Sustainable Mizoroki–Heck reaction in water: remarkably high activity of $Pd(OAc)_2$ immobilized on reversed phase silica gel with the aid of an ionic liquid

Hisahiro Hagiwara,*[a] Yoshitaka Sugawara,[a] Takashi Hoshi[b] and Toshio Suzuki[b]

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Palladium acetate immobilized on reversed phase amorphous silica gel with the aid of an ionic liquid, $[bmim]PF_6$, was highly efficient in the promotion of the Mizoroki–Heck reaction in pure water without a ligand up to the sixth re-use, in 95% average yield with TON and TOF 1,600,000 and 71,000 (h^{-1}), respectively.

The Mizoroki–Heck reaction is undoubtedly one of the most powerful metal-catalyzed C–C bond forming reactions. Tremendous amounts of results have been accumulated and new findings are still increasing.[1] One of the current interests in this reaction is the development of a catalyst of high performance as well as sustainable and environmentally benign reaction conditions.

We previously reported on the immobilization of Pd/C in an ionic liquid, $[bmim]PF_6$, for a recyclable Mizoroki–Heck reaction system.[2] Subsequently reported was the very facile and economically friendly immobilization of $Pd(OAc)_2$ in silica gel pores with the aid of an ionic liquid, $[bmim]PF_6$.[3] The catalyst immobilized on the silica gel was highly effective in *n*-dodecane at 150 °C to realize a 95% average yield and TON 68,000 up to the 6th use.

The hydrophobic nature of $[bmim]PF_6$ led us to investigate the Mizoroki–Heck reaction in water as a solvent,[4] employing the same immobilized catalyst. The major advantage in carrying out the reaction in water is its non-flammable, inexpensive, non-toxic nature. There is no need to desiccate substrates prior to the reaction. Other advantages are the high cohesive energy density (*c.e.d.* = 550 cal cm^{-3}), high dielectric constant and high internal pressure, which might facilitate bimolecular reactions involving ionic intermediates.[5] Furthermore, use of a heterogeneous catalyst is expected to increase Mizoroki–Heck reaction rates by adsorption of substrates on the catalyst.

Initially, an optimum base was investigated at 100 °C in the reaction of iodobenzene and cyclohexyl acrylate employing $Pd(OAc)_2$ immobilized on normal phase silica gel with the aid of $[bmim]PF_6$. Soon after heating, the colour of the catalyst turned from brown to black, which suggested the formation of Pd(0). The reaction began as a triphasic system and terminated as a biphasic system with the aqueous and organic layers homogeneous. The product was partitioned into diethyl ether, purified by medium pressure LC and identified to be the *trans* isomer by NMR spectroscopy. Inorganic bases gave lower yields as shown in Table 1, entries 1 and 2. Especially, silica gel pellets dissolved in 2 h when K_3PO_4[6] was employed (entry 2). Among organic bases, $n\text{-}Bu_3N$ gave better results. The catalysts immobilized on silica gel powder as well as pellets were effective in water and exhibited the same catalytic activity (entries 4 and 5). Compared to the reaction in *n*-dodecane, the reaction was apparently accelerated in water, since the reaction completed at a lower reaction temperature in a shorter period of time.[3]

However an attempt to recycle the catalyst resulted in the unexpected removal of the ionic liquid layer from the silica gel into the aqueous layer to result in leaching of the Pd. Water entered between the ionic liquid layer and the silica gel surface, probably due to hydrophilic nature of the latter.

In order to solve this problem, we focused on immobilization of $Pd(OAc)_2$ on reversed phase silica gels, among which hexylated (HEX), aminopropylated (NAP), and *N*,*N*-diethylaminopropylated silica gel (NDEAP) were employed (Scheme 1). These silica gels were easily obtained by grafting with the corresponding silane coupling reagents.[7] $Pd(OAc)_2$ was successfully immobilized on each of the reversed phase silica gels except HEX, with the aid of $[bmim]PF_6$ according to the same procedure as reported previously.[3] The amount of Pd loading was 0.4 ~ 0.5 mmol g^{-1} by weight gain.

Reactivity of these immobilized catalysts was tested in the reaction of iodobenzene and cyclohexyl acrylate and representative results were compiled in Table 2. The reaction was sluggish, as shown in entries 1 and 2, compared to the catalyst immobilized on normal phase silica gel (entries 4 and 5, Table 1), and NDEAP-Pd gave a better result. The less bulky amino group of NAP-Pd may coordinate to the Pd to block the active site more than the *N*,*N*-diethylamino group of NDEAP-Pd. As expected, sustainability of the immobilized catalyst was improved as shown in the recycle use in entries 3 and 4. The catalyst was easily re-used after decantation of the upper layer followed by washing with diethyl

Table 1 Examination of base in the reaction of iodobenzene and cyclohexyl acrylate in the presence of immobilized catalyst on normal phase silica gel

Entry[a]	Base	Time (h)	Yield (%)[e]
1[b]	K_2CO_3	18	46
2[c]	K_3PO_4	2	32[d]
3[c]	Et_3N	5.5	2
4[b]	$n\text{-}Bu_3N$	4	100
5[c]	$n\text{-}Bu_3N$	3	97

[a] The reaction was carried out with 0.05 equiv. of the catalyst and 2 equiv. of base in water at 100 °C. [b] The catalyst immobilized on silica gel powder (Pd loading: 0.25 mmol g^{-1}) was used. [c] The catalyst immobilized on silica gel pellets (Pd loading: 0.2 mmol g^{-1}) was used. [d] The silica gel pellets dissolved. [e] Isolated yields of pure product based on iodobenzene.

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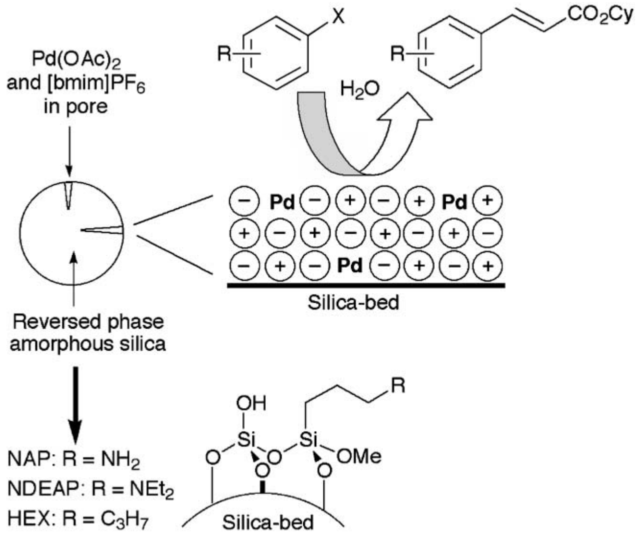
*hagiwara@gs.niigata-u.ac.jp



Scheme 1 Mizoroki–Heck reaction in water catalyzed by immobilized Pd catalyst on reversed phase silica gel.

ether. It is interesting to note that the activity of the NDEAP-Pd catalyst increased in the recycle use as shown in entries 3 and 4. It was assumed that the accumulation of ammonium iodide on the surface of the catalyst accelerated the reaction. Actually, NDEAP/HCl-Pd was found to be very active as shown in entry 5. However, the reactivity was not reproducible, even if the catalyst was washed with dilute HCl prior to re-use (entry 7). Pre-treatment of NDEAP-Pd with n-Bu_3N or cyclohexyl acrylate did not alter this phenomenon. The reason for activation of the re-used catalyst is yet to be discussed.

Recently, de Vries *et al.* demonstrated the higher efficiency of low Pd loading (0.01 ∼ 0.1 mol%) in the Mizoroki–Heck reaction.[8] They suggested that the formation of Pd clusters at higher concentration retarded the reaction. Their observation prompted us to prepare an immobilized catalyst of low $Pd(OAc)_2$ loading (0.043 mmol g^{-1}) on the NDEAP. As shown in Table 3, the catalyst of low Pd loading was more effective to complete the reaction in a shorter period of time. The stability of the catalyst was sufficient to ensure 6 uses in 95% average yield. Different from the reaction in n-dodecane, there is no need, for recycle use, to wash the recovered catalyst with alkaline solution to remove ammonium iodide.[3] Leaching of the Pd into the aqueous layer was 1.1 ppm by ICP analysis in entry 1.

Table 2 Reactivity of immobilized catalysts on reversed phase silica gel in the reaction of iodobenzene and cyclohexyl acrylate

Entry[a]	Catalyst	Time (h)	Yield (%)[c]
1	NAP-Pd	22.5	73
2	NDEAP-Pd	17	100
3	(2nd use)	4	97
4	(3rd use)	7	97
5	NDEAP/HCl-Pd	1.5	96
6	(2nd use)	24	98
7	(3rd use[b])	11	98

[a] The reaction was carried out with 0.05 equiv. of the catalyst pellets (Pd loading: 0.36 mmol g^{-1}) and 2 equiv. of n-Bu_3N in water at 100 °C. [b] The catalyst was washed with dil. HCl before re-use. [c] Isolated yields of pure product based on iodobenzene.

Table 3 Higher reactivity of low Pd loading catalyst and its recycle use in the reaction of iodobenzene and cyclohexyl acrylate

Entry[a]	Cycle	Time (h)	Yield (%)[b]
1	0	10.5	93
2	1	3	96
3	2	1	98
4	3	2	96
5	4	2	94
6	5	2	96

[a] The reaction was carried out with 0.05 equiv. of the catalyst pellets (Pd loading: 0.043 mmol g^{-1}) and 2 equiv. of n-Bu_3N in water at 100 °C. [b] Isolated yields of pure product based on iodobenzene.

Remarkably high activity of the catalyst among other ligandless heterogeneous catalysts[9] was exemplified by the TON and TOF of 1,600,000 and 71,000 (h^{-1}), respectively (Table 4, entry 4).

The catalyst was effective with various aryl halides having both electron-withdrawing and donating substituents (Table 5).

Among the olefinic substrates investigated, acrylates were the best since other electron deficient olefins such as styrene, vinyl ketone, vinyl sulfone or acrylonitrile decomposed under the present reaction conditions.

In summary, a novel heterogeneous catalyst for Mizoroki–Heck arylation of olefins in pure water has been developed. The catalyst was easily prepared by the immobilization of $Pd(OAc)_2$ on the reversed phase silica gel in low concentration with the aid of $[bmim]PF_6$, and exhibited a highly recyclable nature and remarkably high TON and TOF.

Table 4 Performance of low Pd loading catalyst in the reaction of iodobenzene and cyclohexyl acrylate

Entry	Catalyst (equivalents)	Time (h)	Yield[d] (%)	TON	TOF (h^{-1})
1[a]	0.0013	8.5	94	68,400	7,100
2[b]	0.0012	5	95	78,000	16,000
3[b]	0.00014	33	100	740,000	22,400
4[b,c]	0.000058	22.5	96	1,600,000	71,000

[a] The reaction was carried out with the Pd immobilized on normal phase silica gel (Pd loading: 0.25 mmol g^{-1}) and 2 equiv. of n-Bu_3N in n-dodecane at 150 °C.[3] The flask was washed with conc. nitric acid before use. [b] The reaction was carried out with NDEAP-Pd (Pd loading: 0.047 mmol g^{-1}) and 2 equiv. of n-Bu_3N in water at 100 °C. The flask was washed with conc. nitric acid before use. [c] The reaction was carried out in a new flask with a new stirring bar.[10] [d] Isolated yields of pure product based on iodobenzene.

Table 5 Reaction of other aryl halides with cyclohexyl acrylate

Entry[a]	Substrate (4-RPhX)	Time (h)	Yield (%)[d]
1	R = Ac, X = I	6.5	98
2	R = Br, X = I	4.5	92[b]
3	R = I, X = I	21	98[c]
4	R = BnO, X = I	24.5	90
5	R = MeO, X = I	24	94
6	R = THPO, X = I	3.5	96
7	R = NO_2, X = Br	30	76
8	1-Iodonaphthalene	9.5	90

[a] The reaction was carried out with NDEAP-Pd pellets (0.05 equiv.) (Pd loading: 0.047 mmol g^{-1}) and 2 equiv. of n-Bu_3N in water at 100 °C. The flask was washed with *aqua regia* before use. [b] The reaction accompanied by formation of 8% of bis-adduct. [c] Yield of bis-adduct. [d] Isolated yields of pure products based on aryl halides.

Hisahiro Hagiwara,[*a] **Yoshitaka Sugawara,**[a] **Takashi Hoshi**[b] **and Toshio Suzuki**[b]
[a]*Graduate School of Science and Technology, Niigata University, 8050, 2-Nocho, Ikarashi, Niigata, Japan. E-mail: hagiwara@gs.niigata-u.ac.jp; Fax: +81-25-262-7368; Tel: +81-25-262-7368*
[b]*Faculty of Engineering, Niigata University, 8050, 2-Nocho, Ikarashi, Niigata 950-2181, Japan*

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