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QuadraPure Cartridges for Removal of Trace Metal from Reaction Mixtures in Flow

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Abstract:

Packed cartridges of QuadraPure metal scavengers have been used to reduce levels of metal contaminants in a single-pass flow method. Five examples are given of simplified purification of metal-mediated reactions. QuadraPure cartridges demonstrated excellent clean-up in comparison with traditional methods for metal removal.

Introduction

With increasingly complex molecular architecture required for the selectivity of pharmaceutical ingredients, ever more elaborate reactions are employed in their manufacture. Homogeneous precious-metal-catalysed processes contribute a large proportion of these transformations.[1] Such methods are tolerant of a wide range of functional groups and demonstrate excellent chemo- and stereoselectivity.[2]

However, with strict guidelines limiting metal levels in pharmaceuticals,[3] there is a growing need for practical methods for the removal of residual metals from reaction products and waste streams.[4]

Herein, we demonstrate the versatility and numerous practical benefits of a range of functionalised resins for efficient removal of metal contaminants (QuadraPure) using prepacked cartridges compatible with existing flow process equipment.

Results and Discussion

QuadraPure scavengers are functionalised macroporous polystyrene-based resin beads.[5] The beads are monodispersed (~500 μm, Figure 1) and due to high cross-linking (up to 20%) have relatively low swell in organic solvents (up to 30%). They can be used in aqueous or organic systems across a wide range of pH (2−14), and are thermally stable up to 60 °C. Functionality is around 1−7 mmol/g of resin. Batch scavenging is simply achieved by addition of the free-flowing beads to the reactor and agitation at ambient or slightly elevated temperatures with scavenging times of 1−16 h followed by filtration to isolate the loaded beads. To avoid handling loose resin in reactors, and to take advantage of improved scavenging kinetics in flow, we looked at the use of QuadraPure resins in disposable cartridges.[6]

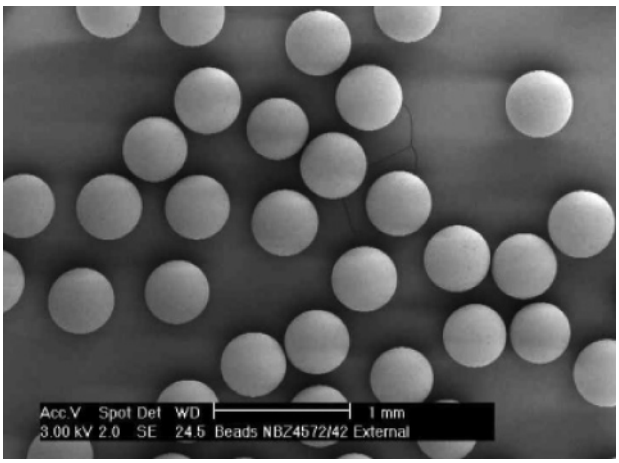

Figure 1. **Optical microscopy image of QuadraPure resin beads.**

An automated chromatography system common in many laboratories was used for the work.[7] Simple polyethylene cartridges of the same design as that of commercial silica-containing chromatography cartridges were prepacked with QuadraPure resin beads (Table 1). The cartridges were loose dry-packed by the equipment manufacturer to allow for some small swell of the resin. At these sizes of cartridges, the swelling has no effect on the flow, and no back pressure is generated.

Initial work on capacity to scavenge concentrated metal solutions determined that flowing up the cartridge (against gravity), rather than down as for the chromatography applications, was necessary for good scavenging. Simply swapping the inlet/outlet connections to the cartridge housing facilitated this. Preliminary work established an optimum flow rate of approximately 5 column volumes per hour (CV/h). At this rate the scavenging capacity is above that for batch

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(3) Note for Guidance on Specification Limits For Residues of Metal Catalysts. *Evaluation of Medicines for Human Use*; The European Agency for the Evaluation of Medicinal Products: London, U.K., 2002.

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(5) QuadraPure resins are available from Sigma-Aldrich at research-scale amounts, and in bulk quantities and cartridge format from Reaxa Ltd., Manchester, U.K. (www.reaxa.com).

(6) Metal value recovery from spent cartridges and used resins by incineration has been demonstrated.

(7) Biotage SP4, see: www.biotage.com/DynPage.aspx?id=22017 (accessed October 2006).

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Table 1. **QuadraPure resin functionality and key metals resin recommended for scavenging**

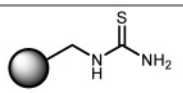
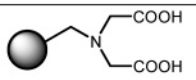
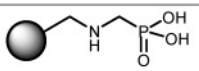
QuadraPure	functionality	key metals scavenged
TU		Pd, Cu, Rh, Pt, Hg
IDA		Cu, Ni, Al
AMPA		Fe, Rh, Co

Table 2. **Recommended loading capacities and flow rates for the cartridge sizes examined**

cartridge size	approx. mass of QuadraPure (g)	metal loading capacity (mmol)	flow rate (mL/min)	approx. residency time (min)
12+M	6	1	1	8
25+S	13	2	2	9
40+M	68	10	8	9

and not affected by the concentration of the solution. The relationship between maximum capacity and a flow rate of 5 CV/h scaled through the cartridge sizes, and thus the flow rate in terms of mL/min is determined only by the cartridge size. Breakthrough tests for solutions of metals recommended for the resin in question were performed,[8] leading to a recommended loading capacity for each cartridge size examined. This data is summarised in Table 2.[9] A key feature was the linearity of metal loading through cartridge sizes. This linearity has been further demonstrated in a prototype pilot-scale cartridge containing 400 g of resin.[10] Flowing palladium acetate solution at 5 CV/h (50 mL/min), scavenged palladium at the same loading per gram of resin as for the cartridges examined here.

To fully test the potential of the cartridges to remove metal species from reaction streams, a series of representative reactions were run using common catalytic systems. A range of metals were used to cover three different QuadraPure resins, and reactions were performed at different scales to confirm scavenging ability at the three different cartridge sizes. ICP analysis of solutions before and after passing through the scavenging media provided comparative data showing the percentage of metal removed from the stream.

A Suzuki reaction[11] (Scheme 1) was chosen as an example to compare the metal-removal methods for "polishing" material following work-up. The substrates were chosen to

Scheme 1

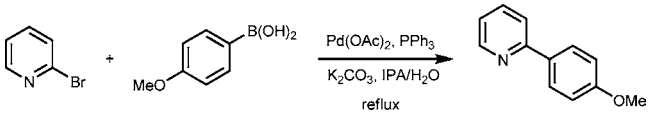
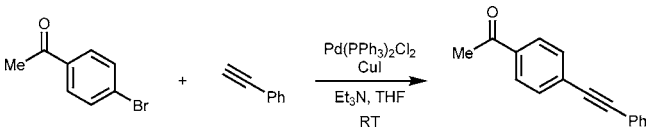


Table 3. **Comparison of common methods for removal of palladium species from a Suzuki reaction**

scavenger	starting metal concentration (ppm)	final metal concentration (ppm)	% metal removed	% product absorbed
silica gel (60 Å)	60	56	7	2
carbon (Nuchar)		26	57	28
QuadraPure TU		<1	>99	<1

Scheme 2



generate a product that may co-ordinate palladium and thus be harder to scavenge.

The coupling was performed on a 15 mmol scale with a >99% conversion overnight. Following a simple work-up the crude product solution (THF, 300 mL) had a purity of >90% and palladium contamination of 60 ppm. The solution was split three ways; the first portion passed through a QuadraPure TU cartridge (12+M), the second passed through a packed carbon (Nuchar) cartridge (Biotage Flash AC, 12+M), and the third was subjected to the more common laboratory work-up procedure of filtering through a pad of silica. ICP analysis of the resulting product-containing solutions (concentrated to 100 mL) and recovered yields showed QuadraPure to selectively remove >99% of the palladium without absorbing the product. Residual palladium on the isolated product was 4 ppm by ICP. Table 3 shows comparative data for the three methods. The silica pad removed very little palladium, whereas the carbon removed more than half but had a significant affinity for the product, leading to tailing on elution[12] and incomplete recovery. It is worth noting that although all palladium contamination was in solution, palladium "black" precipitate is also removed by the QuadraPure resin: loose or in cartridge format.

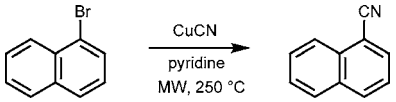
In the remaining examples the QuadraPure cartridge was used in lieu of a work-up to examine efficiency of metal removal. QuadraPure TU was employed to clean up another cross-coupling: a Sonogashira reaction.[13] The coupling (Scheme 2) was carried out with $PdCl_2(PPh_3)_2$ and CuI at room temperature (5 mmol scale, >99% conversion).

It is notable that passing through the cartridge (25+S) removed copper and palladium species, in different oxidation states, to below detectable levels in the presence of ligating molecules such as triphenylphosphine and alkynes. The only treatment prior to QuadraPure was a filtration through Celite to remove insolubles; thus, the mixture was also at relatively high pH due to excess triethylamine.

(8) Common metal salts at 1000 ppm in organic solvents; see Supporting Information for further details.
(9) A representative example is provided; for full experimental details see Supporting Information.
(10) Cartridges compatible with existing plant filter housings developed with Clear-Edge, Glasgow, U.K. (www.clear-edge.com), see http://www.reaxa.com/images/stories/reaxa_clearedge_ssc_flier.pdf for more details.
(11) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483; Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.
(12) UV traces showing this effect are in the Supporting Information.
(13) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566−1568.

QuadraPure IDA resin was used to remove copper by-products from a Rosemund von-Braun cyanation (Scheme 3).[14] The reaction was modified from a literature procedure for convenience and safety using microwave heating. The original paper used a Wood's metal bath to heat the mixture at ~230 °C overnight.[15] Quantitative conversion was achieved under microwave heating at 250 °C in 30 min at a 10 mmol scale.

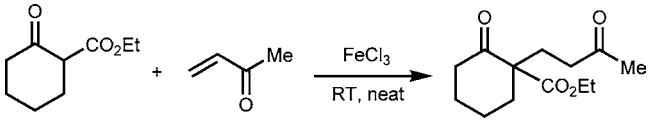
Scheme 3



The literature procedure called for dissolution in warm benzene and exhaustive washing with ammonia solution to remove copper salts, followed by a laborious washing regime to isolate the crude material. By contrast, simply slurrying the contents of the microwave tube in dichloromethane and filtering through Celite gave a brown solution that was cleared by passing through the QuadraPure IDA cartridge (40+M). Copper content before and after flow clean-up was 345 ppm and <1 ppm, respectively. Monitoring of the flow by UV absorption revealed a near ideal "square wave" profile, suggesting no absorption of the product by the resin. Quantitative recovery of 1-naphthonitrile confirmed this observation.

Iron(III) chloride is considered the catalyst of choice for Michael additions;[16] however, removal of iron impurities is not trivial.[17] To demonstrate selective iron removal, a standard published procedure was used (Scheme 4).[18] In the original method the authors used distillation to obtain pure product but noted that washing through silica (~500% w/w) with MTBE also provided product of good quality.

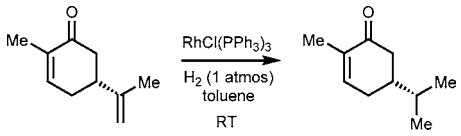
Scheme 4



The reaction was run neat as per the literature procedure (the only change was using the cyclohexanone in place of the cyclopentanone) and on completion was diluted with THF (Fe content measured at 61 ppm). Approximately half was passed through a QuadraPure AMPA cartridge (12+M), and the remainder was washed through silica gel (60 Å, 20 g). The iron content of the resulting solutions was 23 ppm for the silica and <0.2 ppm for the QuadraPure. In both cases there was no observed absorption of product, with the UV trace again showing near ideal peak shape for the product "slug" passing through the QuadraPure cartridge.[12]

QuadraPure AMPA was also used to recover the metal value from a Wilkinson's catalyst-mediated hydrogenation.[19] Another classic literature method (Scheme 5)[20] was repeated, leaving a toluene (in place of benzene) solution of dihydrocarvone and spent Wilkinson's catalyst. In place of any work-up the orange solution (Rh content 309 ppm) was immediately passed through a QuadraPure AMPA cartridge (12+M) to give a clear solution (Rh content 4 ppm) which was concentrated to give the product in >98% yield. This represents a >98% recovery of rhodium metal.

Scheme 5



Conclusions

We have demonstrated the use of QuadraPure scavenger resins in flow clean-up of reactions using organometallic catalysts. The cartridges were straightforward to use in existing purification equipment. In all cases selective removal of metal contaminants was achieved.

Experimental Section

General. All reagents were purchased from Aldrich and used without further purification. Solvents are standard laboratory grade and used from the drum without purification.

Cartridge experiments were run on a Biotage SP4 automated chromatography system with prepacked QuadraPure cartridges.[5] Cartridges were fitted inside the standard compression modules but connected to the valve unit such that the flow was up the cartridge (swap the HPLC connectors around for that channel).

Microwave reactions were carried out in a Biotage Initiator 60.

GC/MS was performed on a Varian Saturn 2100T with GC 3900 containing a CP-Sil 8CB low bleed/MS 30 m × 0.25 mm, 0.25 μm column.

Inductively Coupled Plasma Optical Emission Spectroscopy Analysis. Inductively coupled plasma optical emission spectroscopy (ICP-OES) was performed by Intertek ASG, Manchester, on a Perkin-Elmer Optima 3300. The samples submitted were weighed into beakers, and the solvent was evaporated down. The residue was then digested using nitric acid and sulphuric acid. After cooling, the samples were then transferred to 25-mL volumetric flasks and made to volume with deionized water. The solutions were then analysed against known standards by ICP-OES and the results calculated.

Typical Breakthrough Test Procedure: Palladium Acetate in THF (1000 ppm) through QuadraPure TU, 25+S Cartridge. A solution of palladium(II) acetate (2.11 g) was prepared in THF (1000 mL) which was approximately

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(15) Newman, M. S. *Org. Synth.* **1941**, *21*, 89−91.
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(17) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, D. B.; Mathre, J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198−205.
(18) Christoffers, J. *Org. Synth.* **2002**, *78*, 249−251.
(19) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. (A)* **1966**, 1711−1732.
(20) Ireland, R. E.; Bey, P. *Org. Synth.* **1973**, *53*, 63−65.

1000 ppm with respect to palladium. A 25+S flash cartridge filled with QuadraPure TU (13.0 g of resin, 24-mL column volume) was fitted in a Biotage SP4 Flash Purification System, with the palladium solution as the "strong solvent" and THF as the "weak solvent".

A gradient was programmed at a fixed flow rate of 2 mL/min, starting with an initial 5 CV (120 mL) of THF to wet the resin, then 20 CV (480 mL) of palladium solution, ending with another 2 CV (48 mL) of THF. The programme was set to collect all fractions (51 mL each) with the UV detector collection wavelength set to 232 nm and the monitor wavelength at 320 nm.

The Biotage unit was first primed, bypassing the column, with a 50-mL portion of THF at a flow rate of 20 mL/min to remove air from the lines. The programme was then run, giving a breakthrough point at 12.5 CV (300 mL), depicted by a sharp increase in gradient on the UV trace, and also by the appearance of yellow-coloured fractions. The loading of the cartridge equated to approximately 23 mg Pd/g of resin (0.22 mmol/g).

Suzuki Reaction. 2-Bromopyridine (1.5 mL; 15.7 mmol), 4-methoxybenzene boronic acid (2.96 g; 19.5 mmol), palladium(II) acetate (180 mg; 5 mol %), triphenylphosphine (780 mg, 20 mol %), potassium carbonate (13.0 g; 94 mmol), distilled water (15 mL), and isopropyl alcohol (150 mL) were added successively to a 500-mL round-bottom flask. The reaction mixture was heated under a nitrogen atmosphere at reflux overnight. After this time GC/MS analysis indicated that the reaction had gone to full conversion.

The cooled reaction mixture was partitioned between dichloromethane (150 mL) and water (100 mL). The organic layer was washed with brine solution, dried over magnesium sulfate, and then filtered through Celite. The resulting solution was diluted to 300 mL with dichloromethane and a sample taken for ICP analysis (60 ppm wt/wt with respect to palladium).

Using a Biotage SP4 Flash Purification System, 100 mL of the crude solution was passed through a 12+M cartridge of QuadraPure TU. A gradient was run consisting of initial waste of 4 CV of dichloromethane (48 mL), with 25 CV for the reaction mixture (300 mL, equating to the 100-mL portion of reaction mixture and additional 200 mL of dichloromethane) and 2 CV of dichloromethane (24 mL), at 1 mL/min. Product-containing fractions (51 mL each, identified by UV 232 and 254 nm, see Supporting Information) were pooled and concentrated to 100 mL, and a sample was taken for ICP analysis (<1 ppm wt/wt with respect to palladium). Concentration in vacuo gave the crude product (0.967 g, 4 ppm wt/wt with respect to palladium).

Another 100-mL portion of the crude solution was passed through a Biotage Flash AC 12+M cartridge containing activated Nuchar carbon. A gradient was run consisting of the initial waste of 4 CV of dichloromethane (48 mL), with 25 CV for the reaction mixture (300 mL, equating to the 100-mL portion of reaction mixture and an additional 200 mL of dichloromethane) and 8.2 CV of dichloromethane (99 mL), at 15 mL/min. Product-containing fractions (51 mL each, identified by UV, see Supporting Information) were pooled and concentrated to 100 mL, and a sample was taken for ICP analysis (26 ppm wt/wt with respect to palladium). Concentration in vacuo gave the crude product (0.697 g).

The final 100-mL portion of the original reaction solution was filtered through a bed of silica gel (60 Å), washed with dichloromethane (100 mL), and evaporated back down to 100 mL. A sample was taken for ICP analysis (56 ppm wt/wt with respect to palladium). Concentration in vacuo gave the crude product (0.948 g).

Rosemund von-Braun Reaction.[15] In a new, dry Biotage 2−5-mL microwave reaction tube were put 1-bromonaphthalene (2.2 g; 1.48 mL; 10.6 mmol), dry copper(I) cyanide (1.05 g, 11.7 mmol), and pyridine (0.982 g; 1 mL; 10 mmol) in the order stated. A small stirrer bar was added and the top sealed with a crimper.

The mixture was heated at 250 °C in a microwave reactor (Biotage Initiator 60),[21] and GC/MS analysis indicated complete conversion in 30 min. The reaction mixture was a dark-brown paste, which was slurried in dichloromethane (800 mL). The brown slurry was filtered through Celite. ICP analysis of the filtrate showed a copper content of 345 ppm wt/wt.

Using a Biotage SP4 Flash Purification System, the crude solution was passed through a QuadraPure IDA cartridge (40+M). A gradient was run of 4 CV of dichloromethane (528 mL), with 7.6 CV for the reaction mixture (999 mL) followed by 2 CV of dichloromethane (264 mL) at 8 mL/min. The colourless product-containing fractions (51 mL each, identified by UV) were pooled, and a sample was taken for ICP analysis, which gave a result of less than 1 ppm of copper in the final solution.

Sonogashira Reaction. Dichlorobis(triphenylphosphine)-palladium(II) (175 mg; 5 mol %), copper(I) iodide (95 mg; 10 mol %), triethylamine (726 mg; 1.0 mL; 7.2 mmol), 4-iodoacetophenone (1.23 g; 5.0 mmol), and phenyl acetylene (0.82 mL; 7.5 mmol) were taken up in THF (100 mL) and stirred at room temperature under a nitrogen atmosphere overnight. After 18 h, GC/MS indicated complete conversion. The reaction mixture was filtered through Celite, washing with THF (150 mL).

The filtrate was concentrated in vacuo to 100 mL and passed through a 25+S cartridge of QuadraPure TU using a gradient of 4 CV of THF (96 mL), followed by 12.5 CV for the reaction mixture and additional THF (300 mL), and finally 1 CV of THF (24 mL) at 2 mL/min. The product-containing fractions (51 mL each, identified by UV 232 and 254 nm, see Supporting Information) were pooled, and a sample was taken for ICP analysis (<1 ppm wt/wt of palladium).

Michael Addition. As per the literature procedure,[18] methylvinylketone (5.0 mL, 60.7 mmol) was added dropwise via syringe pump over 30 min to a stirred flask containing ethyl 2-oxocyclohexane carboxylate (9.07 g, 53.3 mmol) and iron(III) chloride (180 mg, 1.1 mmol, 2 mol %) immersed in a water bath acting as a heat sink at room temperature and then stirred overnight. After 18 h, GC/MS indicated complete conversion. Volatiles were removed under reduced

(21) www.biotage.com/DynPage.aspx?id=22001 (accessed October 2006).

pressure (water aspirator) for 4 h, and the residual oil was taken up in THF (100 mL) to give a yellow/brown solution. A sample was taken for ICP analysis (61 ppm wt/wt Fe). A portion of the solution (60 mL) was passed through a 12+M QuadraPure AMPA cartridge using a gradient of 5 CV (60 mL) of THF followed by 5 CV (60 mL) of the solution and 10 CV (120 mL) of fresh THF at 1 mL/min (UV detection 254 and 220 nm). All product-containing fractions (30 mL each, identified by UV 254 and 220 nm) were pooled, and a sample was taken for ICP (<0.2 ppm wt/wt Fe). The UV trace showed near ideal square wave flow profile, see Supporting Information.

The remaining 40 mL of the solution was washed through a pad of silica gel (60 Å, 20 g) with further THF (20 mL) and the filtrate concentrated back to 40 mL and a sample taken for ICP (23 ppm wt/wt Fe). In both cases quantitative recovery of product was achieved.

Wilkinson's Catalyst Hydrogenation.[20] A solution of (*R*)-carvone (2.25 g, 15.0 mmol) and tris(triphenylphosphine) rhodium(I) chloride (695 mg) in toluene (250 mL) was degassed and then stirred at room temperature under an atmosphere of hydrogen gas (balloon). Progress was monitored by GC/MS with full conversion achieved after 2 h. A sample was taken for ICP (309 ppm wt/wt Rh). The orange solution was then passed through a 12+M QuadraPure AMPA cartridge using a gradient of 5 CV (60 mL) of toluene followed by 300 mL of the mixture and toluene wash and then 5 CV (60 mL) of fresh toluene at 1 mL/min (UV detection 254 and 220 nm gave no response). Product-containing fractions (51 mL each, identified by GC/MS) were pooled and concentrated to 250 mL, and a sample was taken for ICP analysis (4 ppm wt/wt Rh). The product was recovered in quantitative yield (2.28 g).

Acknowledgment

We thank Biotage for packing the cartridges and Angus Stewart-Liddon for performing the Wilkinson hydrogenation. ICP analyses were run by Intertek-ASG, Manchester.

Supporting Information Available

Breakthrough tests and screen shots. This material is available free of charge via the Internet at http://pubs.acs.org.

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