The Use of Polymer and Silica Supported Metal Scavengers in Scale Up / Process Chemistry, New Approaches to Todays Challenges: A Detailed Study

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Introduction

Catalytic metal mediated reactions are becoming more widespread in industrial synthesis due to reaction efficiency, atom economy and green credentials. Target limits for metal contamination in final products/APIs are becoming increasingly stringent. Achieving limits [5ppm typically] poses particular difficulties for downstream processing. The use of polystyrene resin or silica bound metal scavengers has increased in recent years due to potential for process improvment[1]. We illustrate the application of PS-DVB co-polymers (MP-TMT) and functionalized silica (Si-TMT and Si-Thiol) to metal scavenging (**Figure 1**).

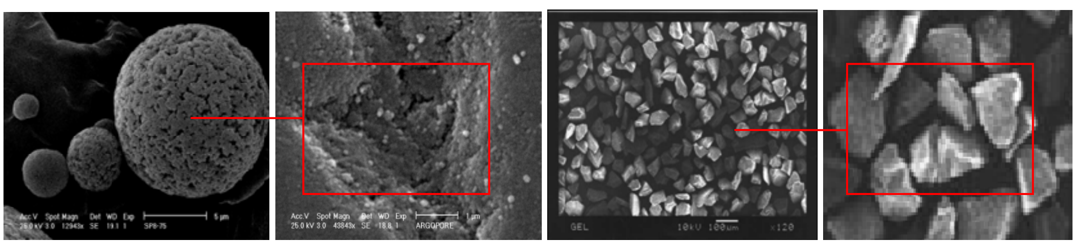

Figure 1) SEM images of **a.** macroporous polystyrene resin (insoluble, cross-linked spherical functionalized polystyrene, 50um – 1000um diameter beads). **b.** Functionalized silicas (surface orientated chemistry, robust irregular shaped particles, iinsoluble, hydrophillic Si-O-Si matrix).

Results and discussion

Historically, measurement of residual metal in final product was achieved by ICP (**Figure 2**). However, the technique is relatively expensive where in-house facilities do not exist. As such, there has been a comparative shortfall of data relating to systematic understanding of metal scavenging variables.

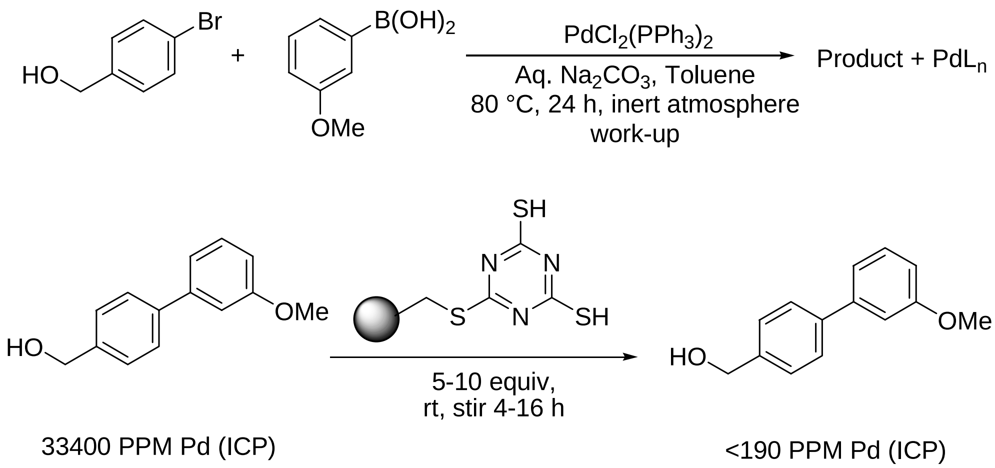

Figure 2. Suzuki reaction of 4-Br-Benzyl alcohol with 3-Methoxyphenylboronic acid. A 'before and after' Pd scavenging approach. 5 equiv of scavenging resin reduced initial Pd contamination from extracted product of Suzuki Reaction, almost 200-fold at RT (99.4% scavenging). In reaction, (resin bound) MP-TMT was optimal in metal scavenging.

UV-ICP Correlation :

We developed an in-house UV-based screen, which allowed correlation of UV-Vis directly with ICP (+/- 2ppm) for standard catalytic solutions (**Figure 3**).

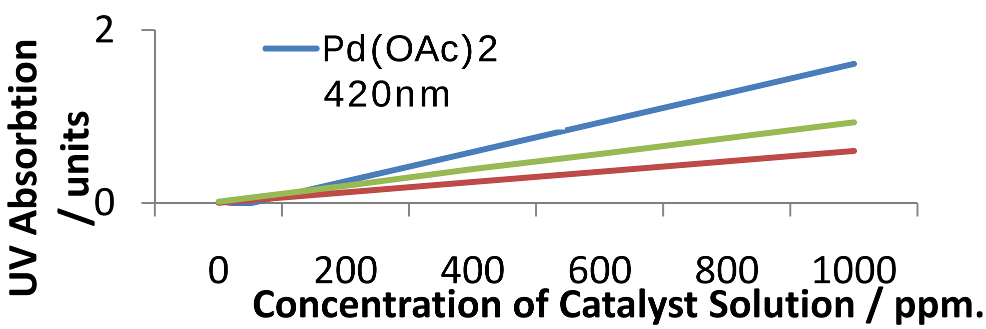

Figure 3. UV-VIS/ ICP correlation and model studies

Geometry of the Fixed Bed in Metal Scavenging

A long-thin fixed bed (**Table 1**, **Entries 1, 4 and 7**) has a smaller surface area/height ratio, than shorter-wider beds (such as **Entries 3, 6, 9**) and this affected the scavenging. When scavengers:Pd affinity is weak, fixed bed geometry is important, (longer columns enhance scavenging). However, the flow rate, backpressure and physical size of the bed must also be practical. When a strong scavenger is used (**Table 1, Entries 1-3 and 7-9**), bed length is less significant, large SA/H beds are as efficient as longer thinner beds. Packing efficiency is also a variable (**Table 1, Entries 3 and 9**). Thus choice of scavenger can be critical. Ease of Pd scavenging depends on the catalyst used, i.e. scavenging Pd from $Pd(OAc)_2$ was relatively efficient (easy) in all cases.

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Entry	SPE Cartridge size	Scavenger	Bed ID (mm^2)	Bed H (mm)	Bed SA/H ratio	% Pd scavenged from 3000ppm starting solution of catalyst		
						$Pd(OAc)_2$	$Pd(PPh_3)_4$	$Pd(Cl)_2(PPh_3)_2$
1	3mL	MP-TMT	8.9	17.8	3.5	72.5	51.7	57.8
2	6mL	MP-TMT	12.6	8.5	14.7	12.1	39.3	16.1
3	12mL	MP-TMT	15.6	5.8	32.9	0.0	39.1	4.1
4	3mL	Si-SH	8.9	13.3	4.6	99.9	65.3	31.0
5	6mL	Si-SH	12.6	6.7	18.6	99.2	64.4	31.0
6	12mL	Si-SH	15.6	4.4	43.1	95.6	61.8	28.9
7	3mL	Si-TMT	8.9	13.0	4.7	99.8	70.6	77.2
8	6mL	Si-TMT	12.6	6.5	19.2	99.2	68.1	69.0
9	12mL	Si-TMT	15.6	3.8	50.4	99.2	68.0	51.4

Table 1. The effect of the fixed bed on Metal Scavenging. A scavenging Pd from a range of different Pd catalysts, using a variety of resin and silica scavengers, packed into 3 different fixed bed configurations, was undertaken.

Optimized Scavenging

To demonstrate implications of **Table 1**, a one-pass experiment was performed using a 1000ppm std solution of $Pd(dppf)_2Cl_2$ (**Figure 4**). Catalyst was passed through 500mg fixed beds of each metal scavenger in SPE cartridges. While Si-Thiol faired well, removing 462ppm Pd from solution (representing a 69eq excess), TMT ligands were more effective. The resin-based TMT reduced Pd from 1000ppm to av16ppm (98.4% with a 32 equiv. excess of scavenger). However, Si-TMT facilitated more effective scavenging, reducing Pd in solution from 1000ppm to 4.2 (99.6% Pd removal, from a 16 equiv. excess of scavenger). Compared to batch experiments, these equivalencies are high, however the contact (residence) time was only a few seconds. When residence time is high (i.e. batch reactions), equivalency can be reduced to 3-5, or 25-50 wt% wrt product, maintaining similar overall scavenging efficiency (99.4%) (**Figure 2**).

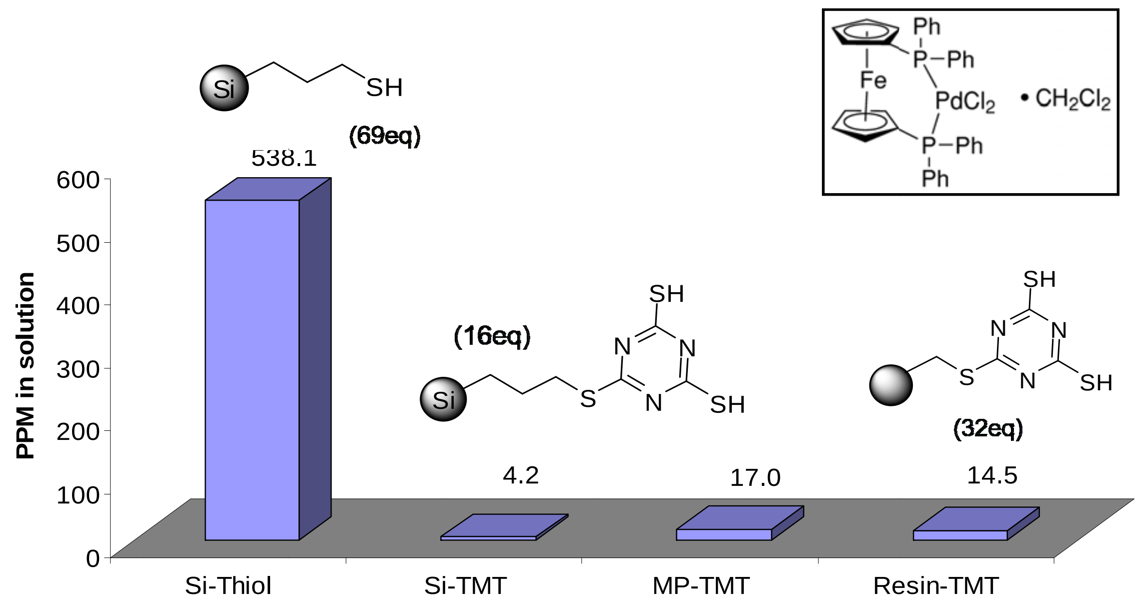

Figure 4. One-pass flow of 1000ppm Pd (in $Pd(dppf)_2Cl_2$. Quantification of residual Pd by ICP. Fixed bed: 500mg / 3mL std fritted polypropylene cartridge. (Right: Resin-TMT = non-commercial bound TMT scavenger)

Optimum place to deploy metal scavenging in a process

When the metal scavenging step was placed at the end of the synthesis, applied to extracted product, the efficiency was highest (94.5% compared to 85.9%) (**Figure 5**).

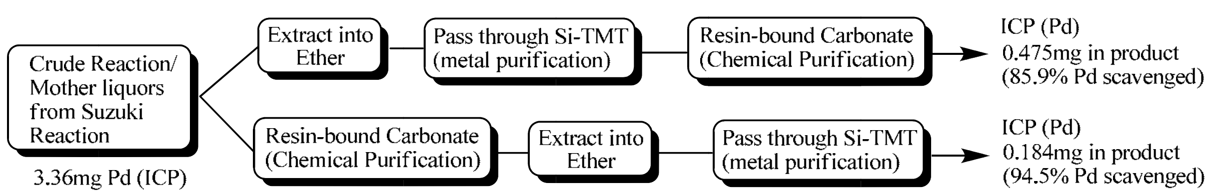

Figure 5. Investigation into the placement of the scavenging step in the process. Crude product (**3**) from 100mmol Suzuki scale-up reaction was used as a basis for Pd scavenging.

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Scavenging in more challenging systems.

In the synthesis of benzothiazoles (**3,6**), the position of the Sulphur atom in the final product was varied via **2** and **5** (**Figure 6**). As expected, less efficient scavenging was observed in the case of the bound Thiol. Scavenging: **3**: Si-Thiol 95% vs Si-TMT 97.4%, **4**: Si-Thiol 95% vs Si-TMT 98.9%) with these more challenging substrates.

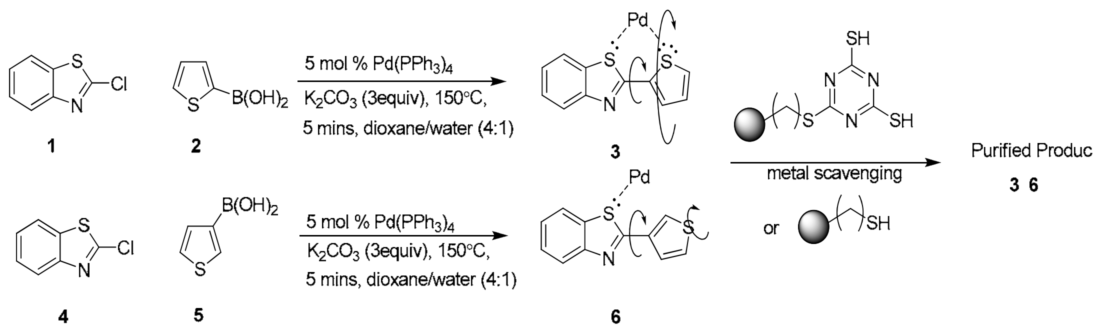

Figure 6: Synthesis and metal scavenging of **3** and **6**, via Suzuki Reaction of 2-chlorobenzothiazole with 2- and 3- thiophene-boronic acid.

Challenging Recrystallization

The reaction of 4-Methoxyphenyl boronic acid (**8**) and 3-bromo-N-ethylcinnamide (**7**) was scaled from lab, 200-fold to 100g (**Figure 7**). Scavenging using Si-TMT and recrystallization were applied to extracted amide product (**9**). Crude product (**9**) (**Figure 7, Image 1**) contained 1300ppm Pd, following recrystallization, 200ppm as a light grey product (**Image 2**). Passing (**9**) through a Si-TMT bed reduced Pd from 1300ppm to 5ppm yielding pure white product (**Image 3**).

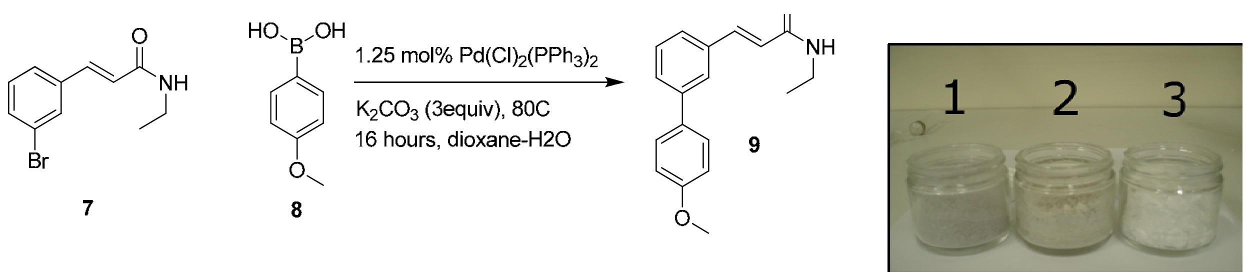

Figure 7: PR+D scale Suzuki reaction and Scavenging.
Right: Photographic images of products, with varying degrees of Pd contamination

Conclusion

Si-Thiol, Si-TMT and MP-TMT were evaluated for metal scavenging. We observed effects based on polymer type, ligand, and Pd catalyst hosting. Bed geometry was investigated and also effect of increasing the scavenging difficulty via complicated substrates. This has allowed construction of a framework of guidelines for expedited metal scavenging

References & notes:

[1] Garrett, C.E.; Prasad, K. *Adv. Synth. Catal*. **2004**, *346*, 889-900. Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Proc. Res.. Dev*. **2005**, *9*, 198-205.

2 The use of the small molecule in metal scavenging is discussed in Ishihara, K.; Nakayama, M.; Kurihara, H.; Itoh, A.; Haraguchi, H. *Chem. Lett*. **2000**, 1218-1219

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