Rapid, Inexpensive, and Selective Removal of Palladium Catalyst from a Suzuki Reaction using Strata™-XL-AW Solid Phase Extraction (SPE)

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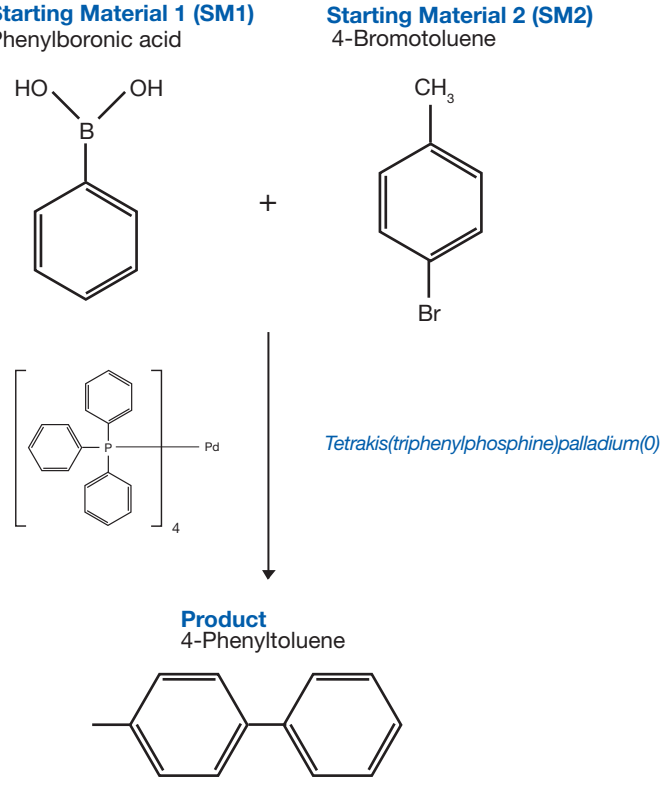
This study evaluates the performance of palladium removal from a Suzuki reaction using Strata-XL-AW solid phase extraction (SPE). It was determined that the large particle Strata-XL-AW sorbent provided a rapid, inexpensive, and selective method for palladium removal from a Suzuki reaction without compromising the purity or recovery of the final product in the post reaction mixture.

Introduction

Palladium, discovered in 1803, is commonly used in catalytic convertors and was even used as a treatment for tuberculosis at one time. Its catalytic properties make it a common addition to facilitate carbon-carbon bond forming reactions such as the Heck and Suzuki reactions (**Figure 1**). These reactions are used by medicinal chemists in the synthesis of intermediates and final products for drug candidates. Along the synthetic pathway, it may be required to remove or scavenge the palladium catalyst to proceed to the next reaction or for purification of an API final product. Purification methods may also include a preparative HPLC chromatography step where presence of palladium in the mixture will quickly destroy expensive preparative HPLC columns. The goal of this study was to determine a quick, inexpensive, and selective process for palladium removal from Suzuki reaction products.

Materials and Methods

Figure 1.
Suzuki Reaction



Reaction Conditions	
Solvent:	100 mL Toluene
Substrates + Additives:	1) Phenylboronic acid: 3.60 g, [0.0295 moles = 5.7 eq. (excess)] 2) 4-Bromotoluene: 1.24 mL = 0.892 g, [0.00522 moles = 1 eq] 3) Sodium carbonate: 1.0 g 4) Catalyst: Tetrakis(triphenylphosphine) palladium(0) 0.35 g, [0.000303 moles = 0.058 eq]
React:	Set temperature to 70 °C and allow to react for 24 hours on orbital shaker.

Substrates and additives were obtained from Sigma Aldrich.

Reaction Purification (Palladium Scavenging)	
Cartridge:	Strata-XL-AW, 500 mg/6 mL
Part No.:	8B-S051-HCH
Condition:	NOT REQUIRED
Equilibrate:	NOT REQUIRED
Load:	Load post Suzuki reaction mixture directly onto cartridge. Collect flow through.
Wash:	Pass 2 mL toluene through the sorbent and pool with the collected flow through that resulted from the load step.

Reaction Monitoring

Reaction monitoring was performed using a binary pump HPLC equipped with a UV DAD detector. An injection volume of 5 µL cleaned up sample was injected. Pre- and post-scavenging samples were monitored as outlined in **Tables 2 and 3**.

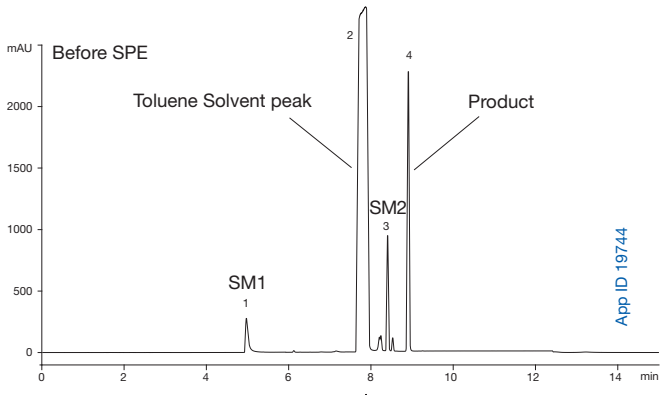
Palladium Removal Quantitation

ICP (inductively coupled plasma) MS was performed by Exova Laboratories to quantitate palladium removal.

Results and Discussion

A simple Suzuki reaction was performed to illustrate the removal of the palladium catalyst and subsequent non-removal of the reaction product using Strata-XL-AW as a scavenging resin. HPLC/UV was used to monitor the reaction and verify that the reaction product 4-phenyltoluene was made.

Figure 2.
HPLC chromatogram of post reaction mixture including phenylboronic acid (SM1), 4-bromotoluene (SM2), and the reaction product, 4-phenyltoluene.



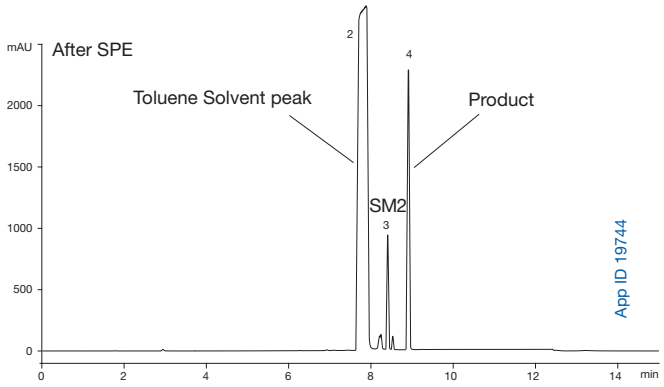
Column: Kinetex® 2.6 µm C18
Dimensions: 150 x 4.6 mm
Part No.: 00F-4462-E0
Mobile Phase: A: 0.1 % TFA in water
B: 0.1 % TFA in acetonitrile
Gradient:

Time (min)	% B
0	5
7	95
10	95

Flow Rate: 1.0 mL/min
Detection: UV @ 254 nm
Temperature: Ambient
Sample: 1. Phenylboronic acid (SM1)
2. Toluene solvent peak
3. 4-Bromotoluene (SM2)
4. 4-Phenyltoluene (Product)

Figure 2 confirms the presence of the reaction product and both starting materials. This post reaction mixture was then passed through the Strata™-XL-AW resin to selectively remove the palladium metal catalyst. Once again, HPLC/UV was performed on the sample to confirm the presence of the product after the reaction mixture was passed through the Strata-XL-AW cartridge.

Figure 3.
HPLC chromatogram of the reaction mixture after passing through Strata-XL-AW cartridge



Running conditions were the same as detailed in **Figure 2**.

As the HPLC chromatogram illustrates, the concentration of final product was not affected by the Strata-XL-AW clean up step. **Figure 3** also shows the removal of phenylboronic acid (SM1). The phenylboronic acid was added in excess, so its removal was a welcomed benefit of the scavenging procedure. The HPLC/UV analysis of the sample before and after scavenging on Strata-XL-AW also allowed for accurate quantitation of the percent removal of the starting materials and product from this step. Results are shown in **Table 1**.

Table 1.
Peak areas of reaction substrates and product from HPLC/UV chromatograms shown in **Figures 2** and **3**.

	Area Before Scavenging	Area After Scavenging	Percent Removal
Phenylboronic acid (SM1)	1251	0.000	100 %
4-Bromotoluene (SM2)	1857	1836	0.50 %
4-Phenyltoluene (Product)	5839	5851	-0.20 %

Once it was determined that there was no loss of final product, the palladium content in the post-extracted mixture was measured to determine percentage of palladium removal by the Strata-XL-AW resin. Prior to measuring the percentage of palladium removed, the theoretical maximum concentration of palladium was calculated to equal 322 ppm. The actual concentration of palladium was measured to be 200 ppm using ICP analysis. The difference between the calculated concentration and the actual concentration is most likely due to unreacted palladium which was visible as a black solid at the bottom of the reaction mixture.

Table 2
Palladium concentrations measured before and after passing through the Strata-XL-AW scavenging resin. Results were measured using ICP-MS courtesy of Exova Laboratories.

	Before Strata-XL-AW Theoretical Max Conc. (ppm)	Before Strata-XL-AW Actual Conc. (ppm)	After Strata-XL-AW Actual Conc. (ppm)	Percent Removal
Palladium	322	200	0.07	99.9 %

As **Table 2** illustrates, 99.9% of palladium was removed from the reaction mixture. The data from this study confirms the selective removal of palladium catalyst using Strata-XL-AW to clean up synthetic reactions. The mechanism by which the palladium was successfully removed was via a coordinate covalent bond being formed between the lone pair of electrons on the primary/secondary amine of the Strata-XL-AW chemistry and the empty d-orbital of the palladium in the tetrakis molecule. Such a mechanism of the Strata-XL-AW allows it to be utilized for selective palladium removal in many synthetic chemistry reactions such as the Suzuki reaction used in this study.

APPLICATIONS

Conclusion

Removing palladium catalysts from reaction mixtures has often plagued synthetic chemists. As mentioned, the presence of colloidal palladium in a mixture can have detrimental effects on the lifetime of the analytical, semi-preparative, and preparative HPLC columns. We have demonstrated that a quick, inexpensive, and selective process for palladium removal is achievable using the Strata™-XL-AW SPE resin. This process can be implemented easily in any laboratory without the purchase of special equipment or any capital investment.

Ordering Information

Strata-XL-AW SPE

Sorbent Mass	Part No.	Unit
Tube		
30 mg	8B-S051-TAK	1 mL (100/box)
60 mg	8B-S051-UBJ	3 mL (50/box)
100 mg	8B-S051-EBJ	3 mL (50/box)
100 mg	8B-S051-ECH	6 mL (30/box)
200 mg	8B-S051-FBJ	3 mL (50/box)
200 mg	8B-S051-FCH	6 mL (30/box)
500 mg	8B-S051-HBJ	3 mL (50/box)
500 mg	8B-S051-HCH	6 mL (30/box)
Giga™ Tube		
2 g	8B-S051-KDG	12 mL (20/box)
2 g	8B-S051-KEG	20 mL (20/box)
5 g	8B-S051-LEG	20 mL (20/box)
5 g	8B-S051-LFF	60 mL (16/box)
10 g	8B-S051-MFF	60 mL (16/box)
20 g	8B-S051-VFF	60 mL (16/box)

Kinetex® Core-Shell HPLC/UHPLC Columns

1.7 µm Minibore Columns (mm)

	50 x 2.1	100 x 2.1	150 x 2.1
C18	00B-4475-AN	00D-4475-AN	00F-4475-AN

2.6 µm Minibore Columns (mm)

	50 x 2.1	75 x 2.1	100 x 2.1	150 x 2.1
C18	00B-4462-AN	00C-4462-AN	00D-4462-AN	00F-4462-AN

2.6 µm Solvent Saver MidBore™ Columns (mm)

	50 x 3.0	75 x 3.0	100 x 3.0	150 x 3.0
C18	00B-4462-Y0	00C-4462-Y0	00D-4462-Y0	00F-4462-Y0

2.6 µm Analytical Columns (mm)

	50 x 4.6	75 x 4.6	100 x 4.6	150 x 4.6
C18	00B-4462-E0	00C-4462-E0	00D-4462-E0	00F-4462-E0

More dimensions and phases available, please inquire.

If Phenomenex products in this technical note do not provide at least an equivalent separation as compared to other products of the same phase and dimensions, return the product with comparative data within 45 days for a FULL REFUND.

APPLICATIONS

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