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A Polymer-Bound Monodentate-P-Ligated Palladium Complex as a Recyclable Catalyst for the Suzuki–Miyaura Coupling Reaction of Aryl Chlorides

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Abstract: A three-fold cross-linked polymer-bound phosphine (POL-Ph_3P) with high phosphorus content has been prepared. The phosphorus-containing polymer forms a monodentate-P-ligated palladium complex, which shows excellent activity in Suzuki–Miyaura cross-coupling reactions of aryl chlorides. Importantly, the catalyst Pd/POL-Ph_3P is highly stable and can be reused for at least 10 times without losing reactivity.

Keywords: heterogeneous catalysts; metal binding ability; monodentate-P-ligated palladium complex; phosphines; Suzuki–Miyaura cross-coupling reaction

Introduction

Palladium-catalyzed cross-coupling reactions, such as Suzuki–Miyaura, Sonogashira–Hagihara and Heck reactions, have played a crucial role in the construction of carbon-carbon bonds.[1] Great efforts have been devoted to develop homogeneous palladium catalysts in the presence of phosphine ligands.[2] However, application of these homogeneous catalysts in industrial settings is still limited because of their high cost and the difficulty in recycling them from the products. Transition metal catalysts can be bound to ligand-containing polymers to form metal-polymer complexes.[3,4] These complexes are used as heterogeneous catalysts to overcome some of the drawbacks of homogeneous catalysts. In this regard, polystyrene-supported phosphines (PS-Ph_3P) have been used as ligands for heterogeneous catalysts.[4] For example, PS-Ph_3P in complex with palladium is employed for the cross-coupling reactions of aryl iodides or bromides and arylboronic acids.[5] From an industrial point of view, the use of aryl chlorides is attractive because they are relatively cheap and readily available. However, it is difficult to activate the less reactive aryl chlorides using catalysts derived from palladium and single-pointed PS-Ph_3P (Figure 1a) or two-fold cross-linked PS-Ph_3P,[6] probably because of the multidentate-P-ligating behavior of the polymeric ligand and the steric effects of the flexible PS backbone. Over the last few years, monoligation of many phosphine ligands in homogeneous catalysis system has been achieved through different strategies and the resulting complexes have successfully induced cross-coupling reactions of aryl chlorides.[7,8] Recently, Sawamura's group reported a three-fold cross-linked PS-Ph_3P covalently bound hybrid (Figure 1b, PS-L_3) which merely formed monodentate-P-ligated transition metal complexes as a heterogeneous catalyst and showed high catalytic activity in Suzuki–Miyaura cross-coupling reactions of aryl chlorides.[9] However, the catalytic activity was reduced dramatically after being recycled for four times. Therefore, the development of heterogeneous catalysts with high reactivity and stability remains a big challenge.

Recently, we reported a porous organic ligand (POL-Ph_3P, Figure 1c) supported rhodium species

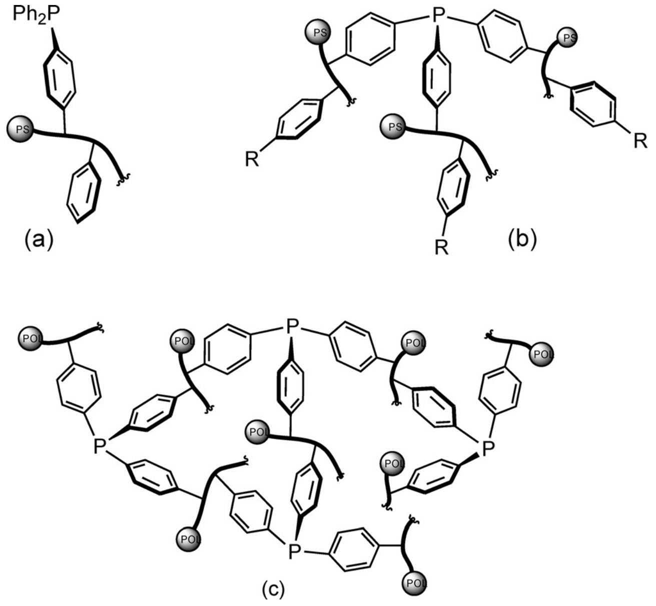
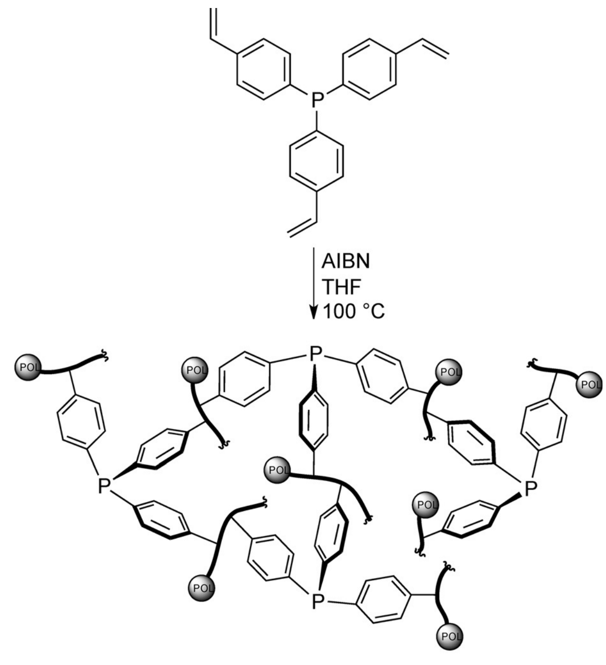


Figure 1. (a) The single-pointed PS-L$_1$. (b) The three-fold cross-linked PS-L$_2$ (R=H); PS-L$_3$ (R=*t*-Bu). (c) The three-fold cross-linked POL-Ph$_3$P synthesized by us.

which exhibits high activity in the hydroformylation of 1-octene.[10] We now hope to employ this polymer as a supporting ligand for palladium-catalyzed Suzuki–Miyaura cross-coupling reactions. POL-Ph$_3$P is a new type of three-fold cross-linked polymer-bound phosphine[11] and can be prepared through solvothermal polymerization of tris(*p*-vinylphenyl)phosphine in the absence of styrene and divinylbenzene (see Scheme 1). Compared with polystyrene-supported phosphine, this novel phosphine possesses a much higher P content and enhances metal binding ability. The POL-Ph$_3$P-metal complex maintains high catalytic activities over many cycles. Furthermore, the three-fold cross-linking results in an increased density of the polymer chain around the P atom, limiting multidentate P-coordination to the palladium. In addition, the monodentate-P-ligated palladium complex (Pd/POL-Ph$_3$P) can be accessed easily by the substrates because of the spacer effect of the three aromatic rings. Herein, we report the catalytic behavior of the Pd/POL-Ph$_3$P complex in Suzuki–Miyaura cross-coupling reactions employing aryl chlorides as substrates.

Results and Discussion

PS-L$_1$ (Figure 1a) and PS-L$_2$ (Figure 1b) were synthesized in accordance with the reported procedure.[9] The catalyst Pd/POL-Ph$_3$P was prepared by impregnation of POL-Ph$_3$P with PdCl$_2$(PhCN)$_2$ in THF for 4 h. The palladium loading was measured to be 0.23 mmol g^{-1} by inductively coupled plasma atomic emission spectrometry (ICP-AES). The resulting Pd/



without the addition of styrene or divinylbenzene!

Scheme 1. Preparation of POL-Ph$_3$P.

POL-Ph$_3$P was characterized by solid NMR, thermogravimetry (TG), nitrogen adsorption-desorption analysis, X-ray diffraction (XRD) and X-ray photoelectron spectroscopy analysis (XPS). The ^{31}P MAS NMR spectrum of fresh POL-Ph$_3$P exhibits an additional small peak at 27 ppm corresponding to an oxidation state of phosphorus (P=O), which indicates oxidation of P atom took place during the polymerization (see the Supporting Information, Figure S3). Remarkably, the ^{31}P MAS NMR spectrum of fresh Pd/POL-Ph$_3$P shows that the peak at 27 ppm is assigned to both the P atom in complex with palladium and oxidation state of phosphorus (P=O) (see the Supporting Information, Figure S6). The ^{31}P MAS NMR spectrum of used Pd/POL-Ph$_3$P shows the peak at 27 ppm with a relatively large peak area, compared with that of fresh Pd/POL-Ph$_3$P, which can be attributed to oxidation of the P atom during the recycling as well (see the Supporting Information, Figure S7). TG shows that the Pd/POL-Ph$_3$P complex remains intact at temperatures up to 430 °C, demonstrating its superior thermal stability (Figure 2c). Nitrogen adsorption-desorption analysis shows that Pd/POL-Ph$_3$P possesses a high surface area and large pore volume, which are desirable for effective catalyst-substrate interactions (Figure 2a and Figure 2b). XPS shows that the binding energies of Pd 3$d_{3/2}$ and Pd 3$d_{5/2}$ in the fresh Pd/POL-Ph$_3$P decrease to 342.7 eV and 337.4 eV from 343.5 eV and 338.2 eV of PdCl$_2$(PhCN)$_2$, respectively, as a result of coordination of PdCl$_2$(PhCN)$_2$

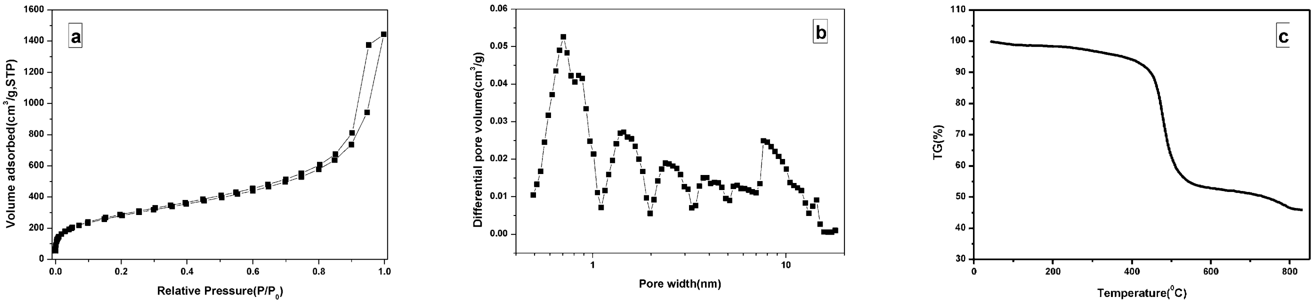
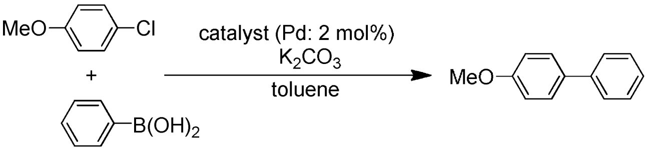


Figure 2. (a) N_2 sorption isotherms of Pd/POL-Ph_3P. (b) Pore size distribution of Pd/POL-Ph_3P. (c) TG curve of Pd/POL-Ph_3P.

with POL-Ph_3P (see the Supporting Information, Figure S12a and Figure S12b). Interestingly, the XPS spectra of P 2*d* show that the fresh and used Pd/POL-Ph_3P give the same binding energy of 132.2 eV (see the Supporting Information, Figure S12e and Figure S12f). Additionally, the used Pd/POL-Ph_3P gives a relatively high binding energy, compared with that of POL-Ph_3P (131.9 eV), demonstrating coordination of Pd nanoparticles with POL-Ph_3P (see the Supporting Information, Figure S12d).

To compare the reactivity of different catalysts, we selected as a model reaction the cross-coupling of 4-chloroanisole and phenylboronic acid (Table 1). The reactions were conducted in toluene at 100 °C using K_2CO_3 as a base. Remarkably, Pd/POL-Ph_3P exhibited a high catalytic activity and afforded the cross-coupling product in 97% yield (Table 1, entry 1). In contrast, Pd/PS-L_1 provided the desired product in only 5% yield (Table 1, entry 2). Low activity was also observed for Pd/PS-L_2 under the same reaction conditions (Table 1, entry 3). It should be pointed out that no conversion of 4-chloroanisole was observed by using the homogeneous catalyst derived from $PdCl_2(PhCN)_2$ and tris(4-vinylphenyl)phosphane (Table 1, entry 7). No conversion of 4-chloroanisole was also obtained on using a commercial Pd/C (5 wt% palladium) (Table 1, entry 4). Traditional homogeneous catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ also failed (Table 1, entries 5 and 6).

Table 1. Suzuki–Miyaura coupling reactions using different Pd catalysts.[a]



Entry	Catalyst	Yield [%][b]
1	Pd/POL-Ph_3P	97
2	Pd/PS-L_1	5
3	PdPS-L_2	61
4	Pd/C	NR
5	$PdCl_2(PPh_3)_2$	4
6	$Pd(PPh_3)_4$	4
7[c]	$PdCl_2(PhCN)_2$/tris(4-vinylphenyl)phosphane	NR

[a] *Reaction conditions:* 4-chloroanisole (0.50 mmol), phenylboronic acid (0.75 mmol), Pd/POL-Ph_3P (0.01 mmol Pd), K_2CO_3 (1.00 mmol), toluene (3 mL), 100 °C, 10 h.

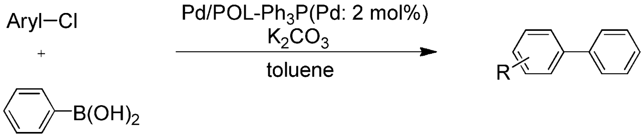
[b] Yield determined by ^{1}H NMR analysis based on 4-chloroanisole.

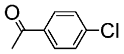
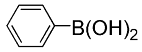
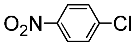
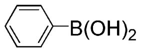
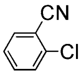
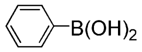
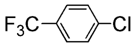
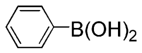
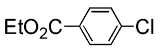
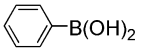
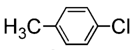
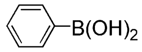
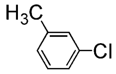
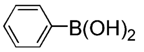
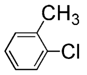
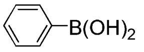
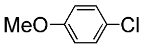
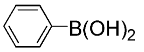
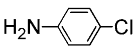
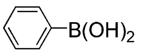
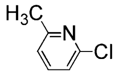
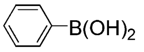
[c] Tris(4-vinylphenyl)phosphane (0.02 mmol) was added.

The catalytic efficiency of Pd/POL-Ph_3P was investigated by employing various substituted aryl chlorides for the cross-coupling reaction (Table 2). The activated aryl chlorides were converted smoothly to the desired products in excellent yields (Table 2, entries 1–5). Deactivated aryl chlorides are usually difficult substrates for palladium-catalyzed cross-coupling reactions.[12] However, under the standard conditions, these substrates also reacted efficiently with phenylboronic acids (Table 2, entries 6–11). Note that the catalyst Pd/POL-Ph_3P promoted the cross-coupling reaction of 4-chloroaniline and 2-chloro-6-methylpyridine with phenylboronic acids (Table 2, entries 10 and 11), which is difficult to achieve under other conditions.[13]

Next, we examined the scope of the arylboronic acids (Table 3). A substrate bearing a fused ring such as naphthylboronic acid was successfully coupled with aryl chloride (Table 3, entry 1). Arylboronic acids containing electron-withdrawing groups (Table 3, entries 2 and 3) or electron-donation groups (Table 3, entries 4 and 5) were converted to the desired biphenyls in high yield. In addition, our Pd/POL-Ph_3P catalyst exhibited outstanding catalytic activity for the coupling of *n*-butylboronic acid with 4-chloroacetophenone (Table 3, entry 6). To the best of our knowledge, there are currently no reports on the cross-cou-

Table 2. Suzuki cross-coupling reactions of aryl chlorides with phenylboronic acids.[a]

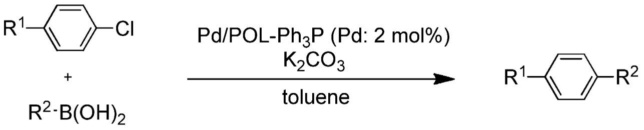


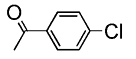
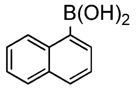
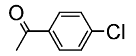
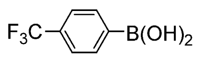
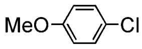
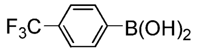
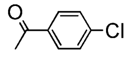
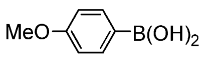
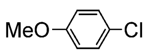
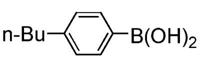
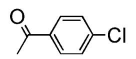
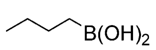
Entry	Aryl chloride	Phenylboronic acid	Time [h]	Yield [%][b]
1			2	96 (98)
2			3	90
3			2	99
4			3	99
5			3	98
6			24	89 (92)
7			24	94
8			24	90
9			3	93 (97)
10			15	80
11			5	92

[a] *Reaction conditions:* aryl chloride (1.00 mmol), phenylboronic acid (1.50 mmol), Pd/POL-Ph_3P (0.02 mmol Pd), K_2CO_3 (2.00 mmol), toluene (6 mL), 100 °C.

[b] Yield of isolated product (^1H NMR yield in parenthesis).

Table 3. Suzuki coupling reactions of aryl chlorides with various arylboronic acids.[a]



Entry	Aryl chloride	Boronic acid	Time [h]	Yield [%][b]
1			2	96 (98)
2			3	98
3			20	80
4			3	99
5			15	88
6			3	94

[a] *Reaction conditions:* aryl chloride (1.00 mmol), boronic acid (1.50 mmol), Pd/POL-Ph_3P (0.02 mmol Pd), K_2CO_3 (2.00 mmol), toluene (6 mL), 100 °C.

[b] Yield of isolated product (^1H NMR yield in parenthesis).

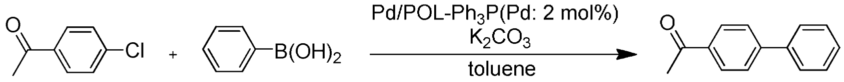
pling reaction of alkylboronic acids with aryl chlorides using a heterogeneous catalyst.

The reaction of 4-chloroacetophenone with phenylboronic acid was selected to evaluate the reusability of Pd/POL-Ph_3P (Table 4). After each run, the catalyst was recovered by filtration and washed with H_2O, THF, and toluene. The catalyst could be effectively used for at least 10 cycles without losing efficiency. During the recycling, the Pd species in the filtrate are undetectable (< 10 ppb), suggesting there is almost no Pd leaching, which is desirable in the synthesis of fine chemicals and pharmaceutical intermediates.[14] The morphology of the catalyst after each run was studied by transmission electron microscopy. There were no Pd nanoparticles on the fresh catalyst, as evidenced by TEM image (Figure 3a) and XRD (see the Supporting Information, Figure S11). However, the TEM images showed that the Pd nanoparticles with a mean diameter of about 5 nm were formed after the third run (Figure 3b and Figure 3c). Interestingly, no obvious aggregation of these nanoparticles occurred up to the 10th run (Figure 3d). With a high ratio of P/Pd (12:1), Pd/POL-Ph_3P could maintain high catalytic activities, although oxidation of a small number of P atoms took place during the recycling.

Conclusions

In conclusion, we have prepared a three-fold cross-linked polymer-bound phosphine with a high content of P. This phosphorus ligand-containing polymer forms a monodentate-P-ligated palladium complex, which displays excellent reactivity in Suzuki–Miyaura cross-coupling reactions of aryl chlorides. Importantly, the catalyst complex is highly stable as demonstrated by the negligible metal leaching and excellent reusability. These desirable properties of Pd/POL-Ph_3P can be attributed to its high P content, which prevents aggregation and agglomeration of Pd nanoparticles. Studies on the application of POL-Ph_3P to other metal-catalyzed reactions are underway in our laboratory.

Table 4. Recycling studies of Pd/POL-PPh$_3$.[a]



Run	1	2	3	4	5	6	7	8	9	10
Yield [%][b]	98	99	98	98	96	97	98	99	97	99

[a] *Reaction conditions:* 4-chloroacetophenone (1.00 mmol), phenylboronic acid (1.50 mmol), Pd/POL-Ph$_3$P (0.02 mmol Pd), K$_2$CO$_3$ (2.00 mmol), toluene (6 mL), 100 °C, 3 h.

[b] Yield determined by ^{1}H NMR analysis based on 4-chloroacetophenone.

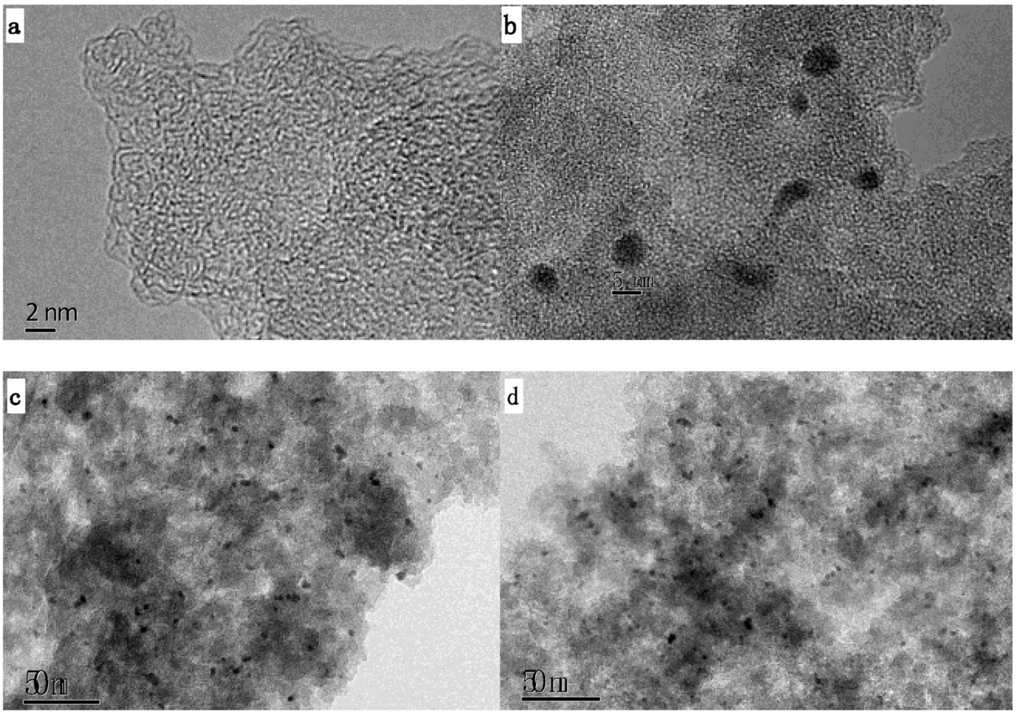


Figure 3. (a) TEM image of Pd/POL-Ph$_3$P before use. (b)and (c) TEM images of Pd/POL-Ph$_3$P recovered after third run. (d) TEM image of Pd/POL-Ph$_3$P recovered after tenth run.

Experimental Section

General Methods and Materials

The liquid-state NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts were reported in ppm. ^{1}H NMR spectra were referenced to CDCl$_3$ (7.28 ppm), and ^{13}C NMR spectra were referenced to CDCl$_3$ (77.0 ppm). All ^{13}C NMR spectra were measured with complete proton decoupling. Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet and *J*, coupling constant in Hz. The solid-state NMR was recorded on a Bruker AVANCE III 400 WB spectrometer equipped with a 4 mm standard bore CP/MAS probehead whose channel was tuned to 400.18 MHz. The samples were packed in the ZrO$_2$ rotor closed with Kel-F cap which was spun at 12 kHz. ^{1}H CP/MAS and ^{13}C CP/MAS spectra were referenced to adamantane (C$_{10}$H$_{16}$) as standard (1.63 ppm). ^{31}P CP/MAS were referenced to adenosine diphosphate (ADP) (0.0 ppm). Nitrogen sorption isotherms at the temperature of liquid nitrogen were peformed on a Quantachrome Autosorb-1. ICP-AES analyses of solid samples were peformed on a Perkin–Elmer ICP-OES 7300DV while ICP-AES analyses of liquid samples were peformed on a Perkin–Elmer ICP-MS 300D. Thermogravimetry analyses were peformed on a Netzsch TG-DSC. Transmission electron microscope (TEM) images were performed using a JEM-2100 with an accelerating voltage of 200 kV. The XRD was peformed on a XRD X·pertPro. The XPS were conducted using a Thermo Scientific and the spectrometer binding energy was calibrated through the reference C 1*s* (284.6 eV).

Preparation of POL-Ph_3P

Under nitrogen, tris(4-vinylphenyl)phosphane (10.0 g) was dissolved in THF (100 mL), followed by the addition of AIBN (1.0 g) at room temperature. Next, the mixture was transferred into an autoclave at 100 °C for 24 h. After evaporation of THF under vacuum, a white solid was obtained; yield: 9.6 g (96%).

Preparation of Pd/POL-Ph_3P

Under nitrogen, $PdCl_2(PhCN)_2$ (104 mg) was dissolved in THF (40 mL), followed by the addition of POL-Ph_3P (1.0 g). Next, the mixture was stirred 4 h at room temperature. After filtration and evaporation under vacuum, a yellow solid was obtained; yield: 1.1 g (99%).

General Procedure for Suzuki–Miyaura Cross-Coupling Reactions

Typically, aryl chloride (1.0 mmol), arylboronic acid (1.5 mmol), K_2CO_3 (2.0 mmol) and palladium catalyst (2 mol%) were added to toluene (6 mL) under an N_2 atmosphere, and the reaction mixture was stirred at 100 °C for the desired number of hours. When the reaction was completed, the solution was filtered and washed with toluene and ether. The filtered solution was subsequently dried over Na_2SO_4 and evaporated under vacuum. The crude was purified directly by silica gel column chromatography eluting with petroleum ether and ethyl acetate to afford the corresponding product.

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