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Non-Cross-Linked Polystyrene-Supported Triphenylphosphine-Microencapsulated Palladium: An Efficient and Recyclable Catalyst for Suzuki–Miyaura Reactions

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Abstract: A recyclable, all-in-one, polystyrene-microencapsulated palladium catalyst has been developed and used as a heterogeneous catalyst in Suzuki–Miyaura coupling reactions. This catalyst can be recovered and reused with only minimal palladium leaching observed.

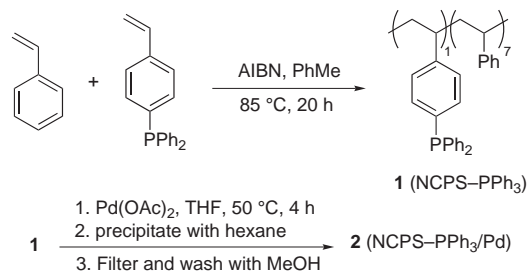
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Polymer-supported reagents, especially immobilized metal catalysts, are of great interest due to practical, economic and environmental considerations.¹ Microencapsulation, a process of entrapping materials in a polymeric coating,² is one method for catalyst immobilization that not only aids in its removal from the reaction mixture, but that can also have the benefit of stabilizing the catalyst. This technology has been extensively studied in medical and pharmaceutical contexts,³ and Kobayashi et al. have applied it to the immobilization of Sc(OTf)₃,⁴ OsO₄,⁵ and Pd(PPh₃)₄⁶ on polystyrene for use in the catalysis of organic reactions. In these cases, immobilization of the catalyst metal on a polymer is based on physical envelopment of the metal and on electronic interaction between the π -electrons of the aromatic rings of the polystyrene polymer and vacant orbitals of the catalyst. This group subsequently described the concept of ‘polymer incarceration’, in which the polymer is cross-linked after the catalyst has been microencapsulated by a polystyrene.⁷ Ley and co-workers have reported the alternative technique of interfacial microencapsulation to immobilize palladium nanoparticles in polyurea microcapsules.⁸ These Pd(OAc)₂/polyurea microcapsules (Pd EnCatTM) have proven to be robust and recyclable catalysts in carbonylation, Heck, hydrogenation, Stille, and Suzuki–Miyaura reactions.⁹ Additionally, Ikegami et al. have reported another highly active and recyclable microencapsulated Pd catalyst for the Suzuki–Miyaura reactions in which a non-cross-linked amphiphilic copolymer is used.¹⁰ This methodology was also used to prepare catalysts for Heck and various oxidation reactions.¹¹ Furthermore, McQuade and Price have recently described the use of cross-linked

reverse-micelle-encapsulated Pd as a catalyst for Heck reactions¹² and the Leadbeater and Gibson groups have reported the use of microencapsulated VO(acac)₂¹³ and a metathesis catalyst,¹⁴ respectively. In related work, Reek et al. reported that palladium–phosphine complexes immobilized to silica could be used as recyclable and regioselective catalyst for allylic alkylation reactions,¹⁵ and amphiphilic palladium–phosphine complexes were designed by Uozumi and Hayashi that showed high catalytic activity in allylic substitution reactions of allyl acetates in aqueous media.¹⁶ Finally, Gilbertson et al. have studied catalyst selectivity of polymer-bound peptide-based palladium–phosphine complexes on six different supports.¹⁷

In this context we have recently reported the preparation of a non-cross-linked polystyrene-supported AsPh₃ reagent.¹⁸ In the course of examining the utility of this reagent as a ligand for Pd in homogeneous Suzuki–Miyura reactions, we found that the Pd–polymer complex could be recovered from the reaction mixtures by precipitation and reused directly without the need for the addition of more Pd. Thus we were interested to see if our analogous non-cross-linked polystyrene-supported PPh₃ reagent (NCPS-PPh₃, **1**)¹⁹ could be used to prepare a microencapsulated, heterogeneous Pd catalyst (**2**) (Scheme 1) that is similar to what was described by Ikegami et al.,¹⁰ but which is composed of only an inert, hydrophobic polymer. Such a catalyst would be an improvement of other polystyrene microcapsules since because the polymer is functionalized by phosphine groups, there would be no need to add separate phosphine ligands to the reaction mixtures, as is currently the case.^{7c,20} Furthermore, since the methodology to prepare **1** (Scheme 1) is uncomplicated and amenable for the preparation of other phosphine functionalized polystyrenes, **2** could serve as a prototype for a range of easily accessible heterogeneous catalysts for use in a wide range of synthetic applications in either non-polar or polar protic solvents in which **1** is insoluble, such as Et₂O, H₂O, MeOH, and *i*-PrOH. Herein we describe the preparation of **2** and its use as a recyclable, heterogeneous catalyst for Suzuki–Miyaura reactions performed in both alcohol and mixed alcohol–water solvents.

Triphenylphosphine polymer **1** was prepared according to the literature method¹⁹ with a ratio of 7 styrene monomer molecules per phosphine-functionalized monomer



Scheme 1 Synthesis of microencapsulated Pd catalyst **2**

molecule (Scheme 1). This was treated with Pd(OAc)₂, approximately 25 mol% compared to phosphine groups of **1**, in THF at 50 °C, followed by precipitation with cold hexane and washing of the resultant material with MeOH to afford **2**.²¹ The Pd content of **2** was determined by X-ray fluorescence analysis to be 2.08%, which is very close to the theoretical value of 2.13%. This corresponds to a loading level of 0.20 mmol Pd/g **2**.

The use of **2** as a stand alone, heterogeneous catalyst in Suzuki–Miyaura reactions²² was examined using a range of aryl halides and arylboronic acids (Table 1).²³ Yields obtained using 0.5 mol% **2** in *i*-PrOH at 70 °C with aryl halides substituted with both electron-donating and -withdrawing substituents in conjunction with electron-rich aryl boronic acids were good to excellent, and the reactions were usually completed within one hour. In most cases the reactions were clean and the only product detectable by TLC analysis was the desired biaryl compound. Only when sterically hindered 2,6-dimethylphenyl boronic acid was used the product yield was poor (Table 1, entry 5). Significantly, even when the loading level of **2** was reduced to 0.005 mol% in 100% water, good yield was still obtained after refluxing for 16 hours (Table 1, entry 18).

Satisfied that **2** functions as an effective catalyst for Suzuki–Miyaura coupling reactions, we next examined its reusability when recovered from such reactions. Two sets of experiments were performed in which biphenyl was repeatedly prepared from iodobenzene and phenylboronic acid in a mixture of *i*-PrOH and H₂O (*v/v* = 11:1).²⁴ In the first set, the sample of **2** was repeatedly recovered at the end of the reaction and reused for the next cycle and no consideration was taken with regard to the small amount of catalyst lost in handling. In other words, the amount of reactants was fixed and therefore the catalyst loading decreased slightly. Generally, due to the small reaction scale, only approximately 95–97% of the catalyst could be recovered for reuse at the end of each reaction. These results are summarized in Table 2. In the second set of experiments, the amounts of reactants for the subsequent reactions were scaled to correspond to the actual amount of recovered catalyst and the results of these experiments are summarized in Table 3. As can be seen by comparing the data, the two sets of reactions yielded very similar results, where isolated yield decreased slightly with each subsequent reuse of **2**. The only notable difference be-

Table 1 Synthesis of Biaryl Compounds^a

$$\text{Ar}'\text{-X} + \text{Ar}''\text{-B(OH)}_2 \xrightarrow[\textit{i}\text{-PrOH}, 70^\circ\text{C}, 1 \text{ h}]{\textbf{2} (0.5 \text{ mol\%}), \text{Cs}_2\text{CO}_3} \text{Ar}'\text{-Ar}''$$

Entry	Ar'-X	Ar''	Isolated yield (%)
1	Ph-I	Ph-	90
2	Ph-I	4-MeO-C ₆ H ₄ -	98
3	Ph-I	3,4-(MeO) ₂ -C ₆ H ₃ -	86
4	Ph-I	2-Me-C ₆ H ₄ -	83
5	Ph-I	2,6-Me ₂ -C ₆ H ₃ -	12
6	4-MeO-C ₆ H ₄ -I	Ph-	88
7	4-MeO-C ₆ H ₄ -I	4-MeO-C ₆ H ₄ -	97
8	4-MeO-C ₆ H ₄ -I	2-Me-C ₆ H ₄ -	85
9	4-MeO-C ₆ H ₄ -Br	Ph-	74
10	4-MeOC-C ₆ H ₄ -I	Ph-	83
11	4-MeOC-C ₆ H ₄ -I	4-MeO-C ₆ H ₄ -	73
12	4-MeOC-C ₆ H ₄ -I	2-Me-C ₆ H ₄ -	87
13	4-MeOC-C ₆ H ₄ -Br	Ph-	85
14	4-MeOC-C ₆ H ₄ -Br	4-MeO-C ₆ H ₄ -	97
15	3-NO ₂ -C ₆ H ₄ -I	Ph-	78
16	3-NO ₂ -C ₆ H ₄ -I	4-MeO-C ₆ H ₄ -	78
17	3-NO ₂ -C ₆ H ₄ -I	2-Me-C ₆ H ₄ -	80
18	Ph-I	Ph-	89 ^b

^a Reaction time for entries 1–17: 1 h.

^b Reaction was performed in refluxing H₂O overnight with 0.005 mol% of **2**.

tween these sets of reactions is that the non-scaled ones required slightly extended reaction times for the later cycles. Importantly, ICP-MS analysis of the scaled reactions indicated that metal leaching did not occur to a significant extent (Table 3).

Table 2 Recycling of Catalyst **2** Using Fixed Quantities of Reactants

$$\text{Ph-I} + \text{Ph-B(OH)}_2 \xrightarrow[\textit{i}\text{-PrOH-H}_2\text{O}, 70^\circ\text{C}]{\textbf{2} (0.5 \text{ mol\%}), \text{Cs}_2\text{CO}_3} \text{Ph-Ph}$$

Cycle	Time (h)	Isolated yield (%)
1	3	89
2	3	86
3	3	78
4	4	73
5	6	71

Table 3 Recycling of Catalyst **2** Using Scaled Quantities of Reactants

$\text{Ph-I} + \text{Ph-B(OH)}_2 \xrightarrow[\text{i-PrOH-H}_2\text{O, 70 }^\circ\text{C}]{\text{2 (0.5 mol\%), Cs}_2\text{CO}_3} \text{Ph-Ph}$			
Cycle	Time (h)	Isolated yield (%)	Pd leached (%) ^a
No substrate	3	–	0.0186
1	3	91	0.2137
2	3	83	0.1097
3	3	79	0.0644
4	3	73	0.0055
5	3	66	0.1375

^a Amount of initial palladium found in the reaction mixture, as determined by ICP-MS analysis.

In conclusion, we have developed a new microencapsulated Pd catalyst in which a non-polar, phosphine-functionalized polymer is used to envelop the metal and render it a heterogeneous catalyst in polar, protic solvents. This catalyst is useful in Suzuki–Miyaura coupling reactions to prepare biaryl compounds and it can be recovered and reused with reasonable efficiency. The value of this report is that the methodology used to prepare **2** is relatively simple and flexible. For example, **1** can be synthesized in two steps and it can be envisioned that polymers functionalized with a wide range of phosphine ligands can be prepared by analogous methods used to synthesize **1**. Thus, a selection of analogues of **2** should be readily available for catalyst screening studies. Furthermore, the insolubility of **1** in non-polar solvents, such as hexanes and diethyl ether, should broaden the range of reaction conditions in which **2** can function as a heterogeneous catalyst and such applications are currently under exploration.

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- (21) **Preparation of Catalyst 2.** Polymer **1** (3.96 g, 4.04 mmol, 1.02 mmol PPh₃/g) was dissolved in THF (40 mL) at 50 °C and to this solution was added Pd(OAc)₂ (0.182 g, 0.81 mmol). The mixture was stirred at this temperature for 4 h and it became dark red in color. After the solution was cooled to 0 °C, the mixture was added dropwise into cooled hexane (80 mL). The resulting orange suspension was stirred at r.t. for 12 h and then filtered and washed with MeOH. Polymer **2** was isolated as an orange powder (3.98 g, ca 100%). ¹H NMR (400 MHz, CDCl₃): δ = 0.86–2.25 (bm, 24 H), 6.48–7.04 (bm, 35 H), 7.51–7.87 (bm, 14 H). The Pd content of **2** was determined to be 2.08% (theoretical value: 2.13%), which corresponds to a loading level of 0.20 mmol Pd/g, by X-ray fluorescence analysis.

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- (23) **General Procedure for Suzuki–Miyaura Reactions.**
A vial was charged with the arylboronic acid (0.7 mmol), Cs₂CO₃ (0.27 g, 0.8 mmol), **2** (0.012 g, 0.5 mol%), the aryl halide (0.45 mmol), and *i*-PrOH (4 mL). The mixture was heated at 70 °C until the reaction was determined to be complete by TLC analysis (generally 1 h), and then allowed to cool to r.t. Catalyst **2** was filtered off and washed with MeOH. The filtrate was concentrated and the resulting crude product was purified by silica gel chromatography (5–10% EtOAc in hexane) and characterized by ¹H NMR and ¹³C NMR spectroscopy and MS analysis. The characterization data obtained agreed with previously reported data or that of commercial samples.
- (24) Water was added to these reactions since it seemed to make **2** easier to recover and handle. However, it had the effect of lengthening the reaction times. When recycling is not an issue, *i*-PrOH alone is the preferred solvent due to the solubility of the reactants in it, and thus shorter reaction times.