True water soluble palladium-catalyzed Heck reactions in aqueous–organic biphasic media

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ABSTRACT

A stable water soluble palladium catalyst has been demonstrated for the Heck reaction in a biphasic medium (water–non-polar organic solvent). Biphasic Heck reactions reported till now generally employ a non-polar solvent along with an aqueous polar water miscible organic solvent as the second phase. The efficiency of the Pd complex of TOTPS [Trisodium salt of tri-(*ortho*-tolyl) phosphine tri sulfonate] for the vinylation of different aryl iodides and olefins is demonstrated. The advantages of a co-solvent for this biphasic system have also been shown. The catalyst has been recycled efficiently retaining the activity with negligible loss of catalyst and without leaching of the Pd.

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The two basic problems of homogeneous catalysis are separation and recycling of the catalyst, which can be elegantly solved by using two-phase catalysis.[1] It serves the purpose of industrial application such as easy separation of the product from the catalyst and recycling of the catalyst, along with reasonable activity. In addition, catalysis in water offers several advantages as water is inexpensive, nontoxic, nonflammable, and readily forms biphasic systems with a variety of organic materials. Therefore, aqueous/organic two-phase catalysis finds wide applications.[2] Kuntz developed a water-soluble catalyst Rh/TPPTS,[3] which served as the starting points of aqueous-biphasic catalysis with water-soluble catalysts. Since then, the utility of a variety of metal-catalyzed reactions in water has been shown.[2,4–17]

Palladium promoted reactions in aqueous media pose major challenges regarding the stability of palladium complex catalysts.[18–20] Hence the applications were mainly restricted to the use of aqueous organic media. Until recently, very few reports have shown that water can be added in the Heck reaction.[21–25] To overcome these problems, the studies using water were carried out in two ways (i) where a non-aqueous biphasic medium is used,[26–29] in which the biphasic system actually comprised of the organic phase along with the ethylene glycol phase and (ii) where a homogeneous medium containing water is used,[21,30–32] (such as water along with acetonitrile) for the Heck reaction, although they do not discuss methods for catalyst recycling.

Palladacycle [Pd₂(P(o-Tol)₃)₂(μ-OAc)₂], discovered by Herrmann and Beller[33] is one of the most convenient forms of palladium complexes applied in homogeneous catalysis with its unique catalytic activity. We report here a sulfonated tri *o*-tolylphosphine that forms a stable water-soluble palladacycle catalyst (complex **1**, Fig. 1). The efficiency of this complex for Heck reactions was demonstrated for a number of aryl halides, olefins, and in the presence of different concentrations of co-solvent. The catalyst was retained in the water phase with no leaching to the organic phase and was recycled efficiently with no loss in activity.

A typical problem of aqueous phase catalysis is the poor solubility of the substrates, viz. styrene and stilbene in the aqueous phase and also the stability of the catalyst. Both these problems were solved by taking the following measures.

The role of NaOAc (sodium acetate) in the stabilization of the catalyst is well reported.[34,35] In these works, Sheldon and co-workers has suggested that the presence of NaOAc prevents the precipitation of Pd black. A minimum concentration of 1 mmol was reportedly required for this purpose. Hence, in this work we used NaOAc for the stabilization of the catalyst. Catalyst **2** prepared with a 1:2.2 Pd:NaOAc ratio was found to be stable and did not form metallic Pd (the synthesis of TOTPS (**1**) and the Pd-complex (**2**) can be found in Supplementary data). In order to check whether Pd had precipitated in the form of Pd colloidal particles, a UV spectrum was taken. No absorption was seen in the range of 350–400 nm, which indicates the absence of Pd colloidal particles. This also shows that the reaction occurs due to soluble catalytic complex and not Pd metal. It was observed that preparation of the catalyst in the absence of NaOAc led to precipitation of Pd, as the catalyst formed was unstable.

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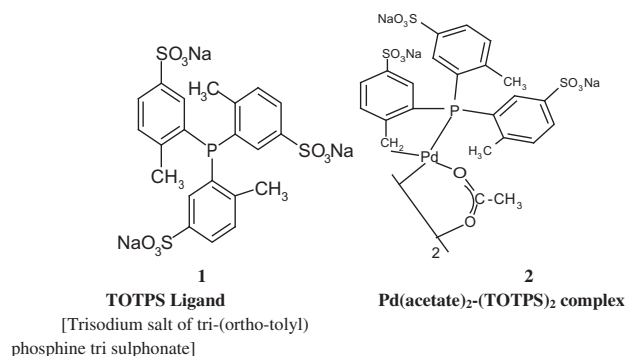† Current address: B.G. College, Sangvi, Pune, India.

Figure 1.

1
TOTPS Ligand
[Trisodium salt of tri-(ortho-tolyl)
phosphine tri sulphonate]

2
Pd(acetate)$_2$-(TOTPS)$_2$ complex

The biphasic system was systematically tailored using the water soluble catalyst (complex **2**) in non-polar solvents such as toluene and *n*-octane along with water. A significant amount of leaching was observed (∼5 ppm) when toluene was used as the organic phase. *n*-Octane was found to be the best option, where no leaching of the catalyst was observed. The solubility issue was overcome by using a co-solvent. Hartung et al.[36] has mentioned the use of DMSO as a co-solvent for the Heck reaction to improve selectivities of non-conjugated aryl olefins in a homogeneous medium. Similarly the application of co-solvents to enhance the activity is well known in the aqueous biphasic hydroformylation reaction,[37] a similar strategy was employed for improving the rates of reaction for Heck coupling reactions.

For this study co-solvents like morpholine, NMP, and 1,4-dioxane (at a 10% v/v aqueous phase concentration) were used in the presence of NaOAc as a base (already present as a stabilizer). Although the solubility of the substrates enhanced in the presence of NMP/1,4-dioxane co-solvent, no reaction was observed (entries 1 and 2, Table 1). This is probably due to the inability of NaOAc to function as a base in aqueous conditions. 60% conversion of iodobenzene was observed, when morpholine was used as a co-solvent (entry 3, Table 1). Since morpholine was also capable of functioning as a base and co-solvent, an experiment was conducted with only stoichiometric equivalent morpholine (as base) in the reaction medium along with NaOAc (Pd:NaOAc 1:2.2). A 20% conversion of iodobenzene was observed after 6 h (entry 4, Table 1). This experiment confirmed that morpholine could have a dual function in aqueous biphasic Heck reactions. Analysis of morpholine in the reaction system showed a conversion of morpholine equivalent to the consumption of the aryl halide.

The feasibility of using NMP/1,4-dioxane as a co-solvent was studied in the presence of morpholine as a base but in the absence of NaOAc. In both these cases Pd metal precipitated (entries 5 and 6, Table 1). Organic bases other than morpholine showed leaching (about 5–15 ppm) which was confirmed by AAS studies. Many inorganic bases showed no activity. It was observed that in the absence of morpholine no reaction takes place.

The above diagnostic experiments confirmed that:

(i) NaOAc was essential to ensure the stability of the Pd complex, and prevent precipitation. The role of NaOAc was not as a base.
(ii) Morpholine was functioning both as a base and a co-solvent.
(iii) Enhancement in the rate was substantial with morpholine as a co-solvent.

Further, detailed studies on the role of morpholine as a co-solvent were conducted. The reactions were taken with varying amounts of morpholine and the conversion of iodobenzene was monitored (entries 2–6, Table 2).

It can be seen from the results, as the percentage of morpholine (as a co-solvent) in the aqueous phase increases, the rate of reaction increases. Since morpholine in this case acts as a base as well as a co-solvent, the concentration of morpholine was varied in such a way that a minimum of 2% morpholine concentration (which corresponds to the mole equivalent of the substrates) is present as a base for all reactions and the remaining as a co-solvent. A linear dependence was observed up to 14% loading of the morpholine in the aqueous phase, beyond which no major rate enhancement was seen. No reaction was observed in the absence of morpholine (entry 1, Table 2), which is due to the absence of any base.

Thus for all further screening studies 10% morpholine as a co-solvent + base was utilized. Under these conditions analysis of the organic phase showed no leaching and recycling of the organic phase also showed no activity, indicating that the reaction was a true aqueous phase reaction.

In order to ensure that the catalyst had not deactivated a few experiments were conducted under the given reaction conditions for varying time periods (1, 4, and 6 h) instead of taking periodic samples.

The results in Table 3 (entries 1–3), show that there is a constant increase in the formation of stilbene and iodobenzene consumption with time. In this case after 6 h reaction, there was practically no reaction. These results confirmed that the catalyst remains active throughout the period. Hence for all the reactions, a fixed period of 6 h was taken and no intermediate samples were withdrawn. The turn over number (TON) was calculated at the end of 6 h reaction (unless otherwise specified).

The catalyst was assessed for its activity for the Heck reaction of various aryl halides and the results are given in Table 3 (entries 3–6). It was seen that 4-iodoacetophenone gives faster rates than 4-iodoanisole and iodobenzene proving that the halides with substituents have more –I effect that is, a strong electron withdrawing character, show high activity toward the vinylation. (It is well known that electron-withdrawing substituents on the aryl halide enhance the rate of oxidative addition of the substrate to the Pd atom.[38]) Bromobenzene gave very poor activity due to the inherent low reactivity of the bromo-substrate under the reaction conditions.

Table 1
Comparison of activity using various co-solvents and use of stabilizer for the Heck reaction in an aqueous biphasic medium

Sr. No.	Stabilizer	Co-solvent	Base	% Of co-solvent	Observation	% Conversion	TON
1	NaOAc	NMP	—	10	No reaction	—	—
2	NaOAc	1,4-Dioxane	—	10	No reaction	—	—
3	NaOAc	Morpholine	Morpholine	10[a]	—	60	555
4	NaOAc	—	Morpholine	2[a]	—	20	215
5	—	NMP	Morpholine	10	Pd metal precipitated	—	—
6	—	1,4-Dioxane	Morpholine	10	Pd metal precipitated	—	—

Reaction condition: Styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed *n*-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol) and co-solvent and base (Morpholine–given in % with respect to the aqueous phase), and a stabilizer (NaOAc–1.0 mmol) (wherever used); 150 °C; 1450 rpm. (time: 6 h).
　[a] 10% = 1.5 ml (17.2 mmol); 2% of co-solvent = 0.3 ml (3.4 mmol).

Table 2
Heck reaction of olefin with iodobenzene in an aqueous biphasic medium using various concentrations of co-solvent

Sr. No.	Co-solvent	Base	% Of co-solvent	Observation	% Conversion	TON
1	–	–	0	No reaction	–	–
2	–	Morpholine	2[a]	–	20	215
3	Morpholine	Morpholine	6[a]	–	39	354
4	Morpholine	Morpholine	10[a]	–	60	555
5	Morpholine	Morpholine	14[a]	–	80	694
6	Morpholine	Morpholine	18[a]	–	87	738

Reaction condition: Styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed *n*-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol) and co-solvent and base (Morpholine—given in % with respect to the aqueous phase) and a stabilizer (NaOAc—1.0 mmol); 150 °C; 1450 rpm. (Time: 6 h).
  [a] 2% of co-solvent = 0.3 ml (3.4 mmol); 6% = 0.9 ml (10.3 mmol); 10% = 1.5 ml (17.2 mmol); 14% = 2.1 ml (24.0 mmol); 18% = 2.7 ml (30.9 mmol).

Table 3
Heck reaction of olefins with aryl halides in an aqueous biphasic medium

Sr. No.	Olefin	Ar-X	Time (h)	% Conversion	TON
1	Styrene	Iodobenzene	1	21	191
2	Styrene	Iodobenzene	4	47	435
3	Styrene	Iodobenzene	6	60	555
4	Styrene	4-Iodo acetophenone	6	100	875
5	Styrene	*p*-Iodoanisole	6	72	663
6	Styrene	Bromobenzene	6	2	5
7	3-NitroStyrene	Iodobenzene	6	86	1008
8	4-Chlorostyrene	Iodobenzene	6	68	737
9	4-MethylStyrene	Iodobenzene	6	53	544

Reaction condition: Olefin (3.3 mmol), Ar-X (3.0 mmol) taken in degassed *n*-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol) and co-solvent (morpholine—10% of aqueous phase inclusive of 3.0 mmol as a base), and a stabilizer (NaOAc—1.0 mmol); 150 °C; 1450 rpm.
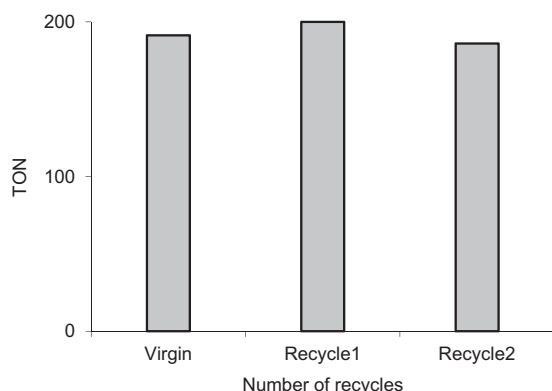

Figure 2. Activity of Pd–TOTPS catalyst on recycling of the aqueous phase in an aqueous–organic biphasic medium for the Heck reaction of styrene with iodobenzene. Reaction conditions: Styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed *n*-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol or recycled) and co-solvent (morpholine—10% of aqueous phase inclusive of 3.0 mmol as a base), and a stabilizer (NaOAc—1.0 mmol); 150 °C; 1450 rpm. (time: 1 h). Selectivity of stilbene >99%.

The activity of Pd–TOTPS complex catalyst was assessed for the Heck vinylation of iodobenzene in the aqueous biphasic reaction. Various olefins were screened for their activity. The results are presented in Table 3 (entries 3, 7–9). Among olefins, 3-nitrostyrene was seen to be more reactive than 4-chlorostyrene, styrene, and 4-methyl styrene. This was a surprising behavior, as generally the presence of electron withdrawing groups attached to the aromatic ring reduces the activity of the aryl halide compared to electron donating groups. This observation could be due to the variation in solubility for the biphasic reaction. The reactivity of acrylates could not be assessed, as the acrylates were found to react with morpholine and form an addition product as a result of which the Heck coupling reaction could not occur. The formation of the addition product was confirmed by GC–MS.

The primary objective of developing an aqueous phase catalyst for the Heck reaction was to facilitate catalyst recycle and recovery.

The Pd–TOTPS catalyst was recycled for two times to demonstrate the feasibility of recycling, and the results are shown in Figure 2. The catalyst gave consistent activity on recycling, with good conversion of iodobenzene (21%, 22%, and 21%, respectively) and with appreciable TON values (191, 200, and 186, respectively). No leaching of the catalyst to the organic phase was observed during the recycling study as confirmed by Pd analysis of the organic phase. The organic phase was recycled to confirm the absence of catalyst in that phase. There was no further reaction when the reaction was conducted with the recycled organic phase along with fresh styrene and iodobenzene.

The idea of using such catalyst in a biphasic system is more useful through industrial point of view. The results produced here are just to show the feasibility of the use of catalyst in a biphasic medium, however proper tailoring of reaction may still improve the activity and a high cumulative turn over number (TON) is achievable.

An aqueous biphasic medium using water and a nonpolar solvent system has been demonstrated first time for the Heck reaction. The reaction conditions are standardized in such a way that there was no leaching to the organic phase. Pd–TOTPS complex catalyst is found to be active for the Heck reaction, in the presence of morpholine co-solvent. The catalyst is stable in water and could be recycled for two times with no loss in the activity. The role of co-solvent concentration, olefins, and aryl halides has been elucidated in the aqueous biphasic system.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.067.

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