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An efficient heterogeneous Heck reaction promoted by a new assembled catalyst of palladium and non-cross-linked amphiphilic polymer

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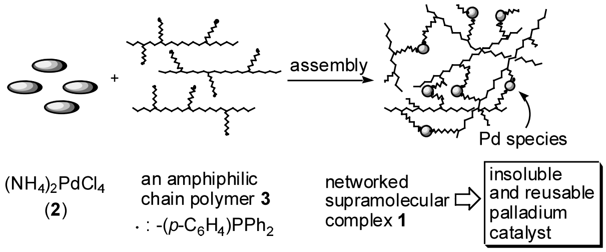
Abstract—A newly assembled insoluble catalyst **1b** composed of palladium and non-cross-linked amphiphilic polymer was developed. It was named PdAS-V: a supramolecular complex of $(NH_4)_2PdCl_4$ (**2**) and poly[(*N*-isopropylacrylamide)$_5$-*co*-(4-diphenylstyrylphosphine)] (**3b**). The use of 8.0×10^{-7}–5.0×10^{-5} mol equiv. of PdAS-V efficiently catalyzed the Heck reaction of aryl iodides with acrylates and styrenes. The turnover number of PdAS-V reached up to 1,150,000, and the catalyst was recycled five times without any decrease in its activity. © 2003 Elsevier Science Ltd. All rights reserved.

From the standpoint of environmentally benign organic synthesis, development of immobilized and insoluble metal catalysts is a challenging goal in recent organic chemistry.[1,2] In an ideal system, they can be recovered from the reaction mixture by simple filtration and reused infinitely, and contamination of products is prevented by metal species. Although metal catalysts immobilized on insoluble resins and silica gels are suitable for this purpose, they often result in lower catalytic activity compared with their soluble counterparts, and the activity of some recycled catalysts gradually decreases owing to leaching of the metal species from their supports.[2] Taking this state into consideration, we have investigated a novel methodology for creating insoluble, reusable, and highly active catalysts which are effective in ppm mol equivalents.

To reach our goal, we focused on a self-assembly process between non-cross-linked amphiphilic polymer ligands and an inorganic species for creating catalysts.[3] This self-assembled material should be composed of networked and supramolecular complexes where the polymers are cross-linked together by the inorganic species. Such insoluble complexes are expected to act as highly reactive catalysts, because the polymers and the inorganic species could construct effective catalytic sites with high affinity to reagents. Based on such working hypothesis, we have developed an assembled insoluble catalyst PdAS (**1a**) (a supramolecular complex of $(NH_4)_2PdCl_4$ (**2**) and *poly*[(*N*-isopropylacrylamide)$_{10}$–*co*-(4-diphenylstyrylphosphine)] (**3a**)) (Schemes 1 and 2), and applied it to the heterogeneous Suzuki–Miyaura reaction.[3c] It is noteworthy that the reactions were catalyzed by only the use of 5×10^{-5}–5×10^{-4} mol equiv. of PdAS, which was reused ten times without any decrease in its activity. Since this self-assembled catalyst exhibited great potential, we next applied PdAS to the heterogeneous Heck reaction, the palladium-catalyzed cross-coupling of sp^2-halides with alkenes.[4,5] However, PdAS was not so effective owing to pulverization. We assumed that cross-linking in PdAS was not sufficient to preserve physical strength for the Heck reaction.[6] Hence, we postulated that a more cross-linked catalyst was needed to overcome the problem. In this letter, we report the development of a reformed assembled catalyst PdAS-V (**1b**) (Scheme 2) and a highly efficient and



Scheme 1. Concept for the preparation of an assembled catalyst of palladium and non-cross-linked amphiphilic polymer.

Keywords: *N*-isopropylacrylamide; Heck reaction; palladium and compounds; polymer support; self-assembly.

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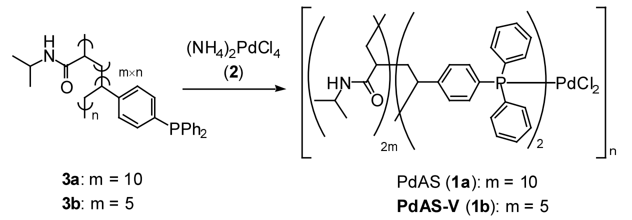
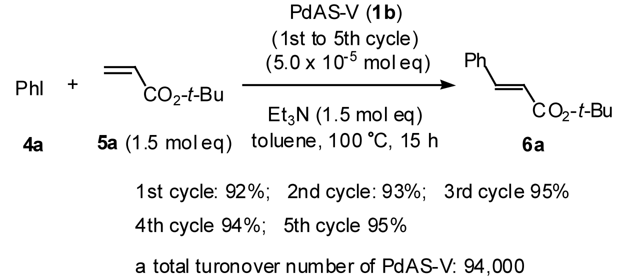


Scheme 2. Preparation of assembled catalysts PdAS (**1a**) and PdAS-V (**1b**).



Scheme 3. PdAS-V as a recyclable catalyst for the heterogeneous Heck reaction of iodobenzene (**4a**) with *t*-butyl acrylate (**5a**).

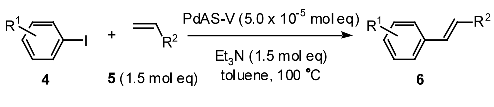
recyclable system for the heterogeneous Heck reaction. It should be emphasized that the reactions were promoted by 8×10^{-7}–5×10^{-5} mol equiv. of PdAS-V with the turnover number (TON (=mol of product/mol of catalyst)) up to 1,150,000. Furthermore, this catalyst was reused five times without any decrease in its activity.

The reformed catalyst PdAS-V was prepared from **2** and **3b** using a similar method to the preparation of PdAS.[3c] PdAS-V was a dark reddish solid that was insoluble in water, methanol, DMF, ethyl acetate, dichloromethane, THF, and toluene as was PdAS. The ratio of the *N*-isopropylacrylamide unit to the phosphine unit was 5/1 in PdAS-V while that in PdAS was 10/1 (Scheme 2).[7] Theoretically, the polymers in PdAS-V were cross-linked eight-fold more than those in PdAS per unit volume, and thus the amount of palladium in PdAS-V increased eight-fold over the PdAS per unit content (cf. Scheme 1). This implied that physical strength of PdAS-V was superior to that of PdAS, so that PdAS-V would be prevented from pulverization. As shown in Scheme 3, the results agreed with our hypothesis. The use of 5×10^{-5} mol equiv. of PdAS-V catalyzed effectively the Heck reaction of **4a** with **5a** to give **6a** in 92% yield.[8] PdAS-V was recycled five times without any loss of its activity. The average yield of five runs was 94%. The total turnover number of PdAS-V in the 1st to the 5th cycled runs was 94,000.

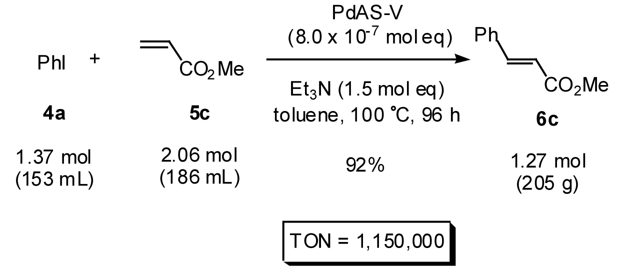
With these results in hand, we next examined the reaction of various aryl halides with alkenes (Table 1). All the reactions in Table 1 were performed in the presence of 5×10^{-5} mol equiv. of PdAS-V with 1.5 mol equiv. of Et_3N in toluene at 100°C. It was found that this system worked effectively to provide the corresponding coupling products in more than 90% yields, with a turnover number of PdAS-V reaching approximately 20,000. The reaction of **4a** with alkyl acrylates proceeded smoothly to give the corresponding coupling products in 93–98% yields (entries 1 and 2). Electron-deficient aryl iodides such as ethoxycarbonyl-, acetoxy-, and chloro-substituted iodobenzenes were also converted to **6d–f** in more than 90% yields (entries 3–5). The reaction system was applicable to the reaction of an electron-rich iodobenzene (entry 6). It is interesting that the coupling of hexafluoroisopropyl acrylate (**5d**), an electron-deficient olefin, proceeded much faster and completed in 5 h to furnish **6h** in 95% yield (entry 7). The reaction of styrene (**5e**) has also proved to proceed efficiently, providing **6i** in 90% yield (entry 8).

Since PdAS-V was found to be a recyclable and highly active catalyst, we studied the limitation of its catalytic activity. We were very delighted to find that PdAS-V used in less than 1 ppm mol equiv. catalyzed dramatically the reaction as depicted in Scheme 4. Treatment of **4a** (1.37 mol; 153 mL) with **5c** (2.06 mol; 186 mL) in the presence of 8×10^{-7} mol equiv. of PdAS-V afforded **6c** in 92% yield (1.27 mol; 205 g) that was isolated by crystallization without column chromatography. The turnover number of PdAS-V reached 1,150,000. As far as we know, this must be the highest turnover number by a reusable catalyst for the Heck reaction.

Table 1. The heterogeneous Heck reaction of aryl halides with alkenes catalyzed by PdAS-V



Entry	R^1	R^2	Time (h)	Yield (%)	TON
1	**4a**	CO_2Bu (**5b**)	20	**6b**: 98	19,600
2	**4a**	CO_2Me (**5c**)	12	**6c**: 93	18,600
3	3-CO_2Et (**4b**)	**5c**	20	**6d**: 95	19,000
4	4-OAc (**4c**)	**5c**	20	**6e**: 92	18,400
5	4-Cl (**4d**)	**5c**	20	**6f**: 95	19,000
6	4-OMe (**4e**)	**5c**	20	**6g**: 92	18,400
7	**4a**	$CO_2CH(CF_3)_2$ (**5d**)	5	**6h**: 95	19,000
8	**4a**	Ph (**5e**)	12	**6i**: 90	18,000



Scheme 4. The heterogeneous Heck reaction catalyzed by 8×10^{-7} mol equiv. of PdAS-V.

In conclusion, we have developed a new insoluble and reusable catalyst, PdAS-V, prepared from self-assembly of $(NH_4)_2PdCl_4$ (**2**) and non-cross-linked amphiphilic phosphine polymer **3b**. The heterogeneous Heck reaction using PdAS-V afforded the corresponding coupling products in high yields with TON up to 1,150,000. Using only 5×10^{-5} mol equiv., PdAS-V was reused up to five times while still retaining its activity.

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6. It is well-known that designing a recyclable system for the Heck reaction is more challenging than that for the Suzuki–Miyaura reaction because the catalysts often decompose physically (e.g. salts accumulated in the reaction lead to degradation of the catalytic system and choke of catalysts.) or chemically (e.g. the reductive elimination of phosphonium cation causes depletion of catalyst.), see: Refs. 4a and 4b.
7. 'V' is the Roman numeral for 5 which was the ratio of *N*-isopropylacrylamide unit to phosphine unit.

8. **General procedure for the recyclable heterogeneous Heck reaction catalyzed by PdAS-V**. The mixture of an aryl halide **4** (36.5 mmol), an alkene **5** (54.7 mmol), Et_3N (7.6 mL; 54.7 mmol) in toluene (18 mL) was degassed by ultrasonication for 30 min under an argon atmosphere. To the solution was added PdAS-V (5.0 mg; 1.82 μmol), and the mixture was stirred at 100°C under an argon atmosphere. After the reaction was completed and cooled to room temperature, the mixture was filtered through a glass filter with degassed MeOH under an argon atomsphere. The filtrate was evaporated, diluted with AcOEt and H_2O, extracted with AcOEt, washed with H_2O and brine, dried over $MgSO_4$, filtered, and evaporated, and purified by column chromatography to give the corresponding product **6**. The filtered PdAS-V was reused after drying in vacuo.