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Phosphine-functionalised polymer resins as Pd scavengers

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Abstract—Three phosphine-functionalised polymer resins were used as scavengers of palladium catalysts from Buchwald–Hartwig aryl amination reactions. The purity of the products was assessed, and residual palladium analysed by ICP-AES. Scavenging efficiencies of up to >98.5% were demonstrated.

Palladium catalysis is a powerful tool in synthetic chemistry for C–C and C–X bond formations.[1] In recent years, significant advances have been made in the discovery and design of highly active catalysts, which fall into either one of the two categories: those that are thermally stable and deliver extremely high turnovers, typically at temperatures of >100 °C;[2] or those that are catalytically active under ambient temperatures.[3] Naturally, the latter systems are more desirable due to their greater energy efficiency and better accommodation of thermally sensitive moieties. Nonetheless, fairly high catalytic loadings (typically 1–3 mol %) are usually required to provide acceptable rates.

As palladium catalysis gains greater popularity in fine chemicals and pharmaceutical processes, the removal and recovery of the precious metal from the products have become important issues,[4] due to the significant cost of palladium, as well as the decreasing regulatory limit of heavy metal residues in pharmacologically active compounds.

Several palladium catalyst scavengers have been marketed in recent years, including several polymer resins (Fig. 1). These contain chelating polyamines **1**–**3**,[5] macroporous resins functionalised with 2,4,6-trimercaptotriazine (MP-TMT) **4**,[6] or the macroporous resin beads carrying a dithiothreitol functionality, **5**[7] (Fig. 1). These resins remove palladium efficiently from organic and aqueous solutions.

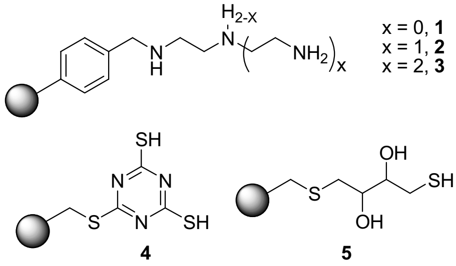

Figure 1. Commercially available Pd scavenger resins.

The coordination of the homogeneous catalyst onto the solid support is envisaged to be dependent on the nature of the palladium species and the arresting moiety. Herein, we report the use of three commercially available phosphine-functionalised polymer supports (PS-TPP, $PS-PPh_2$ and $PS-PCy_2$, Fig. 2) as scavengers of Pd catalysts from reaction mixtures.

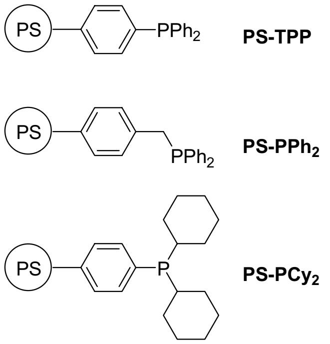

Figure 2. Phosphine-functionalised polymer resins.

Keywords: Palladium catalysis; Scavenger; Polymer resin; Phosphine.

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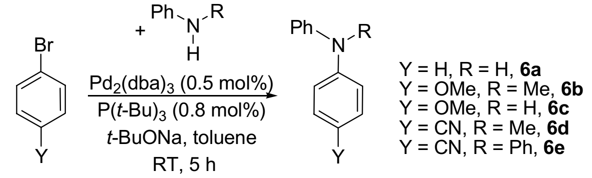


Scheme 1. Buchwald–Hartwig aryl amination reaction.

In the present work, these scavengers were used to recover residual catalyst from products of the aryl amination reaction (Scheme 1). As far as we are aware, the attempted recovery of the catalysts from this system has never been reported before using the other scavengers. This is thought to be particularly challenging, as the system contains amine substrate and product that may compete for binding to the metal centre. Hence, the three polymer resins were chosen for the difference in their Lewis basicity.

Tri-*tert*-butylphosphine ligand was chosen for the homogeneous reaction. Sterically bulky phosphine ligands are able to stabilise highly reactive coordinatively unsaturated Pd species.[3] Thus, we envisage that this will also make it more susceptible to capture by the functionalised supports.

The catalytic reactions were performed under ambient conditions according to the established procedures.[8] Using 1 mol % of Pd(0) with 0.8 mol % of P(t-Bu)$_3$, reactions of three aryl halides (4-bromobenzene, 4-bromoanisole and 4-bromobenzonitrile) proceeded smoothly, with aniline or *N*-methylaniline, to furnish the secondary and tertiary arylamine products **6a**–**e**. At the end of the reaction (5 h), the polymer resin was added to the reaction mixture, and the resultant suspension was swirled gently overnight in an orbital shaker (14 h). The polymer beads were recovered by filtration, and the filtrate was subjected to a simple aqueous wash to remove inorganic salts. After removal of solvents, the composition of the arylamine was examined without further purification.[9]

^{1}H NMR spectroscopy was employed to confirm the formation of the arylamine product and the presence of any starting materials. Most of the time, the presence of any palladium residues is clearly detectable as it gives rise to coloured NMR samples, ranging from green, orange to dark red-brown. ^{31}P–{^{1}H} NMR spectroscopy can be used to detect the presence of any phosphorus species in the solutions. Wherever applicable, the purity of the isolated diarylamine products was assessed by determining their melting points. Finally, ICP-AES analyses were performed to determine the amount of Pd residue and the efficiency of the recovery process (Table 1).

As expected, high levels of Pd residue were present in the products when the reactions were performed without the scavenging procedure (entries 1 and 10).

Different equivalents of the polymer resins were employed as scavengers, to establish the optimal amount required for the efficient removal of the palladium

Table 1. Removal efficiency of Pd from aryl amination reactions (Scheme 1)[a]

Entry	Y, R	Product	Scavenger[b]	Yield/%[c]	Mp/°C[d]	δP/ppm[e]	Residual Pd[f]
1	H, H	**6a**	—	85	—	+63 s, +66 s	0.63%
2	H, H	**6a**	PS-TPP (10)	60	—	+66 s, +35 s	
3	H, H	**6a**	PS-TPP (20)	40	—	+66 s, +35 s	
4	H, H	**6a**	PS-PPh$_2$ (10)	75	50–51	n.d.	<0.01%
5	H, H	**6a**	PS-PPh$_2$ (7.5)	85	50–51	n.d.	
6	H, H	**6a**	PS-PPh$_2$ (5)	80	—	+66 s, +63 s	
7	H, H	**6a**	PS-PCy$_2$ (10)	80	50–51	n.d.	
8	H, H	**6a**	PS-PCy$_2$ (7.5)	80	50–51	n.d.	
9	H, H	**6a**	PS-PCy$_2$ (5)	85	48–49	+66 s, +63 s	
10	OMe, Me	**6b**	—	90	—	+63 s, +66 s	1.44%
11	OMe, Me	**6b**	PS-TPP (10)	100	—	+66 s, +63 s	
12	OMe, Me	**6b**	PS-TPP (20)	100	—	+66 s, +63 s	
13	OMe, Me	**6b**	PS-PPh$_2$ (10)	80	—	n.d.	0.027%[g]
14	OMe, Me	**6b**	PS-PPh$_2$ (7.5)	75	—	n.d.	
15	OMe, Me	**6b**	PS-PPh$_2$ (5)	50	—	+66 s, +63 s	
16	OMe, Me	**6b**	PS-PCy$_2$ (10)	85	—	n.d.	
17	OMe, Me	**6b**	PS-PCy$_2$ (7.5)	90	—	n.d.	
18	OMe, Me	**6b**	PS-PCy$_2$ (5)	70	—	+66 s, +63 s	
19	OMe, H	**6c**	PS-PPh$_2$ (10)	82	103–104	n.d.	0.05%
20	CN, Me	**6d**	PS-PPh$_2$ (10)	82	104–106	n.d.	0.18%
21	CN, Ph	**6e**	PS-PPh$_2$ (10)	84	—	n.d.	0.10%

[a] The reactions were conducted with aryl halide (1 equiv), aromatic amine (1 equiv), Pd$_2$(dba)$_3$ (0.5 mol %), ligand (0.8 mol %) and NaO(t-Bu) (1.5 equiv) in toluene, room temperature, 5 h.

[b] Value in parenthesis denotes equivalents used.

[c] Isolated yields, verified by ^{1}H NMR.

[d] Mp (**6a**): 51–53 °C, **6b** and **6e** are viscous oils at room temperature.

[e] ^{31}P–{^{1}H} NMR resonance(s), n.d. = not detected.

[f] Determined by ICP-AES analysis.

[g] 267 ppm in 50 mg.

catalyst. Triphenylphosphine-functionalised resin (PS-TPP) was found to be an ineffective scavenger, even when it was employed in large quantities (entries 2, 3, 11 and 12). The NMR samples were invariably coloured, and the corresponding ^{31}P NMR spectra indicated the presence of a large amount of phosphorus impurities. Furthermore, the deployment of a large excess (20 equivalents per Pd) of the polymer also led to a decrease in the recovered yield (entry 3), which was attributed to the product being trapped within the polymer resins.

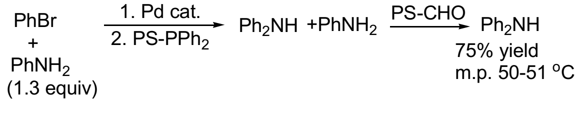
In comparison, 7.5–10 equiv of PS-PPh_2 (entries 4–6 and 13–15) and PS-PCy_2 (entries 7–9 and 16–18) were found to remove the catalysts effectively. Products were recovered in high yields (between 80% and 90%) and good product purity was obtained, as indicated by the agreement between the mp of the product **6a** with reported values. Less than 0.01% of Pd was found in the product **6a** (entry 4) and 0.027% in **6b** (entry 13), corresponding to scavenging efficiencies of >98.5% and 98%, respectively (calculated by comparison to unscavenged reactions—entries 1 and 10). These values were found to be comparable to those reported for the ethylene diamine-derived polymer scavengers **1**–**3** in the Suzuki–Miyaura cross-coupling[5a] and that of a polymer-supported chelate phosphine for the removal of Grubbs' catalyst.[10]

Attempts to reduce the amount of the scavengers to 5 equiv were clearly insufficient, as indicated by the presence of phosphorus residues in the recovered product (entries 6, 9, 15 and 18).

However, when 4-bromobenzonitrile was employed as the substrate, %Pd residue was particularly high (entries 20 and 21), which is attributed to the complexation of the nitrile moiety to Pd. Thus, the efficiency of Pd scavenging is dependent on the functional groups present on the substrate.

PS-PPh_2 and the Wang-aldehyde (PS-CHO) resins may be used in tandem for the synthesis of secondary amines, to remove Pd and excess amine, respectively (Scheme 2). Thus, the reaction between bromobenzene and aniline furnished diphenylamine in 75% yield, with high product purity (NMR, GC–MS and mp). The procedure is practically simple, and we envisage that it is amenable to automated procedures for the construction of libraries of arylamines.[11]

None of the recovered polymer beads (PS-PPh_2 or PS-PCy_2) were found to be catalytically active at room temperature, or at 80 °C.[12] As an excess of the polymer resin was used in the scavenging process, this may be due to the low Pd loading and the presence of a large effective concentration of the phosphine moiety present in these resin beads, which may prevent the formation of the catalytically active species in the homo- and heterogeneous reactions.



Scheme 2. Successive scavenging.

In summary, we have demonstrated that certain phosphine-functionalised polymer supports, particularly the inexpensive PS-PPh_2, can be used to capture palladium-catalysts effectively. The scavenging efficiency is comparable to other commercially available Pd scavengers in less-challenging processes. We are currently investigating the use of these polymer resins as heterogeneous supports in palladium catalysis, and the results will be reported in due course.

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9. Typical reaction procedure: Aryl bromide (1.0 mmol), arylamine (1.0 mmol), $Pd_2(dba)_3$ (5.75 mg, 0.005 mmol), $P(tBu)_3$ (10 wt % in hexane, 16 μL, 0.008 mmol) and sodium *tert*-butoxide (150 mg, 1.5 mmol) were weighed into a round-bottomed flask or in a Radley's carousel reaction tube, under an atmosphere of N_2. A stirrer bar was added followed by anhydrous toluene (2 mL). The resultant purple mixture was stirred at rt and monitored by TLC. After complete consumption of starting materials (typically about 5 h), polymer-bound phosphine resin was added to the brown suspension, and the resultant mixture was swirled in an orbital shaker at rt for 14 h (overnight). The resin was recovered by filtration, and the filtrate was diluted with diethyl ether and washed with H_2O (3 × 5 mL). After evaporation of the solvents, the product was subjected to analyses (NMR, melting point and ICP-AES) without further purification.
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11. The recyclability of the Wang-aldehyde resin had been demonstrated by one of us in an earlier paper: Guinó, M.; Brulé, E.; de Miguel, Y. R. *J. Comb. Chem.* **2003**, *5*, 161–165.
12. No leaching of the Pd species into the homogeneous solution was observed, even at high temperature.