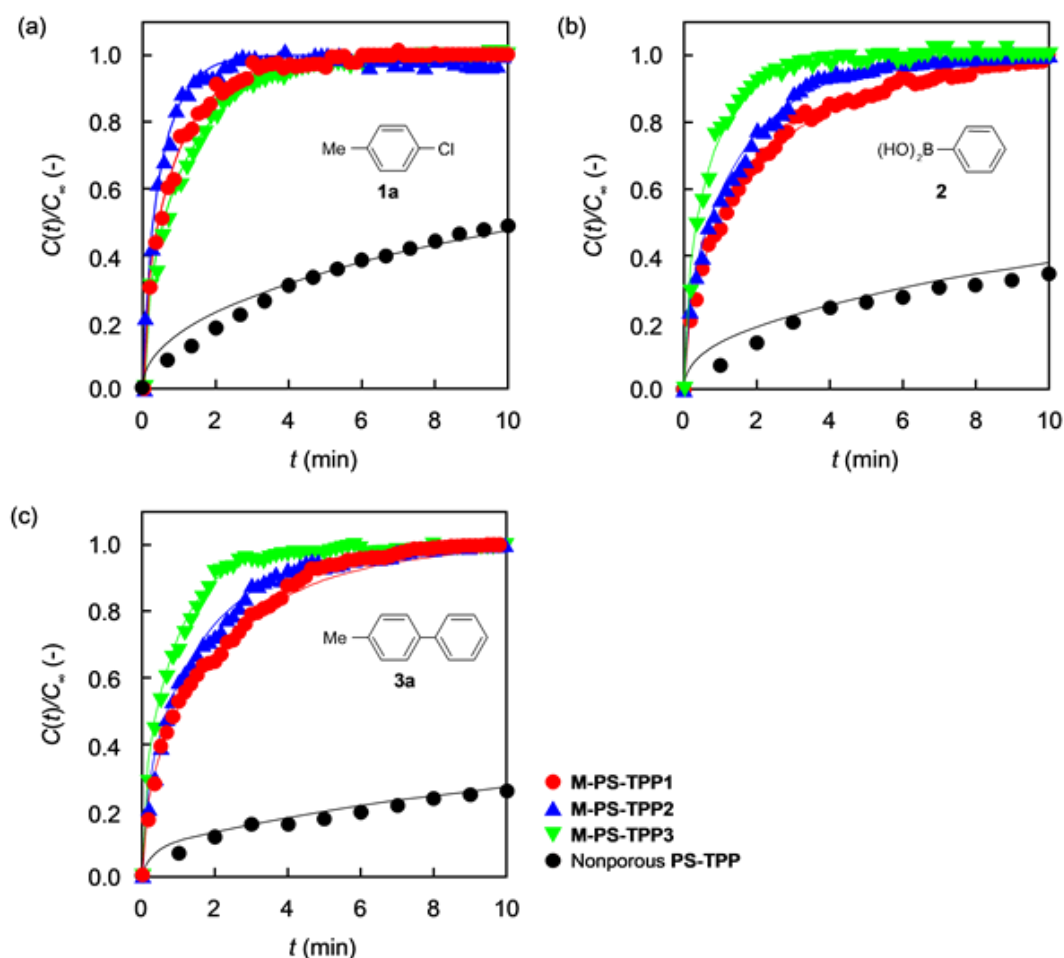


Figure 3-15. Diffusion curves for **1a**, **2**, and **3a** from cylindrical **M-PS-TPPs** and nonporous **PS-TPP**. Solid lines present the least squares curves for determination of D .

Table 3-5. D of Substrates and Product in M-PS-TPPs and Nonporous PS-TPP

ligand	$D (\times 10^{-9} \text{ m}^2 \text{ sec}^{-1})$		
	1a	2	3a
M-PS-TPP1	2.72	3.66	1.46
M-PS-TPP2	4.14	4.68	2.49
M-PS-TPP3	4.06	1.28	2.58
Nonporous PS-TPP	0.07	0.19	0.06

3.4 Conclusions

In summary, a monolithic porous PS-three-fold crosslinked TPP hybrid, **M-PS-TPP**, was synthesized via polymerization-induced phase separation using a porogenic solvent. Tuning the DVB content in the **M-PS-TPP** arranged the TPP units for site-isolation and selective formation of the mono-P-ligated Pd^{II} complex. The **M-PS-TPP**-Pd complex exhibited good catalytic efficacy in Suzuki-Miyaura cross-coupling reactions of chloroarenes, which was enhanced by fast molecular diffusion and selective mono-P-ligation. These insights into monolithic porous polymers featuring macroporous structures, fast molecular diffusion, and controlled coordination mode of supported TPP should be broadly extended to transition-metal catalysis.

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Chapter 4

Development of Macroporous Organogel Monolith for Continuous-Flow Cross-Coupling in Organic Media

Chapter 4 Development of Macroporous Organogel Monolith for Continuous-Flow Cross-Coupling in Organic Media

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, 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 is reported. 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%).

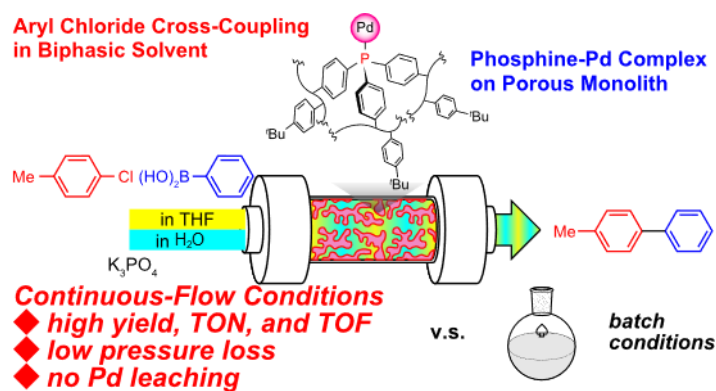


Figure 4-1. Schematic illustration of **M-PS-TPP** for Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl chlorides under continuous-flow conditions.

4.1 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 ($> 80^{\circ}\text{C}$) 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 ($> 100^{\circ}\text{C}$) 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 hydrodynamics 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] It is also believed 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, a combination of sophisticated design of ligand and porous materials for challenging chemical transformation in continuous-flow manner is reported. 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. ³¹P 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 K₃PO₄ 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 4-2). 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.

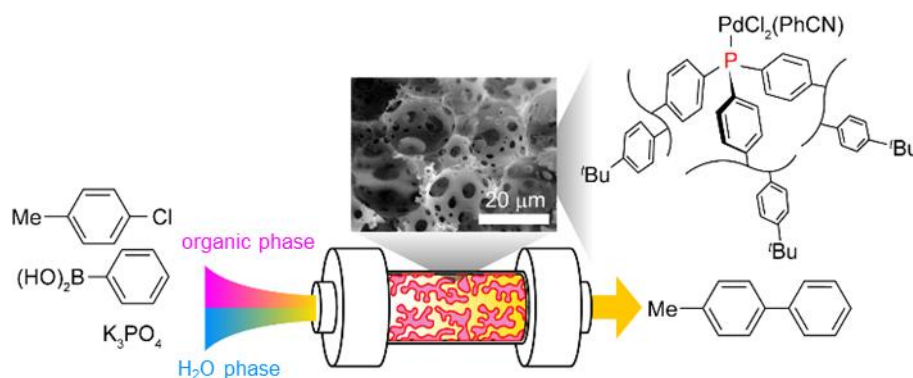


Figure 4-2. Macroporous polystyrene-TPP monolith (**M-PS-TPP**) to Pd-catalyzed cross-coupling reaction containing aryl chloride in continuous-flow system.

4.2 Experimental Section

4.2.1. *Generals*

The samples for field emission scanning electron microscopy (FE-SEM) analysis were coated with platinum (approx. 4 nm thickness) using an JEOL JFC-1600 auto fine coater (JEOL Ltd., Tokyo, Japan). FE-SEM analysis was performed on a Hitachi SU8000 microscopy (Hitachi High-Technologies Corporation, Tokyo, Japan). Hg intrusion porosimetry analysis was performed on a Micromeritics AutoPoreIV9520 (Micromeritics Instrument Co., Norcross, GA, USA). Solution nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECZ400S spectroscopy, operating at 400, 101, and 162 MHz for ^1H , ^{13}C , and ^{31}P NMR, respectively. Chemical shifts values for ^1H , ^{13}C , and ^{31}P NMR spectra were referenced to Me_4Si , the residual solvent, and 85% H_3PO_4 , respectively. Cross polarized magic angle spinning (CP/MAS) NMR spectra were recorded on a Bruker AVANCE III 500 spectroscopy (Bruker Co., Billerica, MA, USA), operating at 203 MHz for ^{31}P NMR. Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis was performed on a Seiko Instruments SPS-1700 HVR spectroscopy (Seiko Instruments Inc., Chiba, Japan). X-ray photoelectron spectroscopy (XPS) analysis was performed on a Shimadzu/Kratos AXIS-

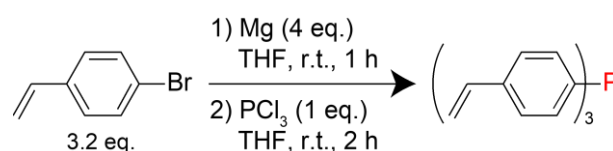
ultra (Kratos Analytical Ltd., Manchester, UK, Shimadzu Co., Kyoto, Japan). All XPS spectra energy-referenced to the C(1s) photoemission peak at 285.0 eV. The samples for transmission electron microscopy (TEM) analysis were prepared by placing a drop of THF suspension of monoliths onto a carbon-coated copper grid and allowing THF to be evaporated under air. TEM analysis was performed on a Philips FEI Tecnai 20 (Philips FEI, Hillsboro, OR, USA) with accelerating voltage of 200 kV. High-performance liquid chromatography (HPLC) analyses were performed on a JASCO LC-2000Plus system equipped with a JASCO DG-980-50 degasser, a JASCO PU-980 pump, a Kanto Chemical Mightysil RP-18 GP 250-4.6 column (Kanto Chemical Co., Tokyo, Japan), a JASCO UV-2077Plus UV detector, and a JASCO CO-2065Plus column oven (JASCO Co., Tokyo, Japan). Acetonitrile/water (80:20 v/v) containing trifluoroacetic acid (0.1 vol%) was employed as a mobile phase in the HPLC measurements. In continuous-flow setup, SGE glass gas-tight syringe (SGE Analytical Science Pty. Ltd., Melbourne, Australia), which was mounted on YMC YSP-101 syringe pump (YMC Co. Ltd., Kyoto, Japan), and Krone KDM-30 pressure gauge (Krone Co., Tokyo, Japan) were connected to column in a thermo-controlled incubator with PTFE or PFA tubing (0.75 mm inner diameter). For residence time distribution (RTD) studies, a FLOM VI-11 injection valve (FLOM Co., Tokyo, Japan) with a 10 μ L loop, an Ocean Optics USB2000+ ultraviolet-visible (UV-Vis) spectrometer, an Ocean Optics tungsten halogen light source, and an Ocean Optics FIA-Z-SMA-TEF Z-type flow cell (Ocean Optics Inc., Dunedin, FL, USA) were included in continuous-flow setup. For continuous-flow catalysis, two syringe pumps were used to deliver THF and water phase, which were mixed through PTFE T-shaped mixer. Thin-layer chromatography analyses were performed on aluminum sheers bearing 0.17–0.22 mm layer of Merck Silica gel 60F₂₅₄. Merck silica gel 60 (40–63 μ m, neutral, Merck Co., Darmstadt, Germany) was used for column chromatography.

All the solvents for preparation of polymer and catalytic reactions were degassed by sonication for > 30 min before use unless otherwise noted. Materials were obtained from commercial suppliers unless

otherwise noted. 4-*t*-butylstyrene (>99% GC purity, stabilized with 4-*t*-butylcatechol, Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) and divinylbenzene (DVB, 3- and 4- mixture, contains ethylvinylbenzene and ethylbenzene, >80% GC purity, stabilized with 4-*t*-butylcatechol, Sigma-Aldrich Co., St. Louis, MO, USA) were purified using basic alumina column. 2,2'-Azobis(isobutyronitrile) (AIBN) was purified by recrystallization from MeOH. PCl₃ was purified by distillation under nitrogen atmosphere before use.

4.2.2. Syntheses of TPP Ligand Monomers

Scheme 4-1. Synthesis of Tris(4-vinylphenyl)phosphane

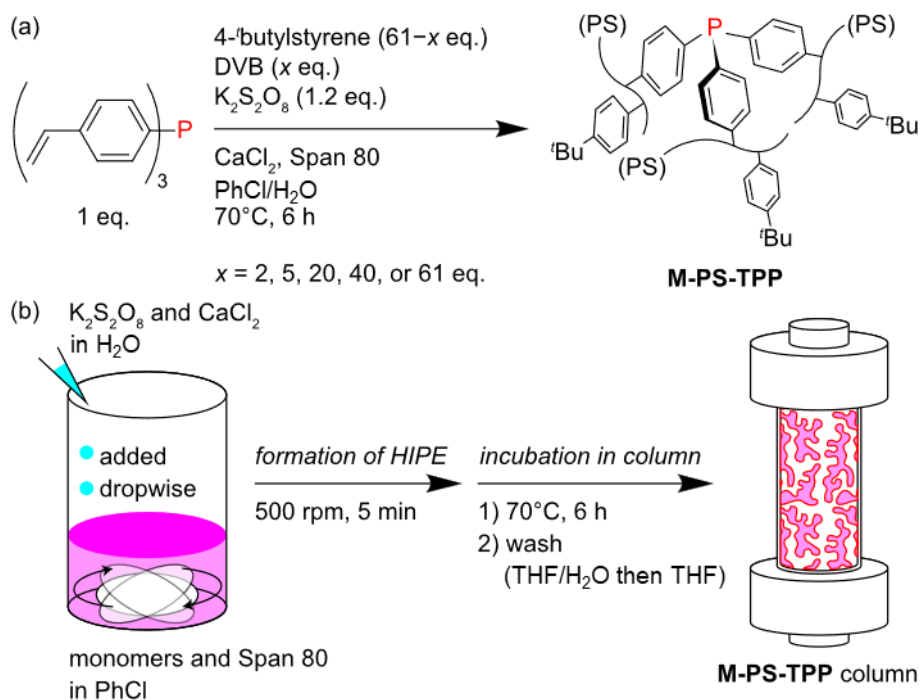


Threefold vinylated TPP was synthesized according to the previous reports (Scheme 4-1).^[7a-c] Mg turnings (2.40 g, 100 mmol, 4 eq) were placed in a 300-mL round-bottom flask equipped with a magnetic stirring bar. After addition of anhydrous THF, 80 mL) under N₂, *p*-bromostyrene (14.64 g, 80 mmol, 3.2 eq) was slowly added to the flask followed by stirring at room temperature for 1 h. Next, PCl₃ (3.43 g, 25 mmol, 1 eq) was added to the solution in ice water bath over 0.5 h followed by stirring at room temperature for 4 h. Quenching with aq. NH₄Cl, the mixture was extracted with Et₂O. The organic layer was washed with water, dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc 97:3 v/v) to give desired product as white solids (4.82 g, 57% yield).

¹H NMR (CDCl₃): δ 5.27 (d, *J* = 11.0 Hz, 3H), 5.77 (d, *J* = 17.4 Hz, 3H), 6.70 (dd, *J* = 17.4, 11.0 Hz, 3H), 7.23–7.38 (m, 12H). ¹³C NMR (CDCl₃): δ 114.85 (3C), 126.44 (d, *J*_{C-P} = 7.1 Hz, 6C), 134.00 (d, *J*_{C-P} = 19.2 Hz, 6C), 136.45 (3C), 136.72 (d, *J*_{C-P} = 10.1 Hz, 3C), 138.07 (3C). ³¹P NMR (CDCl₃): δ -6.21.

4.2.3. Syntheses of **M-PS-TPP** for Characterization

Scheme 4-2. Synthesis of M-PS-TPP in the Presence of HIPE Template



Typically, a solution of tris(4-vinylphenyl)phosphane (0.016 mmol, 1 eq.), DVB (0.32 mmol, $x = 20$ eq.), 4-*t*-butylstyrene (0.66 mmol, 61- x eq.), and Span 80 (0.061 mL) in chlorobenzene (0.19 mL) was placed in a glass vial (21.0 mm i.d.) equipped with a magnetic stirring bar (~20 mm) (Scheme 4-2a).^[21] The organic phase was degassed by three freeze-pump-thaw cycles. Separately, $CaCl_2$ (0.33 mmol) and $K_2S_2O_8$ (0.019 mmol, 1.2 eq.) was dissolved in water (3.3 mL). The aqueous phase was degassed by N_2 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.

For characterization of **M-PS-TPP**, the HIPE was incubated in the vial at 70°C for 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

diameter (d) and length (L) of swollen **M-PS-TPP** was measured to estimate a swelling volume (V_M) in THF. The yield of **M-PS-TPP** was determined after drying under vacuum at room temperature overnight, to give a white solid polymer (92% dry yield). The amount of TPP moiety incorporated ($[P]$) was 0.11 mmol g⁻¹ based on feed ratio of monomers. The internal structure of the dried **M-PS-TPP** were observed using FE-SEM. Hg intrusion tests were conducted to determine the pore sizes and porosities of **M-PS-TPP**. ³¹P CP/MAS NMR analyses was performed for the analyses of TPP ligand of **M-PS-TPP**. In independent experiments, the **M-PS-TPP** was polymerized with polymerization time of 3–24 h, which showed no significant difference of yield and macroporous structure of **M-PS-TPP** polymerized for 6 h or more. For further experiment, the polymerization time was fixed to be 6 h. For the preparation of **M-PS-TPP** with different cross-linking density, DVB contents in the monomer solutions was varied to be 2, 5, 20, 40, and 61 eq. (Table 4-1).

Table 4-1. Yields, V_M , and $[P]$ of Monoliths^a

monolith	DVB (eq.)	yield (%)	V_M (cm ³ g ⁻¹) ^b	$[P]$ (mmol g ⁻¹) ^c
M-PS-TPP1	2	95	29.8	0.10
M-PS-TPP2	5	96	27.0	0.10
M-PS-TPP3	20	92	26.2	0.11
M-PS-TPP4	40	92	23.1	0.11
M-PS-TPP5	61	91	25.1	0.12

^aConditions: three-fold vinylated TPP (1 eq.), DVB (x eq.), styrene derivatives (61– x mol%), monomer = 1.0 mmol, Ph-Cl (0.19 mL), Span 80 (0.06 mL), CaCl₂ (0.10 mol L⁻¹), K₂S₂O₈ (1 eq.), oil/water 1:9 v/v, 70°C, 6 h. ^bMeasured in THF. ^cEstimated on the basis of feed ratio of TPP.

4.2.4. Syntheses of **M-PS-TPP** Column for Continuous-Flow Application

For application to continuous-flow system, stainless-steel tubes (4.4 mm i.d.) with different lengths (2.5, 5.0, or 10.0 cm) were filled with HIPE using a syringe and sealed at the ends with septa (Scheme 4-2b). After incubation at 70 °C for 6 h, the seals were removed, and the L of the monolith column within the stainless-steel column was measured using calipers. For continuous-flow application, the **M-PS-TPP** column was provided with fittings and attached to a syringe pump. Superficial linear velocity (u) and residence time (τ) in the column were defined as follows:

$$u = \frac{Q}{\pi d^2/4} \quad (4-1)$$

$$\tau = \frac{L}{u} \quad (4-2)$$

where Q is flow rate of feed. THF/water (2:1 v/v) and THF were successively permeated through the column for wash (2.5 h each, $\tau = 0.50$ h). At various u ($\tau = 0.25, 0.50, 1.00, 1.50$, or 2.00 h), the pressure losses (ΔP) were monitored for more than 48 h. The Darcy's permeabilities (k_D) of **M-PS-TPP** columns were estimated as follows:

$$k_D = \frac{\mu L u}{\Delta P} \quad (4-3)$$

where μ is viscosity of feed.^[22]

4.2.5. ³¹P CP/MAS NMR Studies for Reactions of TPP-supporting Monolith and [PdCl₂(PhCN)₂]

The dried **M-PS-TPP** (0.022 mmol P) was grinded into powder using pestle and mortar, then placed in a glass vial. [PdCl₂(PhCN)₂] (0.011 mmol Pd, Pd/P 1:2) was dissolved in degassed THF (11 mL), and this Pd solution was added to the vial. The mixture was stirred at room temperature for > 1 h. The suspension was filtered, washed with THF, and dried in vacuo at room temperature overnight to give yellow powder. From ICP-AES analyses for the filtrate, all the Pd added was loaded on **M-PS-**

TPP to give 0.05 mmol g⁻¹ of Pd loading. The powder before and after loading of Pd were analyzed using ³¹P CP/MAS NMR spectroscopy.

4.2.6. RTD Studies and Estimation of Gel Porosity with Pulse Tracer

Typically, **M-PS-TPP3** column ($d = 4.4$ mm, $L = 4.5$ cm) was provided with fittings and attached to a syringe pump, UV-Vis spectrometer, deuterium halogen light source, and Z-type flow cell (Figure 4-3).^[18] As mobile phase, THF was permeated through the column, then methyl red (in EtOH, 1 g L⁻¹) as pulse tracer was injected (10 μL) into the THF stream. At various u ($\tau = 0.25, 0.50, 1.00, 1.50$, or 2.00 h), UV-Vis absorbance at 475 nm wavelength at each time (t) was measured to monitor the concentration of tracer in the eluent ($C(t)$). RTD function ($E(t)$) and τ were calculated as follows:

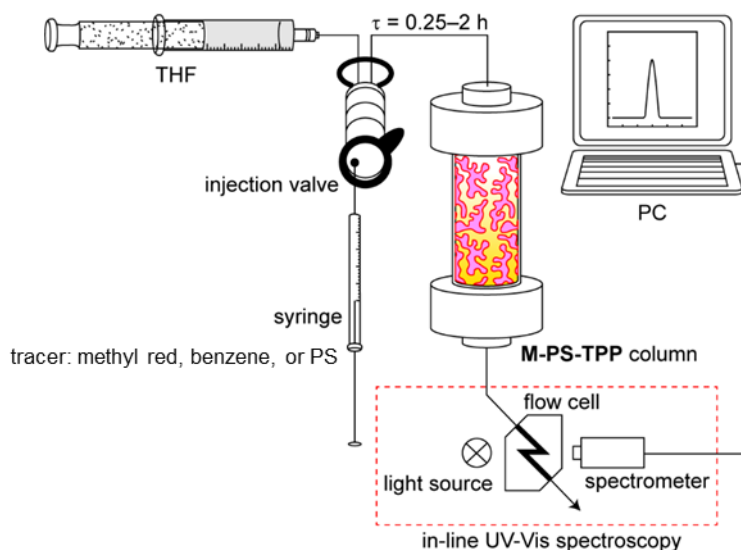


Figure 4-3. Continuous-flow setup for RTD studies using in-line UV-Vis spectroscopy.

$$E(t) = \frac{C(t)}{\int_0^{\infty} C(t) dt} \quad (4-4)$$

$$\tau = \int_0^{\infty} tE(t) dt \quad (4-5)$$

The τ obtained in the RTD studies (Equation 4-5) were in good agreement in those calculated from the

flow rate (Equation 4-2). In order to facilitate the comparison of the results obtained under different flow condition (different τ), dimensionless time (θ) and dimensionless RTD function ($E(\theta)$) were employed as follows:

$$\theta = \frac{t}{\tau} \quad (4-6)$$

$$E(\theta) = \tau E(t) \quad (4-7)$$

The RTD tests were repeated at least three times in each run. For parametric RTD analysis, the dimensionless variance (σ^2) are further introduced as follows:

$$\sigma^2 = \int_0^\infty (1 - \theta)^2 E(\theta) d\theta \quad (4-8)$$

σ^2 were determined at various u ($\tau = 0.25, 0.50, 1.00, 1.50$, or 2.00 h) for **M-PS-TPP3** column.

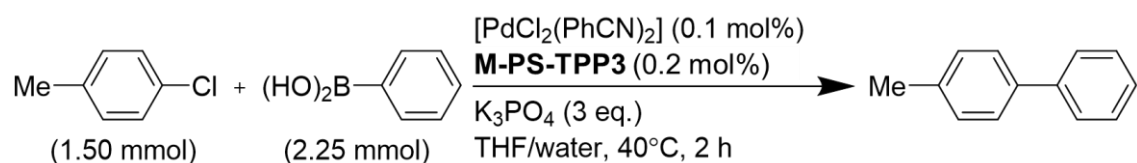
From the elution volume of tracer, the gel porosity of **M-PS-TPP3** column (ϵ_g) was calculated as follows:^[23]

$$\epsilon_g = \frac{Qt_e}{V_M} \quad (4-9)$$

where t_e is elution time of top peak. Using benzene (in THF, 2 g L^{-1}) or PS with molecular weight (M.W.) of 1.25×10^3 – 2.78×10^6 (in THF, 2 g L^{-1}) as pulse tracers ($10 \text{ }\mu\text{L}$), the RTD tests were also conducted monitoring UV-Vis absorbance at 254 or 260 nm wavelength for other **M-PS-TPPs**.

4.2.7. Batch Suzuki-Miyaura Cross-Coupling Reaction in Biphasic Solvent System

Scheme 4-3. Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction in Batch System

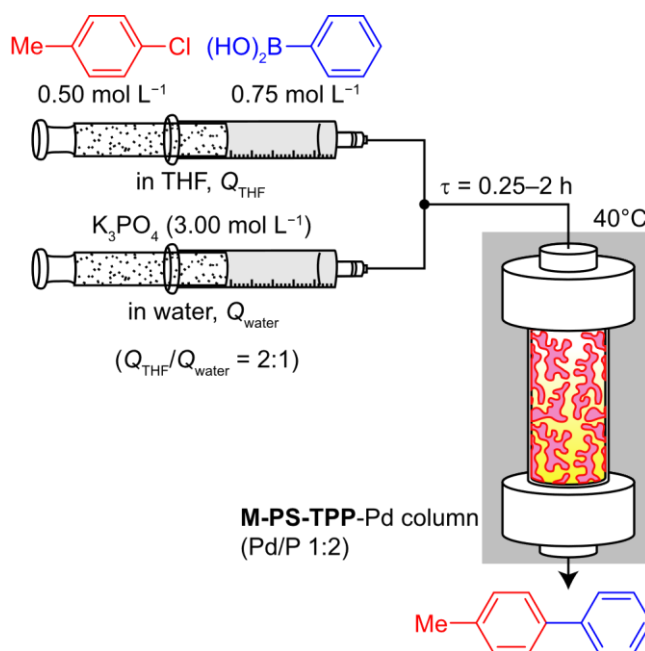


M-PS-TPP3 ([P] 0.11 mmol g^{-1} , 27.3 mg, 0.0030 mmol, 0.2 mol% P) was placed in a glass vial

(21.0 mm inner diameter). A solution of $[\text{PdCl}_2(\text{PhCN})_2]$ (0.58 mg, 0.0015 mmol, 0.1 mol% Pd, Pd/P 1:2) in THF (1.5 mL) was added to the vial followed by magnetic stirring for 1 h (500 rpm). 4-chlorotoluene (189.9 mg, 1.5 mmol, 1 eq.) and phenylboronic acid (274.3 mg, 2.25 mmol, 1.5 eq.) in THF (1.5 mL in total), and K_3PO_4 (955.2 mg, 4.5 mmol, 3 eq.) in water (1.5 mL in total) were added successively. Tetrabutylammonium bromide (TBAB, 24.2 mg, 0.075 mmol, 5 mol%) was dissolved in the THF phase with aryl substrates if needed. The reaction mixture was incubated at 40°C for 2.00 h with magnetic stirring (0, 250, or 500 rpm). A small aliquot was taken out from the THF phase, then analyzed using HPLC to determine a yield of 4-methylbiphenyl (Scheme 4-3).

4.2.8. Flow Suzuki-Miyaura Cross-Coupling Reaction in Biphasic Solvent System

Scheme 4-4. Continuous-Flow Setup for the Cross-Coupling Reaction between 4-Chlorotoluene and Phenylboronic Acid



Suzuki-Miyaura cross-coupling reaction of aryl chloride under continuous-flow mode was realized using **M-PS-TPP-Pd** column (Scheme 4-4). $[\text{PdCl}_2(\text{PhCN})_2]$ (0.005 mol L⁻¹) in THF was permeated

through **M-PS-TPP** column ($\tau = 2.00$ 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, $\tau = 0.50$ 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. Tetra-*n*-butylammonium bromide (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 flow rate of THF phase (Q_{THF}) and water phase (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. In continuous-flow catalysis, u and τ was calculated based on the total flow rate of THF phase and water phase substrate solutions ($Q = Q_{\text{THF}} + Q_{\text{water}}$, Equations 4-1 and 4-2). The elution from the column was continuously collected, and the THF-phase was analyzed using HPLC. Turnover number (TON) were defined as follows:

$$\text{TON} = \frac{\text{total amount of 4-methylbiphenyl produced}}{\text{moles of Pd loaded}} \quad (4-10)$$

After run, THF/water (2:1 v/v) and THF was successively permeated through the column for washing. The eluted THF phase and water phase from the column was diluted in aqueous solution of HCl (1 mol L^{-1}) and analyzed using ICP-AES. The Pd-loaded monoliths before and after long-term run was observed using TEM.

4.3 Results and Discussion

4.3.1. Synthesis and Characterization of **M-PS-TPPs**

In the presence of water-in-oil HIPE template, white and monolithic **M-PS-TPPs** were obtained from all the monomer compositions via bulk polymerization (Figure 4-4, inset). The d of swollen **M-**

PS-TPP3 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 the reactant.^[24] The swollen **M-PS-TPPs** was dried under vacuum at room temperature overnight to give a white solid polymer with high yield (87–96% dry yield, Table 4-1).

The dried **M-PS-TPPs** were observed using FE-SEM, and the characteristic void and window structures were observed in the monoliths, except for **M-PS-TPP1** (Figure 4-4). The observed voids were negative images of the aqueous phase in the HIPE, which were inter-connected with neighbors to give window structures during polymerization.^[21] Hg intrusion porosimetry analysis indicated that the **M-PS-TPP2–5** had a bimodal pore size distribution with 1st- and 2nd-mode pore sizes of 7420–13740 and 2990–4390 nm, respectively. On the other hand, the lowest DVB content in the **M-PS-TPP1** gave the fractured polymer scaffold and monomodal pore size distribution with low porosity ($\epsilon_{\text{dry}} = 67\%$) than the volume ratio of the aqueous phase (90 vol %) in the starting HIPE (Figure 4-5 and Table 4-2). These were probably due to the collapse during drying for sample preparation. It should be noted that the swelling behavior of monoliths in organic solvent significantly influence on their porous properties.^[23]

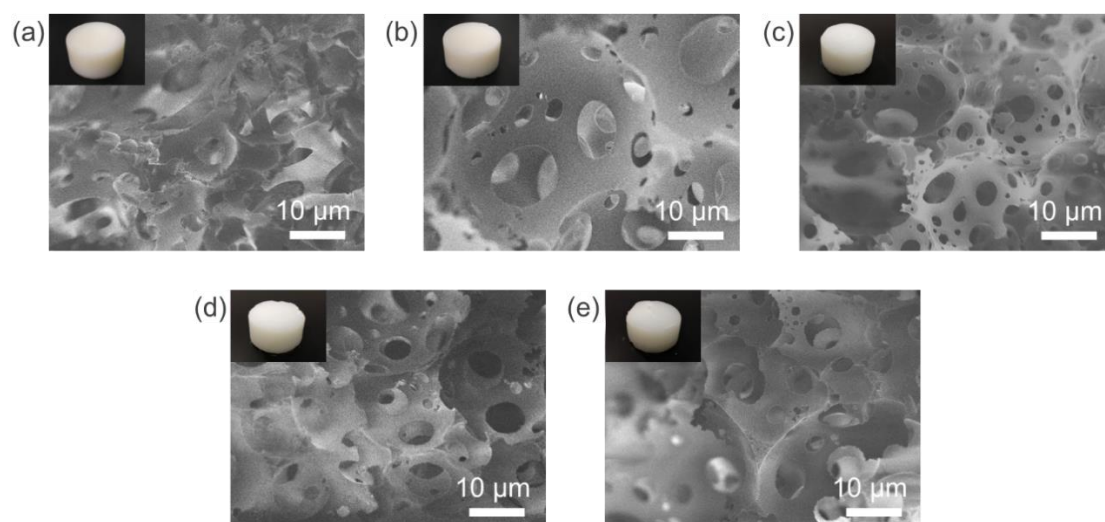


Figure 4-4. Photographic (inset) and FE-SEM images of (a) **M-PS-TPP1**, (b) **M-PS-TPP2**, (c) **M-PS-TPP3**, (d) **M-PS-TPP4**, and (e) **M-PS-TPP5**.

Table 4-2. 1st- and 2nd-Mode Pore Sizes, Specific Surface Areas, and ϵ_{dry} of M-PS-TPPs^a

monolith	1st-mode	2nd-mode	specific surface	ϵ_{dry} (%)
	pore size	pore size	area	
	(nm)	(nm)	(m ² g ⁻¹)	
M-PS-TPP1	4350	n.d. ^b	9	67
M-PS-TPP2	7420	4390	11	70
M-PS-TPP3	10690	3600	6	81
M-PS-TPP4	10690	3630	5	89
M-PS-TPP5	13740	2990	4	79

^aDetermined using Hg intrusion porosimetry. ^bNot determined.

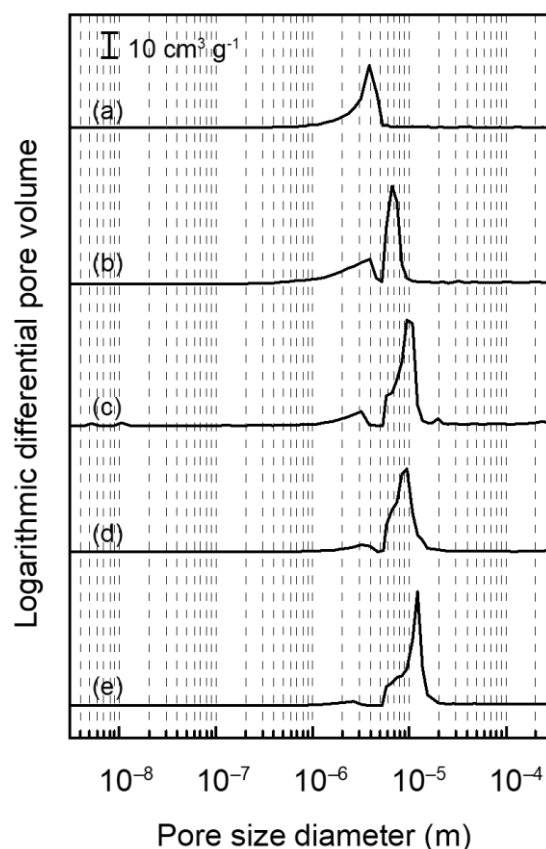


Figure 4-5. Pore size distributions of (a) **M-PS-TPP1**, (b) **M-PS-TPP2**, (c) **M-PS-TPP3**, (d) **M-PS-TPP4**, and (e) **M-PS-TPP5** determined using Hg intrusion porosimetry.

The ^{31}P CP/MAS NMR spectra (Figure 4-6a–4-10a) of the monolith confirmed the incorporation of coordinatively active TPP (-7 – -4 ppm) accompanied by some contents of TPP oxide (24 – 25 ppm) due to partial oxidation of the P atom during synthesis of monolith.^[7a,b]

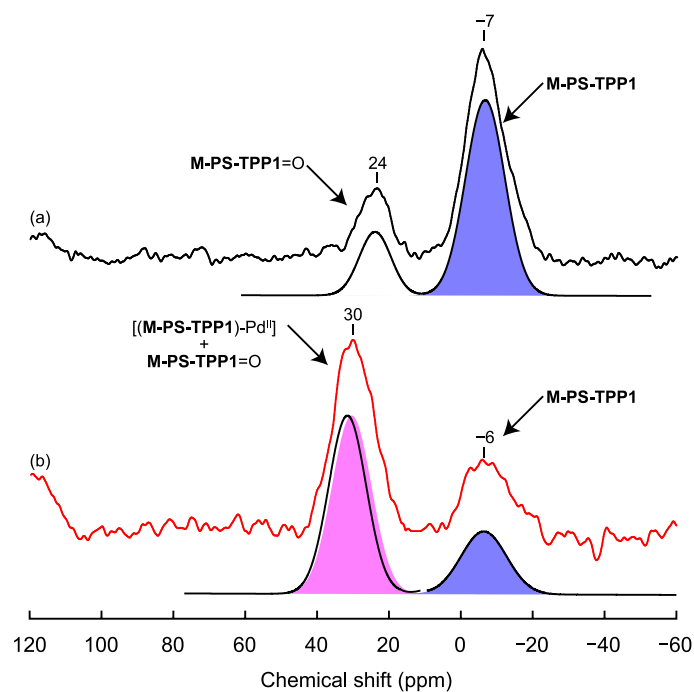


Figure 4-6. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP1** (DVB 2 eq.) (a) before and (b) after reactions with $[\text{PdCl}_2(\text{PhCN})_2]$ (Pd/P 1:2).

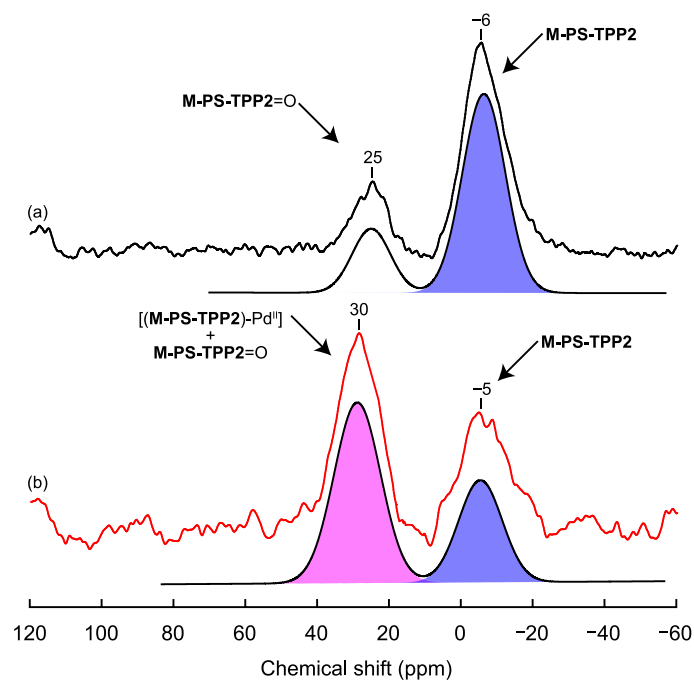


Figure 4-7. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP2** (DVB 5 eq.) (a) before and (b) after reactions with $[\text{PdCl}_2(\text{PhCN})_2]$ (Pd/P 1:2).

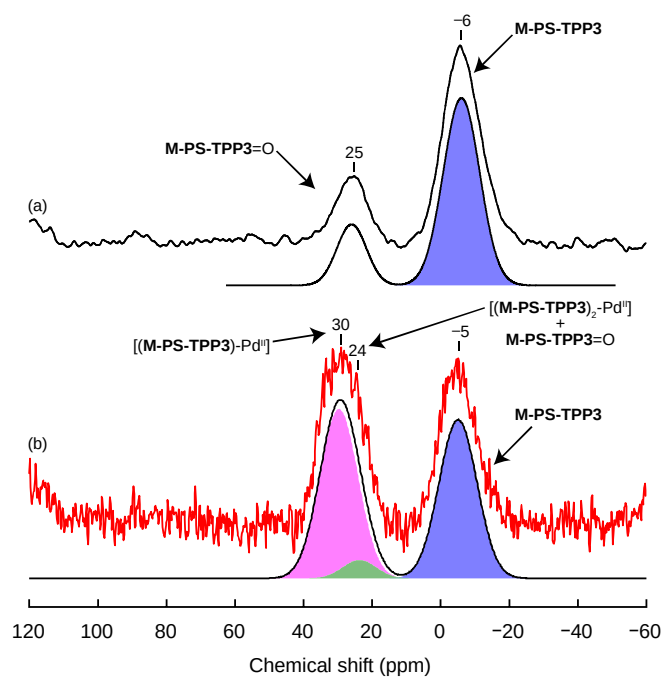


Figure 4-8. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP3** (DVB 20 eq.) (a) before and (b) after reactions with $[\text{PdCl}_2(\text{PhCN})_2]$ (Pd/P 1:2).

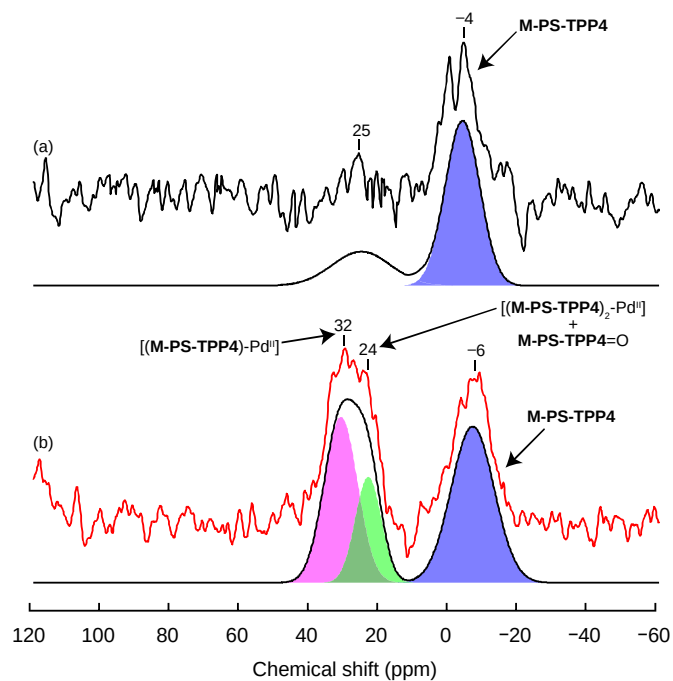


Figure 4-9. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP4** (DVB 40 eq.) (a) before and (b) after reactions with $[\text{PdCl}_2(\text{PhCN})_2]$ (Pd/P 1:2).

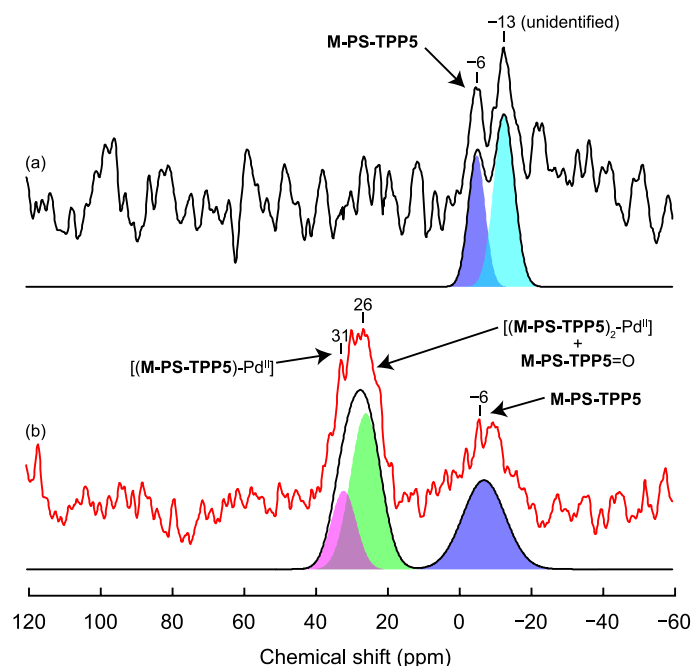


Figure 4-10. ^{31}P CP/MAS NMR spectra obtained from **M-PS-TPP5** (DVB 61 eq.) (a) before and (b) after reactions with $[\text{PdCl}_2(\text{PhCN})_2]$ (Pd/P 1:2).

4.3.2. Coordination Behavior of **M-PS-TPPs**

The coordination abilities of **M-PS-TPPs** toward Pd were confirmed by ICP-AES and ^{31}P CP/MAS NMR analyses after treatment with $[\text{PdCl}_2(\text{PhCN})_2]$ in THF (Pd/P 1:2). ICP-AES analysis indicated that the Pd source in THF was completely loaded on **M-PS-TPPs** to give a Pd loading of 0.05 mmol g^{-1} . In the ^{31}P CP/MAS NMR spectra, all the **M-PS-TPP**-Pd formulated the mono-P-ligated Pd^{II} complex ($[(\text{M-PS-TPP})\text{-Pd}]$ (30–32 ppm) (Figure 4-6b–4-10b).^[7a,b] It is noteworthy that the peak gradually broadened toward the lower chemical shift side as the amount of DVB increased. The peak area ratio in ^{31}P CP/MAS NMR of **M-PS-TPP**-Pd was calculated using Gaussian peak fitting (Table 4-3). In the spectra of **M-PS-TPP1**-Pd and **M-PS-TPP2**-Pd (DVB2 and 5 eq.), the peaks assigned to the bis-P-ligated Pd^{II} complex $[(\text{M-PS-TPP})_2\text{-Pd}]$ (24–26 ppm)^[7a,b] and $\text{TPP}=\text{O}$ were not predominantly observed. On the other hand, increasing DVB content significantly decreased the

relative peak area of the mono-P ligated Pd^{II} complex, especially in the **M-PS-TPP4**-Pd and **M-PS-TPP5**-Pd (DVB contents of 40 and 61 eq.).

In the previous studies, the selectivity for the mono/bis-P-ligation of supported TPP was considerably affected by the cross-linking degree of PS-DVB monolith,^[25] which was explained by the bis-P-ligated Pd^{II} complex formed in TPP-rich domains within the heterogeneously cross-linked network of PS-DVB.^[26,27] During the cross-linking in the presence of high DVB concentration, the DVB is preferentially polymerized to form highly cross-linked region due to the bifunctional nature as cross-linker. If a three-fold cross-linking TPP is incorporated into this dense region, the distance between TPP may become closer and subsequently form a bis-P-ligated Pd^{II} complex. As clearly demonstrated in **M-PS-TPP4** and **M-PS-TPP5** (DVB contents of 40 and 61 eq.), increasing the DVB contents may have created more unfavorable gel network for the formation of site-isolation of TPP units. This mono-ligated TPP-Pd complex reportedly leads to excellent activity in challenging transition-metal-catalyzed reactions.^[7a,b]

Table 4-3. Relative Peak Area of ³¹P CP/MAS NMR Spectra for Pd-Loaded Monolith

monolith	DVB (eq.)	Relative peak area [(M-PS-TPP)-Pd]/[(M-PS-TPP) ₂ -Pd] ^{a,b}
M-PS-TPP1	2	100: 0
M-PS-TPP2	5	100: 0
M-PS-TPP3	20	91: 9
M-PS-TPP4	40	67:33
M-PS-TPP5	61	30:70

^aDetermined using ³¹P CP/MAS NMR spectra. ^bBecause of the difficulty of peak splitting, the peak area from [(**M-PS-TPP**)₂-Pd] included the peak area from TPP=O in **M-PS-TPP**.

4.3.3. Permeabilities of **M-PS-TPP** Columns

Under continuous-flow conditions, ΔP through the **M-PS-TPP** columns were monitored at τ of 0.25–2.00 h by varying the u . During the permeation of THF/water (2:1 v/v) or THF, the 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, and the k_D (Equation 4-3) of the **M-PS-TPP** columns was calculated by the least-squares method (Figure 4-11, 4-12, and Table 4-4). For the permeation of THF and THF/water (2: 1 v/v), the k_D of the **M-PS-TPP** columns varied in the range 10^{-14} – 10^{-13} m². In all the **M-PS-TPP** columns, the k_D for THF/water was greater than those for THF. The **M-PS-TPP3** column with shorter or longer L values (2.3 or 9.5 cm) had almost the same k_D (Figure 4-11), showing the high mechanical stability of **M-PS-TPP** against continuous permeation through the column reactor. When **M-PS-TPP1–3** columns were used, the k_D for THF/water was 7.3–10.9-times higher than those for THF. Interestingly, when **M-PS-TPP4–5** columns were used, the solvent dependency was significantly suppressed (Figure 4-12).

The k_D of the **M-PS-TPP1–3** (DVB2–20 eq.) column changed dramatically against the mobile phase, which reflected the swelling behavior of the PS gel network. The k_D of **M-PS-TPP4–5** (DVB40–61 eq.) column was not significantly affected by the mobile phase, suggesting the suppressed swelling of PS gel network due to high cross-linking density. In continuous-flow catalyses, the swelling behavior of the **M-PS-TPP** column may greatly affect the mass transport of the substrate and hence the catalytic efficiency. On the other hand, the observed k_D of **M-PS-TPP** columns were enough high comparable to those previously reported for porous PS-DVB monolith.^[28b]

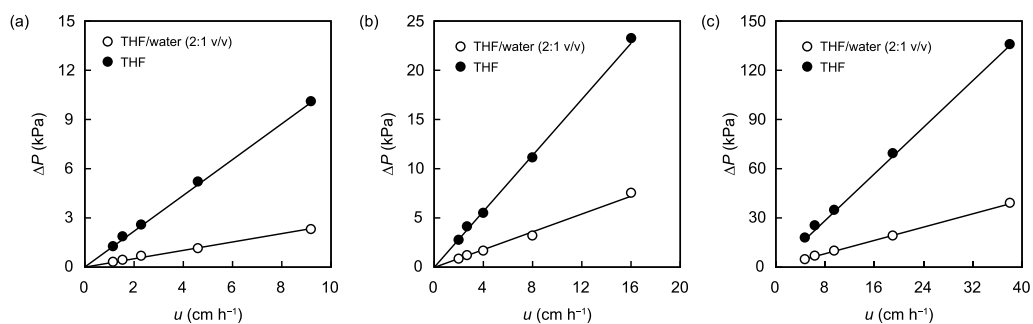


Figure 4-11. ΔP v.s. u diagram through **M-PS-TPP3** with L of (a) 2.3, (b) 4.0, and (c) 9.5 cm.

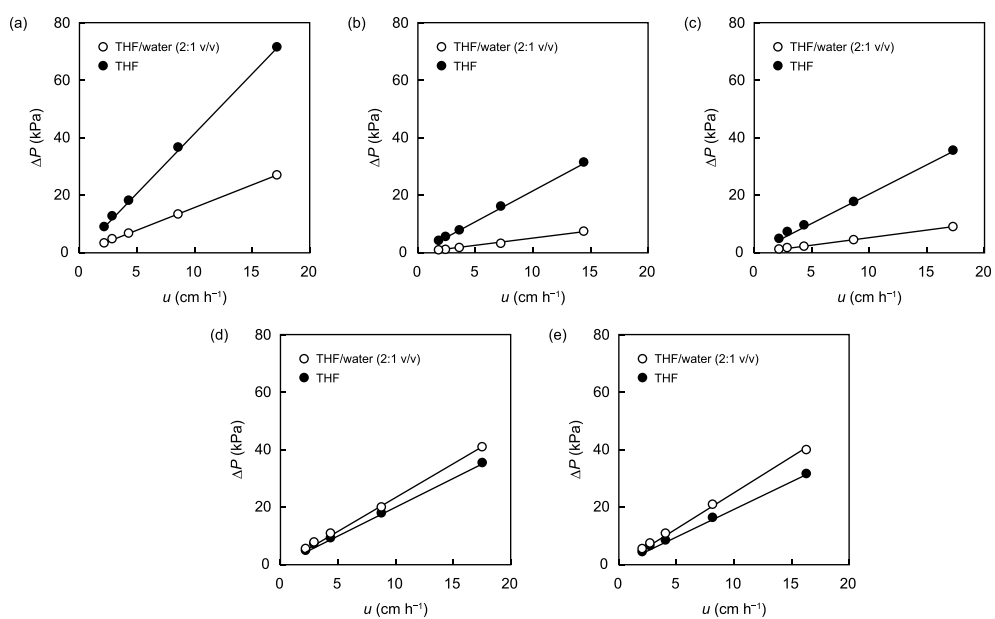


Figure 4-12. ΔP v.s. u diagram through (a) **M-PS-TPP1**, (b) **M-PS-TPP2**, (c) **M-PS-TPP3**, (d) **M-PS-TPP4**, and **M-PS-TPP5** columns in different mobile phase.

Table 4-4. k_D of M-PS-TPP Columns in Different Mobile Phase

monolith	DVB (eq.)	L (cm)	$k_D (\times 10^{-14} \text{ m}^2)^a$	
			THF	THF/water (2:1 v/v)
M-PS-TPP1	2	4.3	1.4	10.2
M-PS-TPP2	5	3.6	2.2	26.6
M-PS-TPP3	20	2.3	2.8	33.8
M-PS-TPP3	20	4.0	3.8	32.8
M-PS-TPP3	20	9.5	3.6	34.7
M-PS-TPP4	40	4.3	2.9	7.0
M-PS-TPP5	61	4.1	2.8	6.1

^aDetermined using Darcy's law.

4.3.4. Flow Behavior of Pulse Tracers and Gel Porosity in **M-PS-TPP** Columns

In order to understand and control the variables governing the hydrodynamics, **M-PS-TPP3** column was characterized by RTD studies with pulse tracer. An inert tracer dye, methyl red, was injected into the stream of THF through the **M-PS-TPP3** column and its distribution was continuously monitored using in-line UV-vis spectroscopy at the outlet over time. Calculating the θ and $E(\theta)$, the flow behavior of the tracer was analyzed (Figure 4-13). It was noteworthy that the narrow and high $E(\theta)$ curves were observed for **M-PS-TPP3** 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 (Table 4-5). A σ^2 approaching to 0 suggests an ideal plug flow, while a σ^2 close to 1 indicates severe longitudinal mixing due to non-uniform velocity distribution and diffusion.^[29] The obtained σ^2 in RTD experiments for **M-PS-TPP3** column were 0.010–0.024, demonstrating that the flow-through porous structure of **M-PS-TPP3**

column 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]

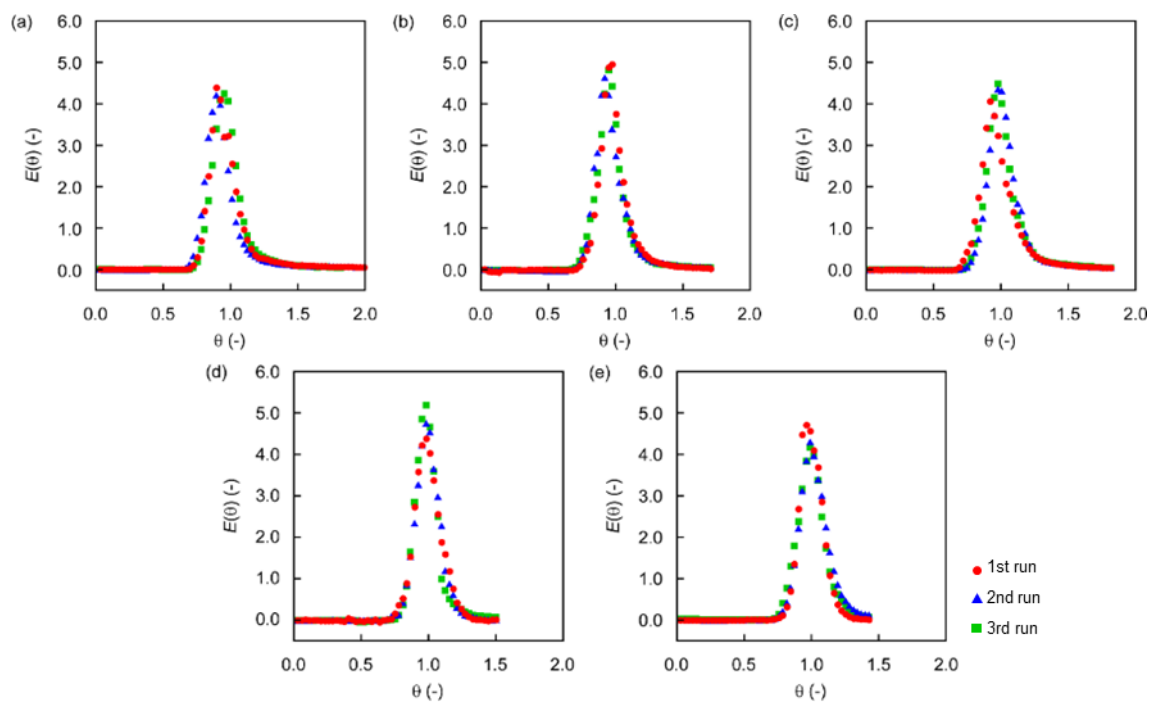


Figure 4-13. $E(\theta)$ v.s. θ diagram for a pulse injection of methyl red in EtOH (1 g L^{-1} , $10 \text{ }\mu\text{L}$) into a THF stream through **M-PS-TPP3** column ($L = 4.5 \text{ cm}$) at τ of (a) 0.25, (b) 0.50, (c) 1.00, (d) 1.50, and (e) 2.00 h.

Table 4-5. σ^2 and ε_T for M-PS-TPP3 Column under Different Flow Conditions^a

τ (h)	u (cm h ⁻¹)	σ^2 (-) ^b
0.25	18.0	0.024 ± 0.003
0.50	9.0	0.020 ± 0.003
1.00	4.5	0.023 ± 0.003
1.50	3.0	0.010 ± 0.002
2.00	2.3	0.012 ± 0.004

^aConditions: **M-PS-TPP3** column ($L = 4.5$ cm), methyl red in EtOH (1 g L⁻¹, 10 μ L) as pulse tracer, THF as mobile phase, r.t. ^bObtained from three independent runs and the average values with standard deviations were shown.

Using tracers with different M.W., size exclusion chromatograms through the **M-PS-TTP** columns were obtained (Figure 4-14). As the M.W. of the tracer increased, the shape of the chromatogram became more asymmetric and tailing became prominent. The t_e , which corresponds to the time at the peak top of the chromatogram, decreased with increasing M.W. of tracers. The radius of gyration (R) of PS in THF could be calculated from the following empirical formula based on the static light scattering experiments:^[30]

$$R \text{ (nm)} = 0.0123 \times \text{M.W.}^{0.588} \quad (4-11)$$

The relationship between $2R$ of tracer and ε_g of the **M-PS-TTP** columns were obtained (Figure 4-15). For the diameter of benzene, space-filling model was adopted ($2R = 7.8 \times 10^{-10}$ m). Increasing the $2R$ of tracers decreased the available ε_g in all the **M-PS-TTP** columns. For example, the **M-PS-TTP** columns showed very high ε_g (92–99%) for the smallest tracer, benzene (M.W. 7.80×10^1). On the other hand, for the largest PS tracer (M.W. 2.78×10^6), the ε_g of the **M-PS-TTP** columns were reduced to be 79–85% (Figure 4-15). In the tested range of $2R$, lower DVB contents of the **M-PS-TTP** columns

resulted in the larger ϵ_g .

Some reports have succeeded in the size exclusion separation of PS standard markers through PS-DVB monolith columns in THF as mobile phase.^[31] For tracers with different $2R$ in THF, the swollen **M-PS-TPP** column showed different elution times based on the size exclusion mechanism (Figure 4-14). Although the Hg intrusion tests revealed that the dried **M-PS-TPPs** had ϵ_{dry} in the range of 67-89% (Table 4-2), the **M-PS-TPP** column provides significantly greater ϵ_g (92–99%) to benzene ($R = 7.8 \times 10^{-10}$ m) for the tracer experiments in THF. The deviation of ϵ_g from ϵ_{dry} of **M-PS-TPP** suggested that the **M-PS-TPP** swelled in THF as organogel^[23] and had microporous network (< 2 nm) in the cross-linked PS, where would function as reaction platform. The **M-PS-TPP1** and **M-PS-TPP2** columns (DVB2 and 5 eq.) showed relatively large ϵ_g , indicating that a large reaction space could be provided under continuous-flow conditions. Even in the **M-PS-TPP3–5** columns (DVB20–61 eq.), size exclusion behaviors for the tracers were also observed and large ϵ_g (92–94%) was obtained when using benzene. The organogel-based reactor would provide the full molecular diffusion of reactants and maximize the performance of catalytic reactor.^[32]

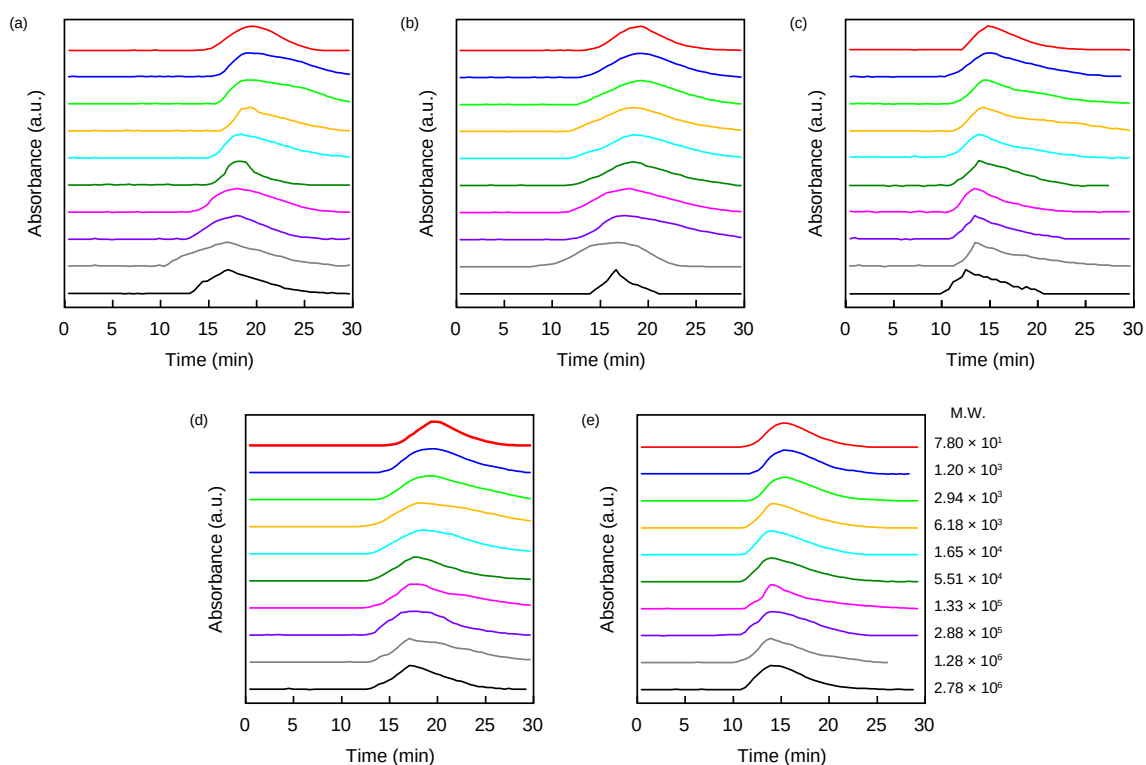


Figure 4-14. Size exclusion chromatograms of benzene (M.W. 7.8×10^1) and PS (M.W. 1.20×10^3 – 2.78×10^6) through (a) **M-PS-TPP1**, (b) **M-PS-TPP2**, (c) **M-PS-TPP3**, (d) **M-PS-TPP4**, and **M-PS-TPP5** columns.

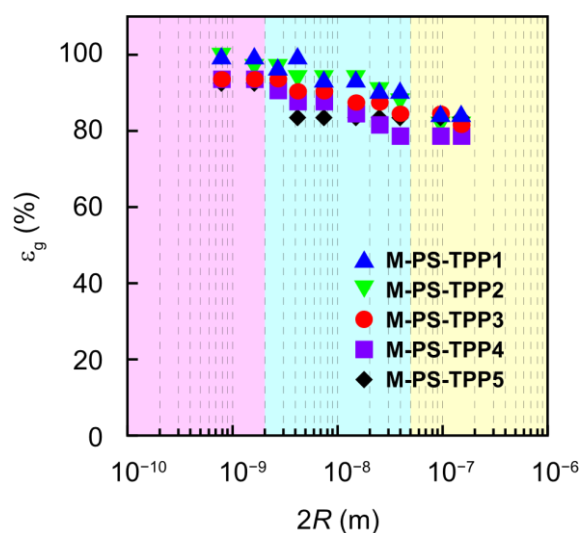


Figure 4-15. Changes in ϵ_g of **M-PS-TPP** columns with $2R$ of tracers. The micro (< 2 nm), meso (2–50 nm), and macropore (> 50 nm) sizes were highlighted in red, blue, and yellow, respectively.

4.3.5. Flow Suzuki-Miyaura Cross-Coupling Reaction using **M-PS-TPP**-Pd Columns

The **M-PS-TPP3**-Pd column was fabricated by the treatment of **M-PS-TPP3** column with $[\text{PdCl}_2(\text{PhCN})_2]$ solution in THF under continuous-flow conditions. After washing by permeating of 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-TPP3**-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-TPP3**-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 Q_{THF} to Q_{water} to be 2:1 v/v (Scheme 4-4). 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 in the HPLC charts. Using ICP-AES, it was confirmed that there was no leakage of Pd in the total fraction (THF and the aqueous phase) from all the **M-PS-TPP**-Pd columns. 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 4-16). The **M-PS-TPP3**-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-TPP3**-Pd column drastically increased the yield within the same range of τ values. At a τ of 2.00 h, the **M-PS-TPP3**-Pd column with longer L values (4.0 and 9.5 cm) achieved excellent yields of 86 and 88%, respectively.

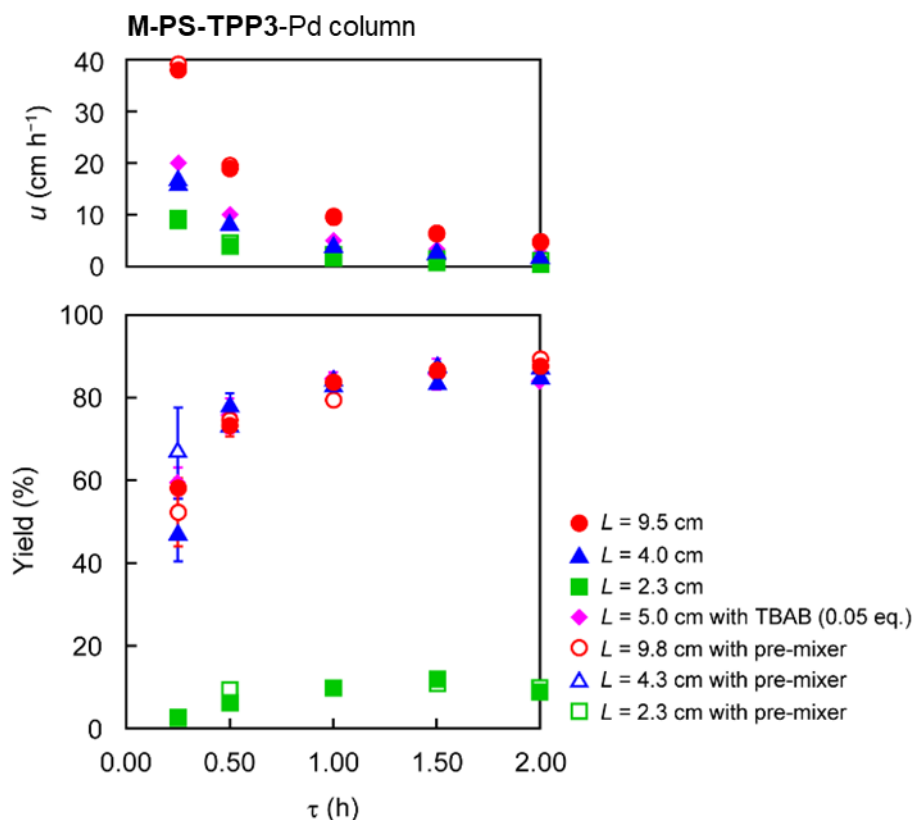


Figure 4-16. Effects of L of **M-PS-TPP3-Pd** column and τ on yield of 4-methylbiphenyl in continuous-flow Suzuki-Miyaura cross-coupling reaction using biphasic solvent. Conditions: 4-chlorotoluene (0.50 mol L^{-1} , 1 eq.) and phenylboronic acid (0.75 mol L^{-1} , 1.5 eq.) in THF, K_3PO_4 (3.00 mol L^{-1} , 3 eq.) in water, **M-PS-TPP3-Pd** column (Pd/P 1:2), $Q_{\text{THF}}/Q_{\text{water}}$ 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 the present system, a higher u was realized using a longer L at the same range of τ (Figure 4-16). This positive effect might be 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-TPP3-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-TPP3**-Pd column (blank circle, blank triangle, and blank rectangle, Figure 4-16). In the presence of TBAB (0.05 eq.) as a phase transfer catalyst in the biphasic reaction mixture, the productivity of the **M-PS-TPP3**-Pd column was also evaluated (filled rhombus, Figure 4-16), which gave almost the same trend as that without TBAB.

Unlike the previous study using a homogeneous catalyst,^[11] the present results demonstrated that mass transfer at the organic/aqueous 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.^[33] 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-TPP3**-Pd column. In addition to RTD behavior close to plug-flow (Figure 4-13 and Table 4-5), the accelerated external diffusion of reactants also boosted productivity of monolith column.

In the Suzuki-Miyaura cross-coupling in the biphasic reaction media, aqueous-organic phase with lower pH and aqueous basic phase with higher pH.^[34] In this situation, most of phenyl boronic acid was ionized and present at the biphasic interfaces, while aryl chloride should be present in the aqueous-organic phase. In the presence of aqueous phase, the “on-water” catalysis might enhance the activity of immobilized TPP-Pd complex in the **M-PS-TPP**-Pd.^[35] Under the biphasic reaction media, the Pd species should be present at the THF-aqueous phase boundary to promote the transmetalation including borate anion and aryl-chloride-Pd intermediates. It was reasonable to assume that the most of TPP-Pd complex located within the gel network rather than at the surface layer of gel because of low surface area of **M-PS-TPP**-Pd. These inferred that the immiscible two phases alternately infiltrated the gel network of **M-PS-TPP**-Pd column and catalytic conversion progressed at the liquid-liquid interface. To accelerate the interfacial reaction, tuning the microenvironment of catalytic center

in terms of hydrophilic-lipophilic balance would be important by introduction of styrene derivatives.

4.3.6. *Continuous-Flow Conditions v.s. Batch-Conditions*

The catalytic efficacy of **M-PS-TPP3-Pd** was also evaluated in batch system and compared with that in continuous-flow system. Indeed, the TON and turnover frequency (TOF) of **M-PS-TPP3-Pd** were higher under continuous-flow conditions than those under batch conditions (Table 4-6). Interestingly, increasing the stirring rate and/or employing TBAB enhanced the reaction efficacy of batch cross-coupling reaction using **M-PS-TPP3-Pd** (Figure 4-17). 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 the present system, the merits of the macroporous architecture of the **M-PS-TPP3-Pd** column for mass transfer were highlighted, where molecular diffusion at the organic/aqueous interface was accelerated by the biphasic media co-flowing through the micron-sized pores.^[28b] Moreover, the full accessibility of reactants toward catalyst was realized due to narrow RTD and swelling properties which also supported the high productivity of **M-PS-TPP3-Pd** column. As far as the author 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. Indeed, the **M-PS-TPP3-Pd** achieved the high TON (2704), TOF (47 h^{-1}), and space time yield ($0.45\text{ kg L}^{-1}\text{ day}^{-1}$) in challenging aryl chloride cross-coupling, whose potential was comparable to that of a PS-DVB-supported TPP in similar Pd-catalyzed cross-couplings of aryl bromides.^[37] Using the **M-PS-TPP3-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.

Table 4-6. Comparison of Catalytic Efficacies of M-PS-TPP-Pd for the Cross-Coupling^a

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

^aConditions: 4-chlorotoluene (0.50 mol L⁻¹, 1 eq.) and phenylboronic acid (0.75 mol L⁻¹, 1.5 eq.) in THF, K₃PO₄ (3.00 mol L⁻¹, 3 eq.) in water, THF phase/water phase 2:1 v/v, 40°C. ^b**M-PS-TPP3**-Pd column (Pd/P 1:2, *L* = 4.5 cm), τ = 2.00 h. ^cTime on stream = 58 h. ^d**M-PS-TPP3**-Pd (Pd/P 1:2, 0.1 mol% Pd), 2.00 h.

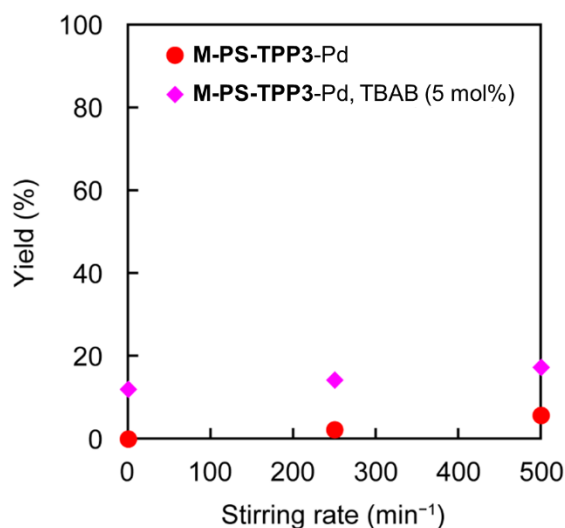


Figure 4-17. Effects of stirring rate and TBAB on yield of 4-methylbiphenyl in batch Suzuki-Miyaura cross-coupling reaction using biphasic solvent. Conditions: 4-chlorotoluene (1.5 mmol, 1 eq.), phenylboronic acid (2.25 mmol, 1.5 eq.), and TBAB (0.075 mmol, 5 mol%) in THF (3.0 mL in total), K₃PO₄ (4.5 mmol, 3 eq.) in water (1.5 mL in total), THF phase/water phase 2:1 v/v, [PdCl₂(PhCN)₂] (0.0015 mmol, 0.1 mol%), **M-PS-TPP3** (0.0030 mmol, 0.2 mol%), 40°C, 2.00 h.

4.3.7. Long-Term Durability of **M-PS-TPP**-Pd Columns

The catalytic performance of **M-PS-TPP1–5**-Pd columns were evaluated in long-term production

of 4-methylbiphenyl via continuous-flow cross-coupling. Using ICP-AES, it was confirmed that there was no leakage of Pd in the total fraction (THF and the aqueous phase) from all the **M-PS-TPP**-Pd columns. Initially, the **M-PS-TPP1-4**-Pd columns showed the high yield (76–93%), which then gradually decreased (Figure 4-18). At column volume = 29 (time on stream = 58 h), the TONs of **M-PS-TPP1**-Pd, **M-PS-TPP2**-Pd, **M-PS-TPP3**-Pd, **M-PS-TPP4**-Pd, and **M-PS-TPP5**-Pd columns were 874, 1170, 2704, 463, and 420, respectively. It is interesting that the maximum TON was observed for **M-PS-TPP3**-Pd (DVB 20 eq.). TEM observations of the **M-PS-TPP**-Pd revealed that the Pd aggregation occurred after use in continuous-flow cross-couplings in all the **M-PS-TPP**-Pd. Particularly, many Pd aggregates could be identified in **M-PS-TPP1**-Pd and **M-PS-TPP2**-Pd (DVB2 and 5eq.). Notably, the number of the Pd aggregates decreased with increasing DVB content (Figure 4-19). Pd(3d) XPS spectra from the spent **M-PS-TPP**-Pd showed the photoemission peaks attributable to Pd⁰, which might be formed during the catalytic reactions (Figure 4-20–4-24). Using Gaussian peak fitting method, the existence ratio of Pd^{II}/Pd⁰ in the spent **M-PS-TPP**-Pd was estimated (Table 4-7).^[38] Peak intensity ratios of Pd^{II}/Pd⁰ were in the range of 32:68–47:53, except for **M-PS-TPP1**-Pd (76:24).

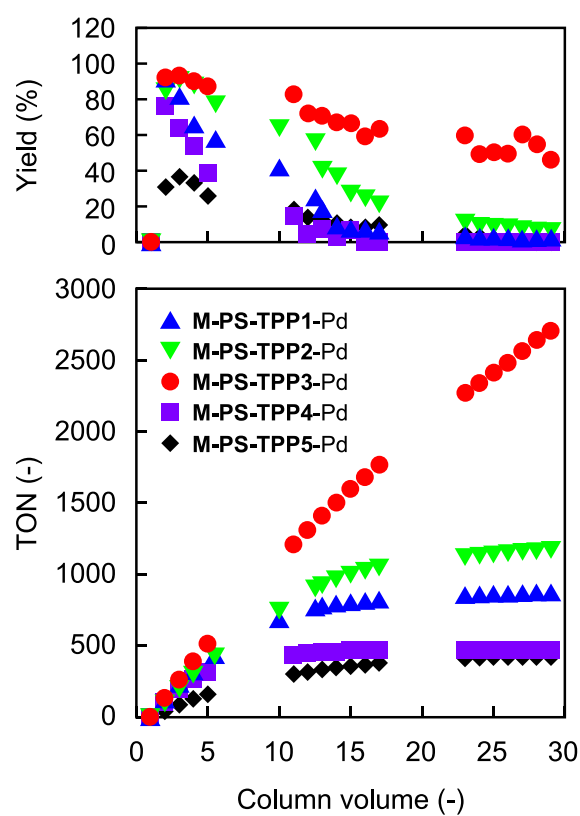


Figure 4-18. Long-term production of 4-methylbiphenyl using **M-PS-TPP-Pd** columns. Conditions: 4-chlorotoluene (0.50 mol L^{-1} , 1 eq.) and phenylboronic acid (0.50 mol L^{-1} , 1 eq.) in THF, K_3PO_4 (2.00 mol L^{-1} , 2 eq.) in water, **M-PS-TPP-Pd** column (Pd/P 1:2), $Q_{\text{THF}}/Q_{\text{water}}$ 2:1 v/v, $\tau = 2 \text{ h}$, 40°C .

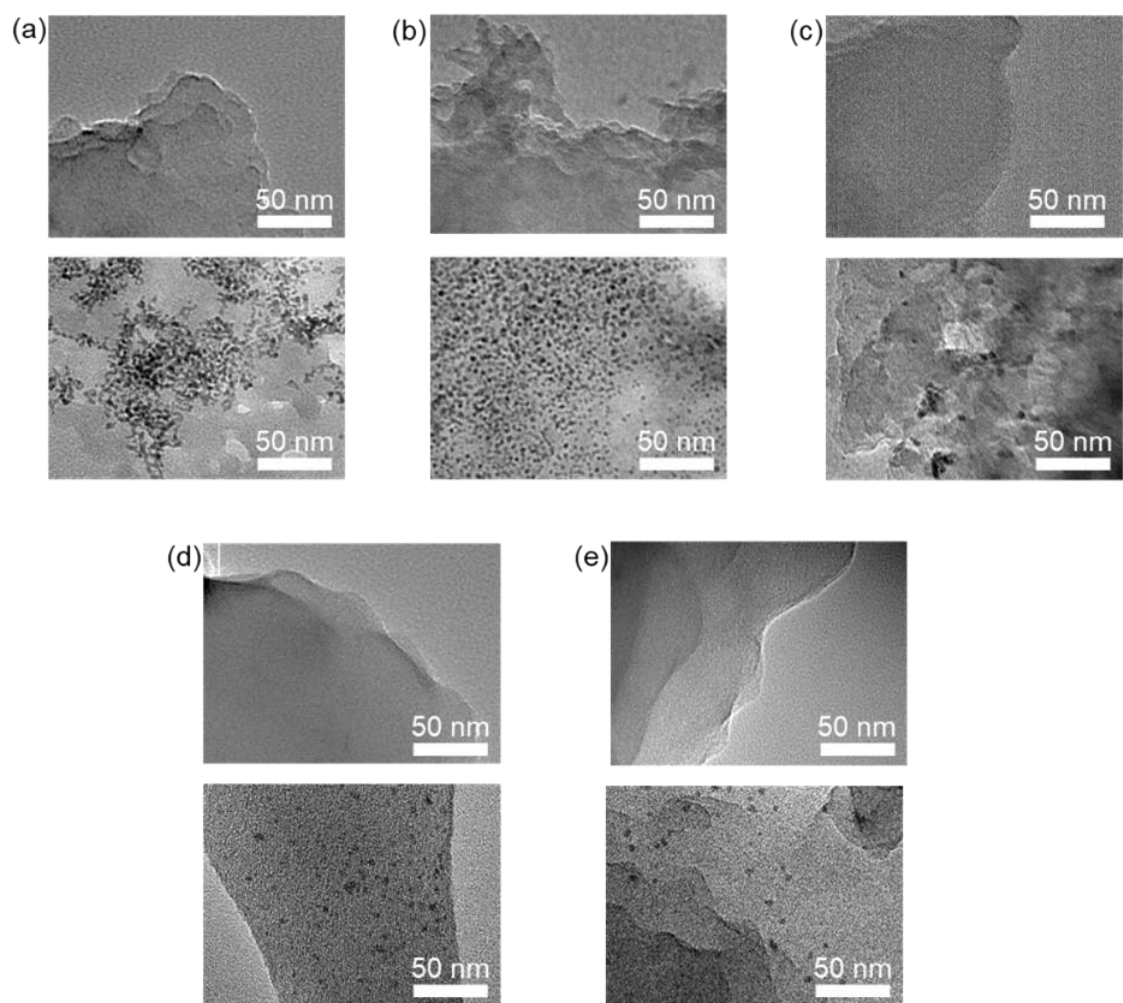


Figure 4-19. TEM images of fresh (top) and spent (bottom) (a) **M-PS-TPP1-Pd**, (b) **M-PS-TPP2-Pd**, (c) **M-PS-TPP3-Pd**, (d) **M-PS-TPP4-Pd**, and **M-PS-TPP5-Pd**.

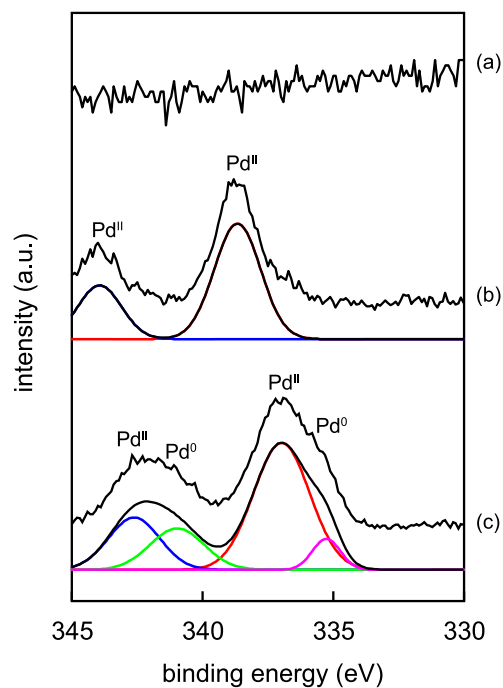


Figure 4-20. Pd(3d) XPS spectra of (a) **M-PS-TPP1**, (b) fresh **M-PS-TPP1-Pd**, and (c) spent **M-PS-TPP1-Pd**.

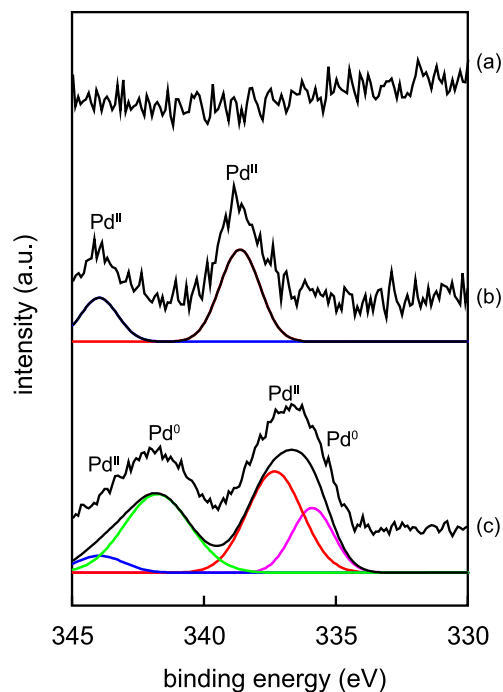


Figure 4-21. Pd(3d) XPS spectra of (a) **M-PS-TPP2**, (b) fresh **M-PS-TPP2-Pd**, (c) spent **M-PS-TPP2-Pd**.

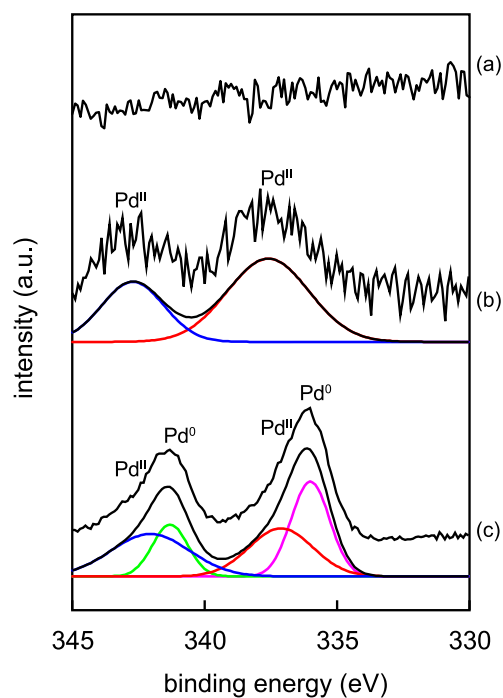


Figure 4-22. Pd(3d) XPS spectra of (a) **M-PS-TPP3**, (b) fresh **M-PS-TPP3-Pd**, (c) spent **M-PS-TPP3-Pd**.

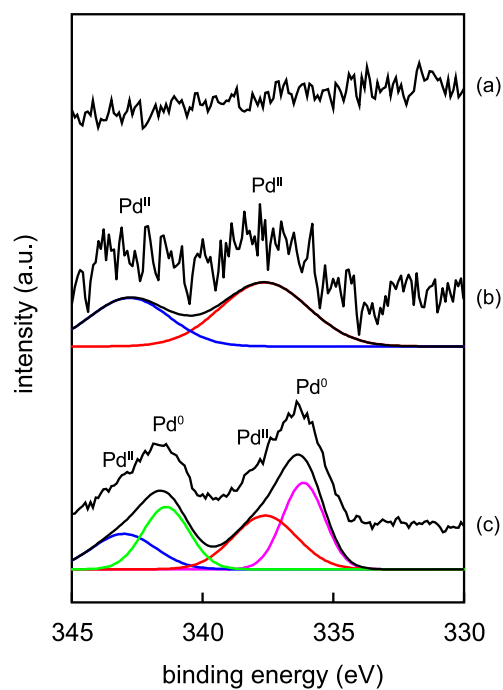


Figure 4-23. Pd(3d) XPS spectra of (a) **M-PS-TPP4**, (b) fresh **M-PS-TPP4-Pd**, (c) spent **M-PS-TPP4-Pd**.

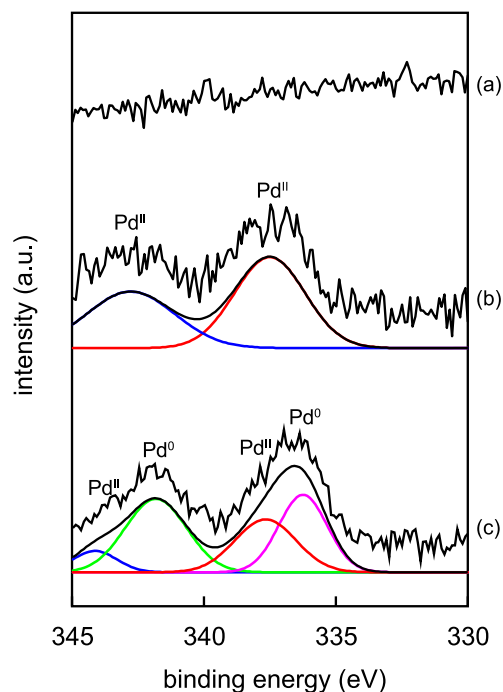


Figure 4-24. XPS spectra of (a) **M-PS-TPP5**, (b) fresh **M-PS-TPP5-Pd**, (c) spent **M-PS-TPP5-Pd**.

Table 4-7. Relative Peak Area of Pd^{II} and Pd⁰ in Pd(3d) XPS Spectra of the Spent Catalysts

monolith	DVB content (eq.)	relative peak intensity
		Pd(II)/Pd(0) ^{a,b}
M-PS-TPP1-Pd	2	76:24
M-PS-TPP2-Pd	5	45:55
M-PS-TPP3-Pd	20	32:68
M-PS-TPP4-Pd	40	47:53
M-PS-TPP5-Pd	61	34:66

^aDetermined by XPS spectra. ^bPeaks at 342.9, 337.8, 340.7, and 335.6 eV were assigned to Pd(3d_{3/2}) and Pd(3d_{5/2}) from Pd(II), and Pd(3d_{3/2}) and Pd(3d_{5/2}) from Pd(0), respectively.^[36]

The chromatograms of tracer through the **M-PS-TPP1** and **M-PS-TPP2** columns (DVB2 and 5

eq.) showed considerably high accessibility ($\varepsilon_g = 99\%$) to benzene, whose size was comparable to the substrate (Figure 4-15). On the other hand, the **M-PS-TPP3** column (DVB 20 eq.) with a slightly lower ε_g (94%) showed the highest catalytic activity, meaning sufficient molecular diffusion of reactants to the immobilized Pd under the present continuous-flow conditions. For the successful cross-coupling reaction of aryl chlorides, the formation of mono-P-ligated Pd^{II} complex plays a very important role.^[7a,b] Modulation of the DVB amount of **M-PS-TPP**-Pd affected the selectivity of the mono-P coordination, and for **M-PS-TPP1-3** (DVB 2–20 eq.), highly active mono-P-ligated Pd^{II} [**(M-PS-TPP)-Pd**] was selectively formulated over bis-P-ligated Pd^{II} [**(M-PS-TPP)₂-Pd**] (mono/bis 91:9–100:0, Table 4-3). However, the lower DVB content (DVB2 and 5 eq.) deteriorated the TONs (Figure 4-18), resulting in many Pd aggregation which were likely inactive (Figure 4-19a and b). Since no leaching of Pd into the eluents was confirmed during the run, all the Pd might remain within the gel network of **M-PS-TPP**-Pd. As observed in the Pd(3d) spectra, all the **M-PS-TPP**-Pd showed the photoemission peaks attributable to Pd⁰ (Figure 4-20–4-24 and Table 4-7), suggesting the in-situ reduction from supported TPP-Pd^{II} species.^[39] The formation of Pd particles observed in the TEM images of the spent catalysts were due to the aggregation between the formed Pd⁰, which dissociated from the supported TPP during the catalytic cycles in the cross-coupling. Although too much cross-linking degree in the organogel failed selective formation of mono-P-ligation to Pd^{II}, the moderate increase in DVB content may amplify steric hindrance from the PS chain and/or the donation of π electrons from the styrene pendant to Pd^[40] in the region with high cross-linking density, and suppress the formation of Pd aggregating. The TOFs based on the existence ratio of mono-P-ligated Pd complex in the **M-PS-TPP**-Pd was calculated to confirm the effect of the cross-linking degree on the “true” catalytic activity (Figure 4-25). Taking the existence ratio of mono-P-ligated Pd into account, the **M-PS-TPP**-Pd columns with higher cross-linking degree also showed the high TOFs comparable with those of lower cross-linking degree at the early stage in the catalytic reactions. This shows the “true”

TOF of Pd complex was mainly dependent on the existence ratio of mono-P-ligation in the present cross-coupling of aryl chloride. Nevertheless, the **M-PS-TPP3-Pd** column showed the highest TOF which was well maintained along the continuous-flow reaction. Too much or strong interactions between π electrons from the styrene pendant and Pd might deteriorate the catalytic cycles. Thus, for highly active and durable **M-PS-TPP-Pd**, it was important to design a polymer gel that simultaneously achieves selective formation of highly active mono-P-ligated-Pd complexes and suppression of Pd aggregation in the cross-linking network (Figure 4-26).

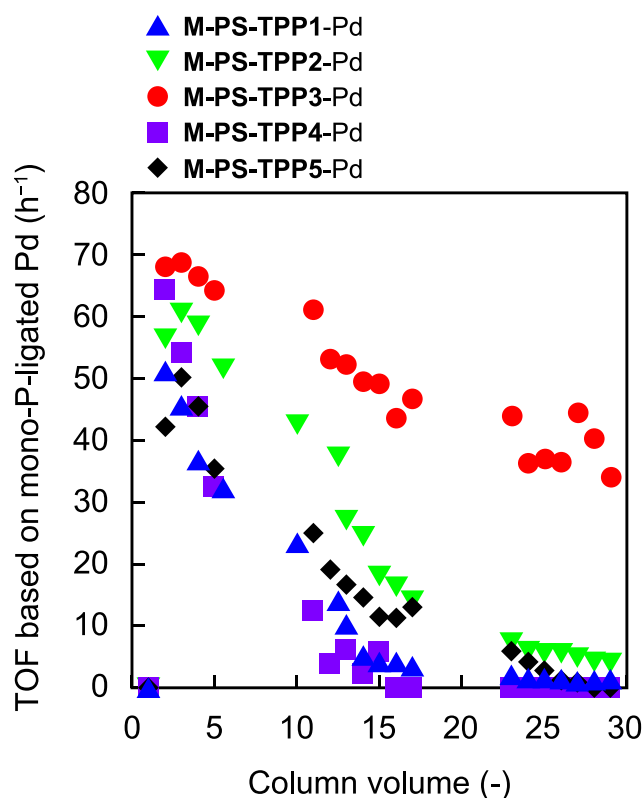


Figure 4-25. Changes in TOFs for **M-PS-TPP-Pd** columns based on the existence ratio of mono-P-ligated Pd complex. Conditions: 4-chlorotoluene (0.50 mol L^{-1} , 1 eq.) and phenylboronic acid (0.50 mol L^{-1} , 1 eq.) in THF, K_3PO_4 (2.00 mol L^{-1} , 2 eq.) in water, **M-PS-TPP-Pd** column (Pd/P 1:2), $Q_{\text{THF}}/Q_{\text{water}}$ 2:1 v/v, $\tau = 2 \text{ h}$, 40°C .

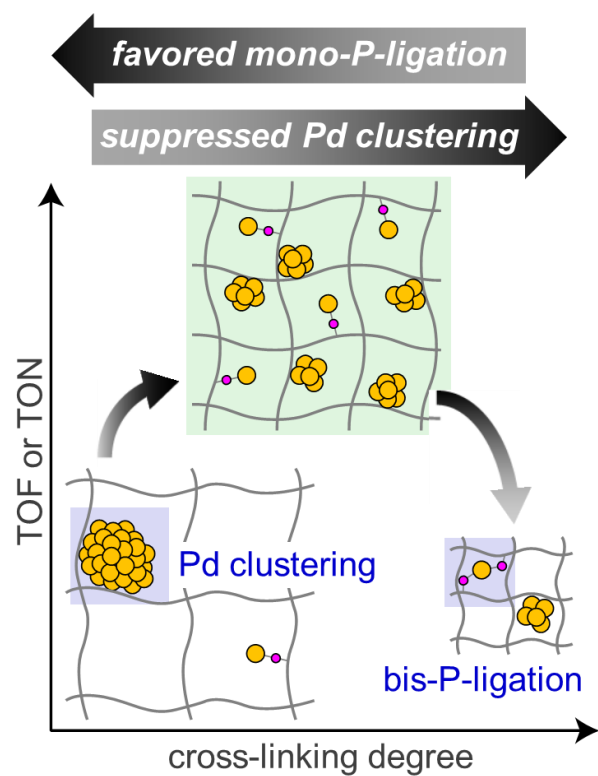


Figure 4-26. Conceptual illustration of **M-PS-TPP-Pd** with optimized cross-linking degree for high TOF and TON controlled by coordination behavior and stabilization of metal. TPP units (pink balls), Pd (yellow balls), and PS chains (gray lines) are shown.

4.4 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, featuring efficient mixing of biphasic media through the macroporous architecture of the monolith column. Additionally, tuning the cross-linking density of the organogel network, the high selectivity for active mono-P-ligation and effective prevention of Pd deactivation was simultaneously realized in the **M-PS-TPP**-Pd system. As far as the author knows, the organogel-based catalysts showed the highest TON in challenging cross-coupling of aryl chloride under continuous-flow condition. This would be broadly extended to transition-metal catalysis in continuous-flow systems for efficient production of fine chemicals.

4.5 References

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Chapter 5

Summary

Chapter 5 Concluding Remarks

5.1 Summary

In this doctoral thesis, monolithic and macroporous polymer gel was developed as supports for metal catalysts and applied to continuous-flow synthesis of fine chemicals. To broaden the scope of reaction systems, hydro- or organo-gel based monoliths were prepared and their catalytic activity in terms of TOF and TON were evaluated in continuous-flow cross-couplings. In particular, the most fundamental parameter, cross-linking degree, in the gel was mainly tuned to provide the suitable reaction platform for the transition-metal catalyses.

Chapter 2 presents the development of macroporous poly(*N*-isopropylacrylamide) (PNIPAm)-based hydrogel for Pd-catalyzed Suzuki-Miyaura cross-coupling reaction under continuous-flow conditions in aqueous media (Figure 5-1). The macroporous structures in the PNIPAm gel was fabricated via polymerization-induced phase separation (PIPS) in water, and tertiary-amine ligand monomer and cross-linking monomer were co-polymerized. Owing to the interconnected macropores and high macroporosity, the gel monolith showed high permeability for aqueous solution comparable with the commercially available filter membranes. Tuning the cross-linker contents, the size of gel network of the monolith changed, which were reflected in different swelling behavior against the temperature changes according to the volume phase transition of the PNIPAm gel matrix. Loading of Pd catalyst in the gel monolith was achieved by Pd^{II} ion adsorption and subsequent reduction into Pd⁰, leading to the gel-confined Pd⁰ clusters with the diameters of 2.1–2.4 nm. Indeed, the gel monolith columns showed significantly high TONs and no Pd leaching compared with the system using inorganic macroporous monolith, silica particles, and carbon in the Pd-catalyzed continuous-flow reactions. Additionally, the cross-linking degree also influenced on the TOF of Pd-loaded gel monolith, which related to the molecular diffusion issue. These results revealed that the mass transfers of

reactants were fully accelerated using polymer gel during the catalytic reactions in aqueous media, boosting the catalytic performance of the immobilized catalysts in continuous-flow system.

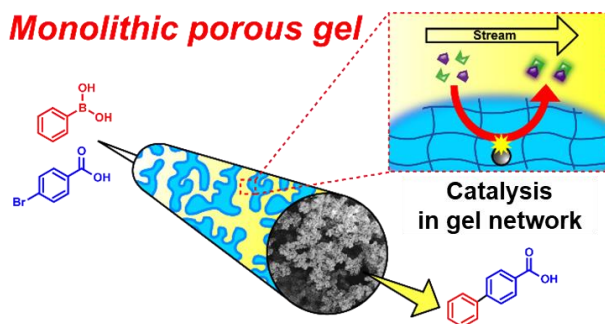


Figure 5-1. Schematic illustration of hydrogel-based monolith reactor for Pd(0)-catalyzed Suzuki-Miyaura cross-coupling reaction under continuous-flow conditions.

Chapter 3 discusses about the strategy for selective formation of highly active metal complex in the organogel monolith modulating the cross-linking structures (Figure 5-2). Polystyrene (PS)-based porous gel was prepared by copolymerization of styrene matrix monomer, cross-linking monomer, and three-fold vinylated triphenylphosphine (TPP) ligand via PIPS in organic solvents. The obtained gel showed unique coordination properties to Pd^{II} source, which selectively formed mono-P-ligation over bis-P-ligation. Additionally, the tuning cross-linking degree improved the selectivity for mono-P-ligation while maintaining the fast diffusivities of small molecules through the PS gel. In fact, the amazingly high activity of the TPP-supported organogel was featured in challenging Suzuki-Miyaura cross-coupling reactions of aryl chlorides in batch systems. Under mild conditions, the Pd-loaded organogel smoothly converted the unactivated substrates into desired products via cross-couplings. The macroporous structure and site-isolation of TPP in the organogel enhanced the mass transfer and activation of metal catalyst at the same time, demonstrating the importance of fine tuning of cross-linking structure of organogel supports.

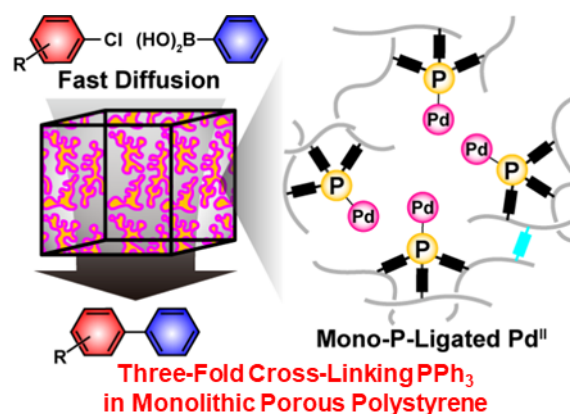


Figure 5-2. Schematic illustration of organogel-based monolith for site-isolation of phosphine ligand and Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl chlorides.

Chapter 4 demonstrated the feasibility of monolithic and macroporous PS gel for durable transition-metal catalyses in continuous-flow systems (Figure 5-3). Using the high-internal phase emulsion template, the highly porous PS-supported TPP organogel monolith was fabricated and allowed the organic/aqueous phase co-flowing through the pores with low pressure losses. Featuring the micron-sized interconnected pores, the mass transfer between the biphasic solvent was fully accelerated and overcome the diffusion limitations at the liquid/liquid interfaces. Controlling the hydrodynamic properties in the monolith by linear velocity of feed, the high yield of desired biaryl was achieved in Pd-catalyzed cross-coupling of aryl chloride compared with batch systems. This significantly high productivity and durability was supported by size exclusion behavior of the organogel, which showed gel porosity in organic solvent and full accessibility of reactants through the gel network. Interestingly, the cross-linking degree in the gel monolith affected on both the selective formation of active TPP-Pd complex and Pd deactivation, which indicated the trade-off relationship. These results revealed the insight into the design of highly durable immobilized metal catalyst by modulation of cross-linking network of support polymer gel.

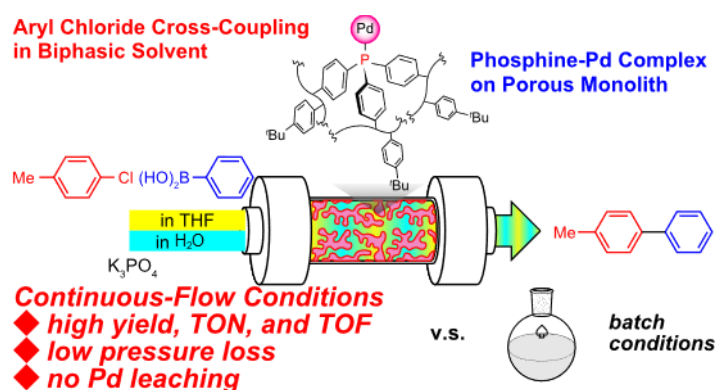


Figure 5-3. Schematic illustration of organogel-based monolith for Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl chlorides under continuous-flow conditions.

Throughout the present research, the advantages of the polymer-gel-based monolith as support for catalysts were highlighted in terms of followings:

- (i) Rapid and full diffusion of reactants and/or catalyst, which mitigates the diffusion limitation in the supports and maximize the loading of catalyst in the limited volume of reactor.
- (ii) Durable immobilization and stabilization of metal catalyst within the gel network by moderate steric hindrance and/or coordination of polymer chain, and multi-point interaction from the ligand.
- (iii) Controllable coordination behavior of ligand toward metal center within the gel network.

To fulfill the recent and urgent demand for sustainable development goals (SDGs), the immobilized catalyses under continuous-flow conditions should be spread in the wide range of organic syntheses and systematized for revolution of present chemical manufacturing. In this situation, combination of organic chemistry, materials science, and chemical engineering have to work together for high reaction efficiency, stability, recyclability, energy/mass transport efficiency during the chemical processes. The results obtained in the thesis must be the guide to create efficient continuous-flow system for the valuable products.

5.2 Research Achievements

5.2.1. Original Articles

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5.2.2. Other Articles

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5.2.3. International Conference

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5.2.4. Domestic Conference

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