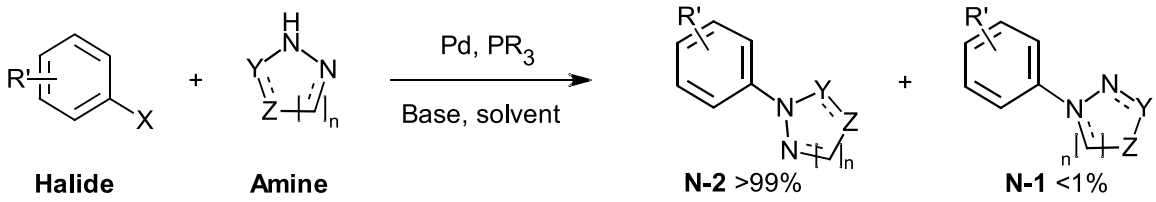
Process Development Whitepaper
Metal Scavenging
Development of a flow scavenging protocol

INTRODUCTION

An optimised palladium-catalysed Buchwald-Hartwig amination reaction delivered the **N-2** isomer with >99% regioisomeric purity at the end of reaction (EOR). Regulatory quality targets require residual palladium levels to be reduced to less than 5 ppm per oral dose and less than 0.5 ppm for each parenteral administration.



Conducting neutral, also basic or acidic washes as part of the post reaction work-up was ineffective at removing palladium, which was found to be approximately 2000 ppm at EOR. Development of a recrystallisation also proved ineffective at purging palladium. Furthermore, it was found that the colour of isolated **N-2** was not indicative of its residual palladium content. The goal of this study was to develop a scavenging protocol that efficiently removed palladium with minimal loss of the **N-2** product.

SCAVENGER SCREENING

A series of scavengers (0.6 w/w with respect to **N-2**) were screened against EOR aliquots (1.50 mL) from a 5 g (10 vol) batch scale reaction and heated to 50 °C under air, over 4 hours (**Figure 1**). Samples were then centrifuged, and the supernatants were submitted for ICP analysis (**Table 1**).

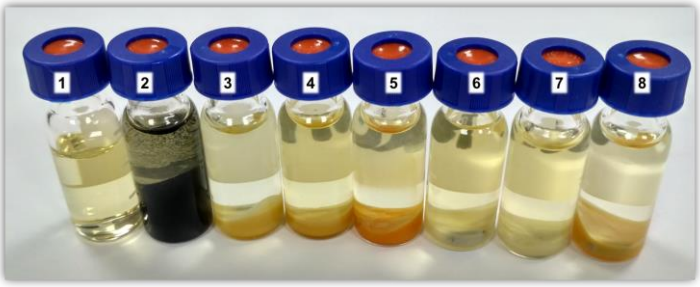


Figure 1 - centrifuged samples post scavenging (numbers correspond to the entries in Table 1)

The three most efficient scavengers were ISOLUTE® Si-TMT (entry **3**, **Table 1**)), SiliaMetS Thiol (entry **5**) and SEM26 (entry **8**), reducing palladium levels by one to two orders of magnitude relative to the EOR control sample.

Entry	Scavenger	[Pd] / ppm
1	EOR Sample (control)	1668
2	DARCO KB-G	633
3	ISOLUTE® Si-TMT	161
4	SiliaMetS DMT	287
5	SiliaMetS Thiol	70
6	SiliaMetS TaCOONa	1145
7	SiliaMetS Triamine	656
8	SEM26	20

Table 1 - residual palladium post-scavenging (average of two measurements)

OPTIMISATION

With proof-of-concept established, further studies on these potential scavengers (**Table 1**) were conducted to investigate (i) mass balance or adsorption of **N-2** onto the active carbon or support; (ii) the effect of work-up on scavenging efficiency; and (iii) the influence of atmosphere on oxidation of the palladium species during scavenging.

Activated carbons were screened under nitrogen and air where the mass loss in **N-2** ranged from 18-36%; scavenging was poor and therefore further investigations with carbons were discontinued.

The silica scavengers were screened under (i) a nitrogen atmosphere without work-up; and (ii) under air after an acidic work-up. The mass recovery of **N-2** following treatment with the silica scavengers was superior to the carbons, ranging from 95-80%. Scavenging under air was found to be more efficient than scavenging under nitrogen in all cases, allowing for the loadings of SiliaMetS Thiol and SEM 26 to be optimised (**Figure 2**). Gratifyingly, the mass recovery of **N-2** remained near quantitative at 50 °C for both scavengers at all loadings over 4 hours. After a 24-hour period the mass recovery for SiliaMetS Thiol (0.15 w/w) had reduced to 94% while for SEM 26 it was 98%.

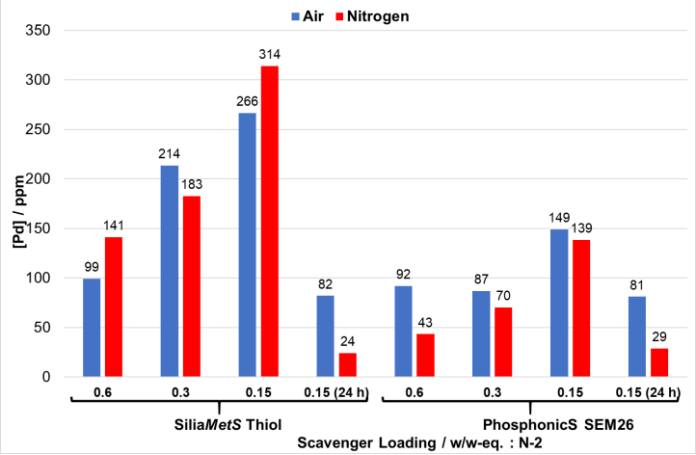


Figure 2 - scavenging efficiency against loading (4 h, 50 °C)
$[Pd]_0$ = 2654 ppm (post HCl work-up) and 1746 ppm (EOR without work-up)

SCALING-UP SCAVENGING

Two 10 mL samples from a 5 g (10 vol) reaction that had been subjected to an acidic work up, each representing nominally 1 g **N-2**, were subjected to scavenging at 50 °C. SiliaMetS Thiol and SEM26 were used at 0.15 w/w loading under nitrogen over 24 hours (**Table 2**). The efficiency of scavenging was poorer for SiliaMetS Thiol on this scale than during the previous experiments, whereas SEM26 performed nearly as well at both scales. Unfortunately, the mass recovery for both scavengers was poorer on scale-up owing to decomposition of **N-2**.

	Trial Scale (150 mg of compound **N-2**)		**Batch Scale** (1 g of compound **N-2**)	
Scavenger	**[Pd] / ppm**	**Mass Recovery / %**	**[Pd] / ppm**	**Mass Recovery / %**
SiliaMetS Thiol	24	95	221	89
SEM26	29	98	53	93

Table 2 - efficiency of scavenging *vs.* scale

EXPERIMENTAL PROCEDURE

Screening experiments were conducted using a 5 g (10 vol) reaction in MEK post an acidic work-up under air. According to the scavenging design EOR samples (1.50 mL) were added to pre-weighed amounts of scavenger in LC vials containing micro-stirrer bars and heated with stirring to 50 °C. After the requisite amount of time samples were centrifuged at 4000 rpm for 5 min and the supernatant was separated and analysed by UPLC and ICP-MS. An internal standard was employed in the scale-up study to quantify reaction conversion and the mass recovery of **N-2** after scavenging.

FLOW SCAVENGING

In order to facilitate tactical delivery of a scavenging protocol that could be used on a process scale SiliCycle's E-PAK purification system was trialled with SiliaMetS Thiol. A 10 g (20 vol) reaction post hydrochloric acid work-up, was scavenged under air at ambient temperature, using a peristaltic pump with a PTFE head and tubing. After the first column pass the system was continuously recirculated at a flowrate of 5 mL min^{-1} for 4 hours, and samples were taken for analysis (**Figure 3**, t = 0 h: 1 column pass; t = 4 h: 9 column passes).

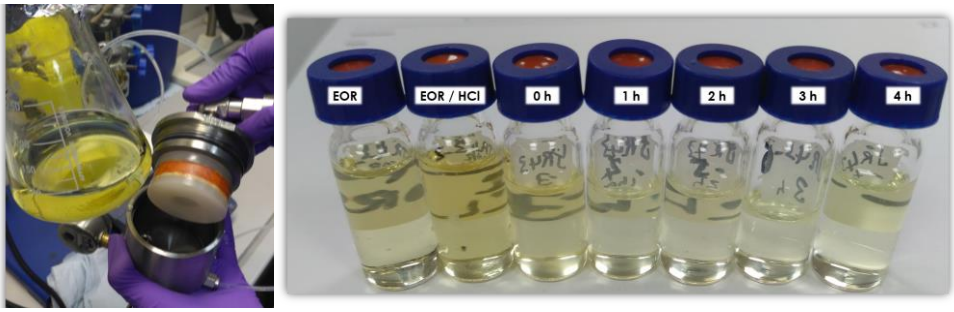


Figure 3 - scavenged **N-2** and Spent E-PAK Cartridge (LHS) & Pre *vs.* post E-PAK scavenging (RHS)
Key - 1 – EOR sample **2** – EOR post work-up **3** – 0 h **4** – 1 h **5** – 2 h **6** – 3 h **7** – 4 h

UPLC data from samples 1-7 demonstrated that near quantitative mass recoveries for **N-2** were achieved throughout with very high purity and decomposition was not observed. Recirculating scavenging with the SiliaMetS Thiol E-PAK cartridge allowed for >90% purge of palladium from **N-2** in 4 hours at ambient temperature under air (**Figure 4**). Further reduction of the residual palladium levels could be achieved by increasing the scavenging time and/or temperature (shifting the position of equilibrium towards palladium binding) or by adding another column in series.

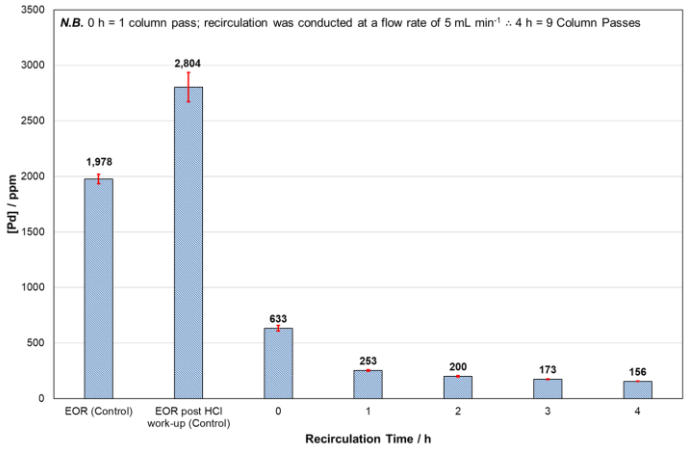


Figure 4 - scavenging efficiency with recirculation time

CONCLUSION

Two functionalised silicas, SiliaMetS Thiol and SEM26, were identified as efficient scavengers for the removal of palladium from **N-2**. Performing scavenging on the neutral compound, post hydrochloric acid work-up, led to high mass recoveries. Loadings of functionalised silica down to 0.15 w/w can be employed with extended reaction times in batch experiments to give <50 ppm levels of residual palladium. The use of SiliaMetS Thiol in an E PAK cartridge system under flow has been demonstrated to lead to a >90% purge of palladium under recirculating conditions in just four hours under ambient conditions.

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