SiliaMetS®

Metal Scavengers

Distributed by

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Greyhound CHROMATOGRAPHY AND ALLIED CHEMICALS

Metal Scavenging with Silia*MetS*®

Silia*Bond* Metal Scavengers BECOME Silia*MetS* Metal Scavengers!

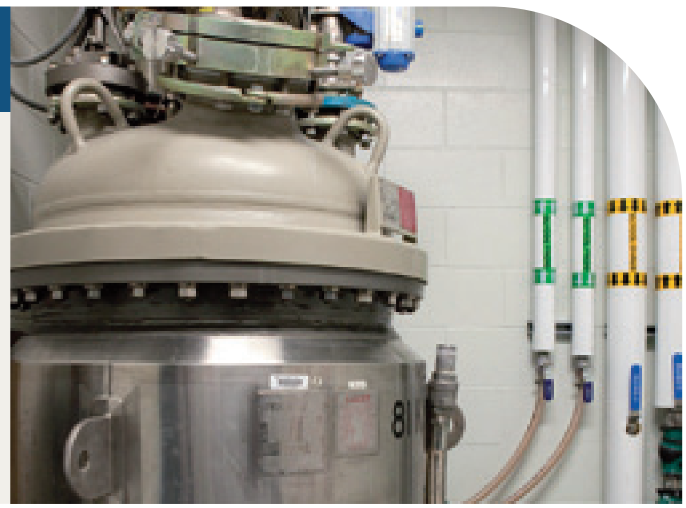
Same Efficient & High Quality Metal Scavenger Products, Brand New Look!

SiliCycle has developed a new look and a new brand for our Metal Scavengers. These products, known as Silia*Bond* Metal Scavengers (*i.e.: SiliaBond Thiol*), are now named Silia*MetS* (*i.e, SiliaMetS Thiol*) with a new color code. We have updated our branding to give more visibility to our metal removal solutions. This new branding will help differentiate these products from other functionalized silica gels available (*reagents and other bonded phases*).

Although we changed our branding from Silia*Bond* Metal scavengers to Silia*MetS*, no change has been made to the products themself; you will still be purchasing the same quality products that you have been enjoying for years.

SiliCycle is THE world leader and THE pioneer in metal scavenging solutions. Reasons to choose us:

- Over 12 years of know-how in silica-grafting and metal scavenging technology
- Strong, extensive, and confidential technical support and scientists to help you
- Broadest portfolio of scavengers (*wide variety of ligands*) and applications developed
- Wide range of formats for all purification scales; from laboratory to plant scale purifications
- Cited in many external publications (*and patents*) used by satisfied customers



Introduction

In recent years, the time pressure associated with quickly bringing candidate drugs to market has increased the number of transition metal-catalyzed reactions progressing from lead optimization to early scale-up. The removal of post-reaction metal residues has become a major issue in the pharmaceutical industry. Purification of APIs from residual metal catalyst by traditional methods (*chromatography, activated carbon, distillation, etc.*) often leads to problems such as high costs, time loss, low efficiency, and reduced API yields. To overcome these limitations, SiliCycle has developed **Silia*MetS* Metal Scavengers**, a range of products that have significantly changed how chemists purify APIs.

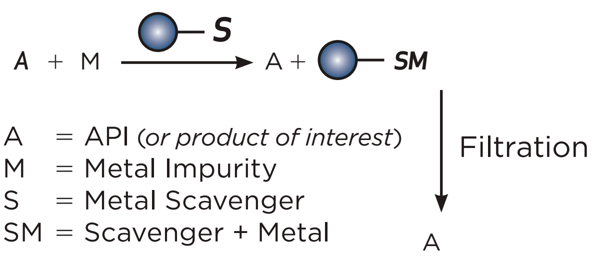
Silica-based metal scavengers have been proven to be the purification method of choice used by several companies from various industries. Take a look at the section "Customer Success Stories with **Silia*MetS***" to read about our satisfied customers. With the silica matrix advantages over polymers (*no swelling, more general solvent compatibility, higher mechanical and thermal stability, easily scalable applications and availability of different formats, including SPE, flash cartridges, and bulk*) and SiliCycle's expertise in grafting technology, **Silia*MetS*** are the solution of choice for metal removal without contamination of drug candidates. **Silia*MetS*** are highly selective and offer a cost-effective alternative for metal removal.

This section includes useful information and tips on **Silia*MetS*** (*properties and selection chart*) uses, experimental procedures, and results.

What are Silia*MetS* Metal Scavengers?

Silia*MetS* Metal Scavengers are functionalized silica gels designed to react and bind excess metal complexes. The process for using scavengers is outlined in the scheme below.

What is a Supported Metal Scavenger?



A = API (*or product of interest*)
M = Metal Impurity
S = Metal Scavenger
SM = Scavenger + Metal

To be effective, the Metal Scavengers need the ability and inherent functionality to remove metals in their various oxidation states from the reaction mixture. For example, upon completion of a palladium metal-catalyzed reaction, the metal residue contained in the reaction can exist in both Pd (0) and Pd (II).

Silia*MetS* - Regulatory Information

For many years, Silia*MetS* Metal Scavengers have been used in pilot plants by GMP pharmaceutical, biotechnology, and fine chemical industries as well as contract research and manufacturing organizations. They have run their own analysis proving Silia*MetS* Metal Scavengers can safely be used without compromising the purity of the material by leaching of the silica-supported product.

Thus, SiliCycle is committed to high quality standards and always striges to provide defect-free products. In doing so, all products are manufactured in an ISO 9001:2008 compliant facility and subjected to a stringent quality control. Every lot needs to meet the quality specifications and a sample from every batch is kept for subsequent analysis. All products are shipped with the following information:

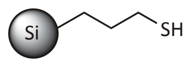
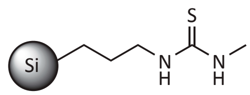
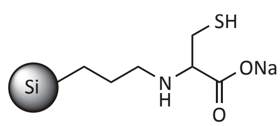
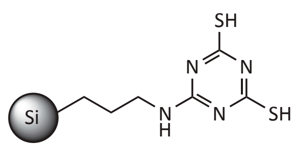
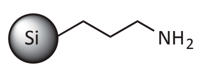
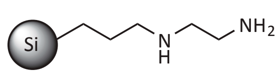
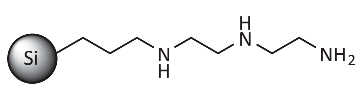
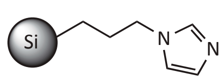
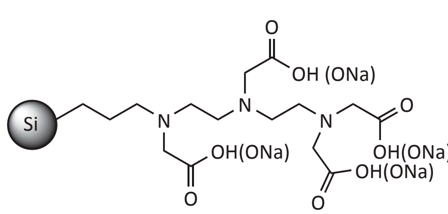
- Certificate of Analysis
  - Purity (*Leachables and extractables*)
  - Molecular loading
  - Surface Coverage
  - Volatile Content
- Material Safety Data Sheets (*MSDS*)
- BSE/TSE Declaration (*no animal origin*)
- Relevant Technical Information

Need specific regulatory files? SiliCycle can work with you to fill your requirements and provide you custom regulatory documentation including specific analytical tests in line with your needs.

Silia*MetS* Product Range

SiliCycle, a leader in functionalized silica gels, has developed a wide range of scavengers to remove a variety of metals at competitive prices.

Silia*MetS* Metal Scavengers Portfolio

Silia*MetS*	Product Number	Structure	Brief Description
Silia*MetS* Thiol	R51030B		**Silia*MetS*** Thiol is our most versatile and robust metal scavenger for a variety of metals under a wide range of conditions. It has been used in pharmaceutical processes up to production scale.
Silia*MetS* Thiourea	R69530B		**Silia*MetS*** Thiourea is a versatile metal scavenger for all forms of palladium and is widely used in the pharmaceutical industry. Once complexed with a transition metal, it has been reported to be an effective catalyst.
Silia*MetS* Cysteine	R80530B		**Silia*MetS*** Cysteine is the silica bound equivalent of the amino acid cysteine. It is a versatile scavenger for a variety of metals and the preferred metal scavenger for tin residues. By attaching the molecule to the backbone via the amino group, the thiol group remains free and accessible for higher metal scavenging efficiency.
Silia*MetS* DMT	R79030B		**Silia*MetS*** DMT is the silica-bound equivalent of 2,4,6-trimercaptotriazine (*trithiocyanuric acid, TMT*). It is a versatile metal scavenger for a variety of metals and the preferred metal scavenger for ruthenium catalysts and hindered Pd complexes (*i.e. Pd(dppf)Cl_2*).
Silia*Bond* Amine	R52030B		Better known for their electrophile scavenging efficiency, and their base reagent quality, **Silia*MetS*** Amine, Diamine and Triamine are also proven scavengers for metals. They are very useful for scavenging Pd, Pt, Cr, W and Zn.
Silia*MetS* Diamine	R49030B		
Silia*MetS* Triamine	R48030B		
Silia*MetS* Imidazole	R79230B		**Silia*MetS*** Imidazole is a versatile metal scavenger for a variety of metals including, Cd, Co, Cu, Fe, Ni, Pd, Os, and Rh, under a wide range of conditions and the preferred metal scavenger for iron catalysts.
Silia*MetS* TAAcOH	R69030B		**Silia*MetS*** TAAcOH & TAAcONa (*Si-Triaminetetraacetic Acid or Sodium Salt*) are supported versions of EDTA in their free and sodium salt forms. These two products are effective metal scavengers for Ca, Mg, Li, Ir, Cs, Os, Sn, Pd, Ni and Cu. **Silia*MetS*** TAAcOH is effective for metals in low or zero oxydation states, compared to **Silia*MetS*** TAAcONa which is useful for metals in higher oxydation states (*2+ or higher*).
Silia*MetS* TAAcONa	R69230B		

All **Silia*MetS*** are made of standard flash silica gel, namely 40 - 63 microns, 60 Å.

Metals Removed	SiliaMetS Typical Characteristics						SiliaMetS
	Color	Endcapping	Molecular Loading	Typical Tap Density	Solvent Compatibility	Prolonged Storage	
Ag, Hg, Os, Pd^{2+}, Pd^{0} & Ru Cu, Ir, Pd, Rh^{1+}, Rh^{2+}, Rh^{3+}, Sc, Sn	White	Yes	1.20 mmol/g	682 g/L	All solvents, aqueous and organic	Keep dry	**Silia*MetS*** Thiol
Pd^{2+}, Pd^{0} Ag, Cu, Fe, Os, Rh^{1+}, Rh^{2+}, Rh^{3+}, Sc, Sn	Off-white	Yes	1.20 mmol/g	767 g/L	All solvents, aqueous and organic	Keep dry	**Silia*MetS*** Thiourea
Cd, Fe, Ir, Os, Ru, Sc & Sn Ca, Cr, Cs, Cu, La, Mg, Pd^{2+}, Pd^{0}, Pt, Rh^{+1}, Rh^{+2} & Zn	Orange	Yes	0.30 mmol/g	665 g/L	All organic solvents	Keep dry under argon	**Silia*MetS*** Cysteine
Ir, Ni, Os, Pd^{2+}, Pd^{0}, Pt, Rh^{+1}, Rh^{+2}, Rh^{+3} & Ru Cd, Co, Cu, Fe, Sc & Zn	Light brown	Yes	0.50 mmol/g	732 g/L	All solvents, aqueous and organic	Keep dry	**Silia*MetS*** DMT
Cd, Cr, Pt, Rh^{+1} & Rh^{+2} Co, Cu, Fe, Hg, Pb, Pd^{+2}, W & Zn	Off-white	Yes	1.20 mmol/g	700 g/L	All solvents, aqueous and organic	Keep cool (<8°C) and dry	**Silia*Bond*** Amine
Cr, Pd^{2+}, Pd^{0}, & Pt Cd, Co, Cu, Fe, Hg, Ni, Pb, Ru, W & Zn	Off-white	Yes	1.20 mmol/g	728 g/L	All solvents, aqueous and organic	Keep cool (<8°C) and dry	**Silia*MetS*** Diamine
Cr, Pb, Pd^{2+}, Pd^{0} & Pt Co, Cu, Fe, Ni, Ru, W & Zn	Off-white	Yes	1.20 mmol/g	736 g/L	All solvents, aqueous and organic	Keep cool (<8°C) and dry	**Silia*MetS*** Triamine
Cd, Co, Cu, Fe, Ni, Os, W & Zn Cr, Pd^{2+}, Pd^{0}, Rh^{1+} & Rh^{2+}	Off-white	Yes	1.20 mmol/g	681 g/L	All solvents, aqueous and organic	Keep dry	**Silia*MetS*** Imidazole
Co, Ni, Os & Sc Cr, Cs, Fe, Pd^{2+}, Pd^{0}, Rh^{1+}, Rh^{2+} & Sn	Off-white	No	0.40 mmol/g	635 g/L	All solvents, aqueous and organic	Keep dry	**Silia*MetS*** TAAcOH
Cd, Cs, Cu, Fe, Ir, La, Li, Mg, Ni, Os, Rh^{3+}, Sc, & Sn Cr, Pd^{2+}, Pd^{0}, Rh^{1+}, Rh^{2+} & Zn	Off-white	No	0.40 mmol/g	712 g/L	All solvents, aqueous and organic	Keep dry	**Silia*MetS*** TAAcONa

Preferred SiliaMetS Metal Scavengers for these metals ***Also Scavenges these metals***

Features & Benefits of Silia*MetS* Metal Scavengers

Silia*MetS* Metal Scavengers are functionalized silica gels designed to react and bind excess metal complexes. The process for using scavengers is outlined in the scheme on page 87.

Features & Benefits of Silia*MetS*

Features	Benefits
No leaching	No API contamination by the metal scavenger
Very High Purity	Each Silia*MetS* product manufactured is submitted to very rigorous quality control in order to provide customers with default-free products and ensure 100% satisfaction
High Selectivity	Total recovery of the API
Wide Range of Metal Species (*various oxidation state*)	Efficient for a wide range of metal catalysts
Fast Kinetics	Even at room temperature
Cost Efficient	Low cost per gram of metal scavenged Less solvent used
Solvent Compatibility	Can be used in any solvent, aqueous (*pH 2 to 12*) and organic
New Technologies Compatibility	Suitable for use in microwave synthesizers and flow chemistry
Excellent Stability (*Thermally and Mechanically*)	Works well with overhead stirring Can withstand very high temperatures
Ease of Use & Scalable	No swelling or static charge Remove easily by a simple filtration Scalable from mg up to multi-ton scale
Various Formats	Amenable to use in Silia*Sep* & Silia*Prep* Cartridges
Controlled Loading	Consistent and accurate loading insure lot-to-lot reproducibility
Available in Bulk Quantities	Available in large quantities and always in stock

Metal Scavenging Screening Service

CONFIDENTIALITY ASSURED

Having a problem removing any residual metal catalyst? Contact us to take advantage of SiliCycle's expertise in metal removal. Our R&D team can find the optimal conditions for you.

Metal Scavenger Screening Services are innovative as they provide an on-hand solution to the pharmaceutical and manufacturing industries. Working with the product that needs to be free of residual metals and the restricted conditions that can be used with the compound (*i.e, solvent, temperature*), SiliCycle's **Metal Scavenger Screening Service** will quickly develop the most efficient metal scavenging process providing both time and cost savings. Confidentiality is assured, as in most cases the solution involves working with API and other patented materials, and easy technology transfer is guaranteed.

Take the step many major pharmaceutical companies have, and contact us to discuss how we can help you to reach your metal purity goals.

Many screening services adapted to your needs & budgets are available.

Silia*MetS* - Typical Experimental Procedures

Screening in Batch Reactor Mode (*bulk*)

To select the best scavenger for initial screening experiments, do the following steps for each Silia*MetS* Metal Scavengers included in the kit. Use 4-8 molar equivalents of each Silia*MetS* in respect to the residual metal concentration.

1. Dissolve the crude product to be treated in a suitable solvent (*or use directly the crude reaction mixture*) and prepare vials containing the same solution volume.
2. Directly, add each Silia*MetS* included in the kit to these vials.
   Note: no pre-wetting of the Silia*MetS* is required. See "Determing the Optimal Amount of Silia*MetS* to use" at page 96.
3. For initial tests, stir the solution for at least one hour at room temperature.
4. Scavenging progress can be followed by normal analytical techniques. The scavenging progress can be estimated by looking at the color of the solution as demonstrated in the figure (*right*). When the scavenging is almost complete, the solution is less colored and Silia*MetS* becomes colored. In some occasional cases, if all the samples are still coloured, try one or all of the following: let them react for a longer period of time; add more equivalents of the Silia*MetS*, increase the temperature of the reaction.

5. At the end of the scavenging, filter off the Silia*MetS* using a fritted funnel or filtration device.
6. Wash the Silia*MetS* with additional solvent for total recovery of the API (*or compound of interest*) and concentrate the solution under vacuum.
7. Analyze the residual metal concentration of each vial to identify the most efficient Silia*MetS* Metal Scavenger

   Note: you can choose more than one scavenger.
8. If you are satisfied with the scavenging efficiency of the best Silia*MetS*, direct scale-up is possible. Otherwise, scavenging optimization can be done with Silia*MetS* identified in #7 (*see next section*).

Screening with Silia*MetS* Fixed Bed Mode (*SPE or Flash Cartridges*)

Silia*MetS* fixed bed formats are a great alternative for metal removal and are directly scalable. Initial screening investigations can be done using Silia*Prep* 2g/6mL SPE cartridges.

1. Condition the cartridge with 3-4 cartridge volume using the same solvent as the solution to be treated.
2. Add the solution containing the API and the metal to the top of the cartridge and let it pass through the cartridge under gravity.
   Note: if needed, a slight positive pressure on the top of the cartridge or a light vacuum can be applied to speed up the flow rate.

3. As shown to the right, a dark coloured band will be observed on the top of the silica bed most of the time.
4. If the residual solution is still coloured, multiple passes through the same cartridge can be done.
5. Once the scavenging is completed, wash the cartridge using at least 3 column volumes of solvent to insure total API (*or compound of interest*) recovery.

   Note: in some cases, additional washing may be required.

Silia*MetS* Compatible with New Technologies

Silia*MetS* In Flow Chemistry

Metal scavenging can also be achieved using Silia*MetS* in flow chemistry applications. Simply place Silia*MetS* inside the solid-phase reactors provided with your flow system (*like Syrris Asia® Solid Phase Chemistry Reactors*) and let the solution to be purified flow through these reactors. Multiple reactors can be placed in series and reactors can be heated to obtain optimum scavenging results.

Silia*MetS* In Microwave

Metal removal using Silia*MetS* can also be done under microwave irradiation to provide excellent scavenging efficiency in just minutes. Simply mix the scavenger and the API dissolved in a suitable solvent a microwave tube and set-up the system with the appropriate parameters. Usually, 5 minutes is enough to scavenge all residual metals.

Experiment Optimization with Silia*MetS*

If, upon completion of the screening procedure, the scavenging is not complete or you wish to either reduce the number of equivalents or the reaction time, optimization steps can be undertaken.

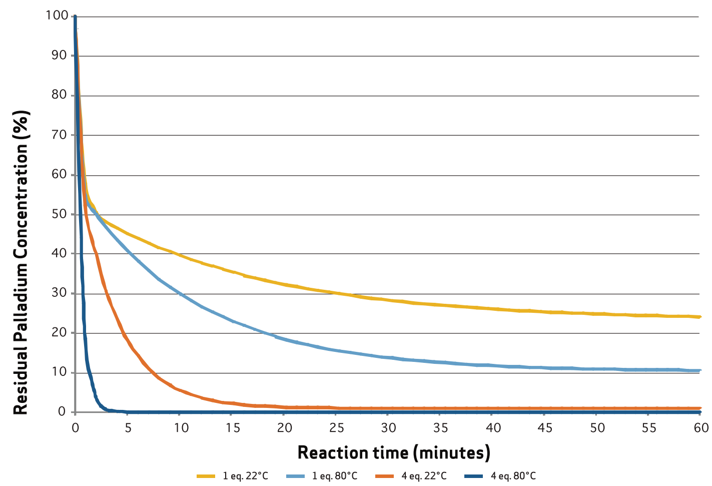
Various parameters can be changed one at a time or simultaneously to improve the metal removal efficiency.

Note: you can mix multiple Silia*MetS* to get superior efficiency.

Number of Silia*MetS* Equivalents

For initial screening experiments we suggest 4-8 molar equivalents be used in respect to the residual metal concentration of each Silia*MetS*. Once the preferred scavenger is identified, further optimization can be done to reduce the number of equivalents used (*typically down to 2-4 equivalents*).

Graph represents residual concentration (%) of $Pd(OAc)_2$ with Silia*MetS Thiol in DMF.*



Subsequent Treatments with Silia*MetS*

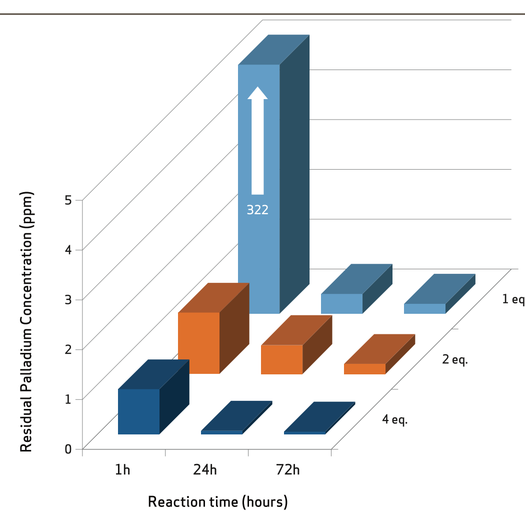
In some cases (*equilibrium process or the presence of multiple species*), multiple treatments with Silia*MetS* is suitable instead of a single treatment with a larger amount.

For optimal results, filtration between each treatment can allow for a higher scavenging efficiency.

Reaction Time

In some cases, where increasing the temperature is impossible, longer contact time with the scavenger can allow higher scavenging efficiency.

Conditions: $Pd(OAc)_2$, THF, SiliaMetS Thiol, RT.

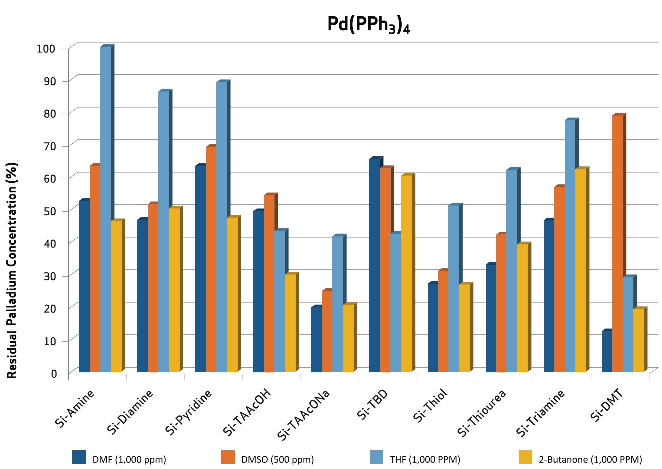


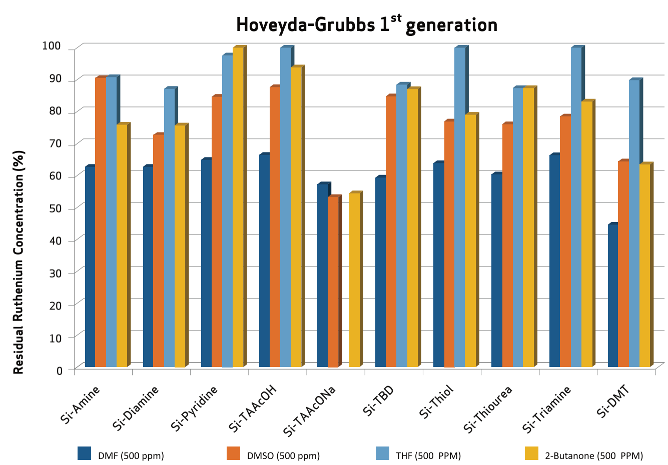
Temperature

In initial screening, we suggest the scavenging experiments be run at room temperature. Usually, metal scavenging is completed after one hour or so. However, when shorter scavenging times are required, higher scavenging rates can be achieved by increasing the temperature. Silia*MetS* can be safely used at elevated temperature without degradation and can be added either at room temperature or directly to a warm solution.

Solvent

Silia*MetS* can safely be used in a wide range of organic and aqueous solvents commonly used in laboratory and in process, such as DMF, DMSO, THF, 2-butanone, alcohols, ethers, chlorinated solvent, etc. As demonstrated in the graphs below, the nature of the solvent does sometimes influence scavenging efficiency. If scavenging or kinetics are too slow, changing solvent or adding a co-solvent should be considered.





Silia***MetS*** Format (*Mode Used*)

One advantage of Silia*MetS* is their compatibility with various technologies. They can be used in batch, in fixed bed (*SPE or Flash cartridges*), in flow chemistry, or in microwave. Scavenging efficiency can be improved by changing the mode used.

Mixing Rate

Silia*MetS* are mechanically stable and offer excellent scavenging efficiency in batch processes agitated by overhead and magnetic stirrers, as well as orbital shaking under low to moderate agitation rates. If required, mixing rates can be increased to get better scavenging results. With faster stirring, you improve Silia*MetS* dispersion in solution.

pH of the Aqueous Solution

When the scavenging is done in aqueous solutions, it is possible to use Silia*MetS* in a pH range of 2 to 12. Depending on the nature of the Silia*MetS*, pH can modify the functional groups present on the scavengers by charging them. Scavenging can be affected (*i.e, amine groups in acidic conditions*).

Determining the Optimal Amount of Silia*MetS*

To get an effective metal removal, the amount of Silia*MetS* Metal Scavenger used is very important. You can determine how much scavenger will be needed by one of two ways:

- from the residual concentration (*more accurate method*)
- from the amount of metal catalyst used (*when the residual metal concentration is unknown*)

From residual metal concentration (*ppm*)

Knowing that the palladium (*Pd*) level in 800 g of material is 500 ppm
(*the oxidation state does not affect the calculation*).

Data needed:

- Loading of the scavenger (*SiliaMetS Thiol*): 1.2 mmol/g
- Metal molecular weight: Ex. Pd = 106.42 g/mol
- Amount of product to be treated : Ex. 800 g
- Residual concentration of metal: Ex. 500 ppm of Pd

1. Determine the amount of palladium to be scavenged

$$\text{Amount of Pd in mg} = \frac{\text{Residual metal concentration x Qty of product to be treated}}{1{,}000}$$

$$\text{Amount of Pd in mg} = \frac{500 \text{ ppm x } 800 \text{ g of product}}{1{,}000} = 400 \text{ mg of Pd in } 800 \text{ g of product}$$

$$\text{Conversion in mmol of Pd} = \frac{\text{Amount of Pd in mg}}{\text{Metal molecular weight}}$$

$$\text{Conversion in mmol of Pd} = \frac{400 \text{ mg}}{106.42 \text{ g/mol}} = 3.76 \text{ mmol of Pd}$$

2. Calculate the amount of scavenger (*SiliaMetS Thiol*) to use (*1 equivalent*)

$$\text{Amount of SiliaMetS Thiol to use} = \frac{\text{Number of mmol of metal concentration}}{\text{SiliaMetS Thiol loading}}$$

$$\text{Amount of SiliaMetS Thiol to use} = \frac{3.76 \text{ mmol of Pd}}{1.2 \text{ mmol/g}} = 3.13 \text{ g of SiliaMetS Thiol for 1 eq.}$$

To scavenge 400 mg of palladium, 3.13 g of Silia*MetS* Thiol is needed if using only one equivalent. However, it is highly recommend that a minimum of 4 equivalents be used at first. In this case, the amount of Silia*MetS* Thiol will be 4 times higher (*4 x 3.13 g = 12.52 g*).

Sometimes, the metal residual concentration is unknown. In such a case, the amount (*g*) of palladium to be scavenged can be replaced by the amount of metal catalyst used for the reaction:

From amount of metal catalyst used

Data needed:

- Amount of metal catalyst used: Ex. 10 g of $Pd(PPh_3)_4$
- Metal catalyst molecular weight: $Pd(PPh_3)_4$ = 1,155.56 g/mol

1. Determine the amount of palladium to be scavenged

$$\text{Amount of Pd in mmol} = \frac{\text{Qty of catalyst used for the reaction used x } 1{,}000}{\text{Metal catalyst molecular weight}}$$

$$\text{Amount of Pd in mmol} = \frac{10 \text{ g of } Pd(PPh_3)_4 \text{ x } 1{,}000}{1{,}155.56 \text{ g/mol}} = 8.65 \text{ mmol of Pd } (\textit{max to be scavenged})$$

The amount of Silia*MetS* Thiol to be used can then be determined as stated above (*see point 2. above*). In this particular case, one equivalent of Silia*MetS* Thiol corresponds to 7.20 g.

Silia*MetS* Selection Guide

When selecting a metal scavenger, every parameter must be considered: metal catalyst, solvent, residual reagents, by-products, structure of the API (*or molecule of interest*) and temperature. The following table, shown below, helps customers in selecting the most efficient scavenger for a specific metal and application. However, since some parameters may affect the efficiency of the scavenging, we highly recommend performing a preliminary screening experiment using the Silia*MetS* Metal Scavenger Kit.

SiliCycle also offers a confidential Metal Scavengers Screening Service. Contact us to take advantage of our expertise in metal removal. See page 93 to learn more about this service.

Silia*MetS* Metal Scavenger Selection Table

Scavenger	Ag	Ca	Cd	Co	Cr	Cs	Cu	Fe	Hg	Ir	La	Li	Mg	Ni	Os	Pb	Pd (II)	Pd (0)	Pt	Rh (I)	Rh (II)	Rh (III)	Ru (II)	Sc	Sn	W	Zn
Si-Thiol	■						□		■	□					■	□	■	■		□	□	□			□		
Si-Thiourea	□						□	□							□		■	■		□	□	□		□	□		
Si-Cysteine		□	■		□	□	□	■		■	□		□		■		□	□	□	□	□		■	■	■		□
Si-DMT			□	□			□	□		■				■	■		■	■	■	■	■	■	■	□			□
Si-Amine			■	□	■		□	□	□							□	□		■	■	■					□	□
Si-Diamine			□	□	■		□	□	□					□		□	■	■	■				□			□	□
Si-Triamine				□	■		□	□						□		■	■	■	■				□			□	□
Si-Imidazole			■	■	□		■	■						■	■		□	□		□	□					■	■
Si-TAAcOH				■	□	□		□						■	■		□	□		□	□			■	□		
Si-TAAcONa		■	■		□	■	■	■		■	■	■	■	■	■		□	□		□	□	■	□	■	■		□

■ Preferred scavengers □ Scavenges

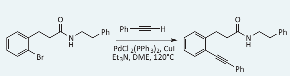
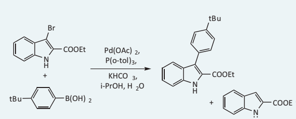
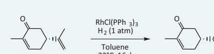
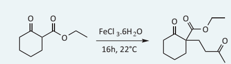
Silia*MetS* Selection Guide *(con't)*

Silia*MetS* Metal Scavengers Selection Guide (*Only Catalyst in Solution*)

Silia*MetS*	Catalyst, Solvent & Conditions (*% of catalyst scavenged*)							
	$Pd(OAc)_2$ DMF 4 eq., 4 h, 22°C	$Pd_2(allyl)_2Cl_2$ DMF 4 eq., 4 h, 80°C	$Pd_2(dba)_3$ DMF 4 eq., 4 h, 22°C	$Pd(PPh_3)_4$ DMF 4 eq., 4 h, 80°C	$PdCl_2(dppf)$ DMF 4 eq., 4 h, 22°C	Grubbs 1st Gen. DMF 8 eq., 16 h, 80°C	Grubbs 2nd Gen. DMF 8 eq., 16 h, 80°C	Hoveyda-Grubbs 1st DMF 8 eq., 16 h, 80°C
Silia*MetS* Thiol	> 99	> 99	98	98		96	99	93
Silia*MetS* Thiourea	> 99	> 99	98	91		98	96	98
Silia*MetS* Cysteine	not screened	not screened	not screened	98	not screened	not screened	not screened	not screened
Silia*MetS* DMT	98	> 99 [22°C]	> 99	> 99	Pd: 94, Fe: 92	> 99 [4 eq.]	99 [4 eq.]	98 [4 eq.]
Silia*Bond* Amine	98	> 99	97			97		
Silia*MetS* Diamine	> 99	> 99	> 99	90		99	94	98
Silia*MetS* Triamine	> 99	90	> 99	80		95		95
Silia*MetS* Imidazole	not screened	not screened	not screened	not screened		not screened	not screened	not screened
Silia*MetS* TAAcOH	98	93	97 [80°C]					
Silia*MetS* TAAcONa	97		80 [80°C]					

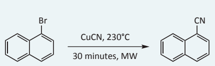
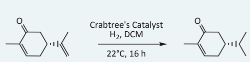
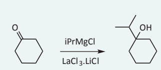
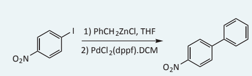
Note: other catalysts results are available on request (*metal screened but not shown: calcium, cobalt, cesium, copper, iron, iridium, lanthane, tin, & tunsgten. Contact us!*)

Silia*MetS* Metal Scavengers Selection Guide (*Catalysts Scavenging in a Reaction*)

Silia*MetS*	Catalyst, Solvent, Condition & Reaction			
	$PdCl_2(PPh_3)_2$, CuI (in DME)  8 eq., 4 h, 22°C Sonogashira Coupling	$Pd(OAc)_2$, $P(o\text{-}tol)_3$ (in i-PrOH, H_2O)  5 eq., 4 h, 40°C Suzuki Coupling	$RhCl(PPh_3)_3$ (in Toluene)  65 eq., 4 h, 22°C Wilkinson Hydrogenation	$FeCl_3.6H_2O$  5 eq., 4 h, 22°C Michael Addition
Silia*MetS* Thiol	Pd: 89, Cu: 29	98		
Silia*MetS* Thiourea	Pd: 72, Cu: 80	92	81	82
Silia*MetS* Cysteine		84	88	> 99
Silia*MetS* DMT	Pd: 98, Cu: > 99	> 99	94	98
Silia*Bond* Amine		80	93	98
Silia*MetS* Diamine		80		> 99
Silia*MetS* Triamine				98
Silia*MetS* Imidazole		88	92	98
Silia*MetS* TAAcOH			81	98
Silia*MetS* TAAcONa			88	> 99

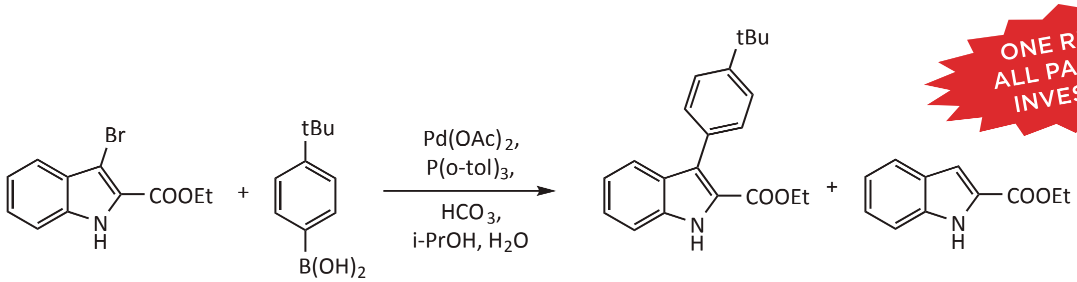
Scavenging > 99 %	Scavenging 95 - 99 %	Scavenging 90 - 94 %	Scavenging 80 - 89 %

Catalyst, Solvent & Conditions (*% of catalyst scavenged*)								
Hoveyda-Grubbs 2nd DMF 8 eq., 16 h, 80°C	TPAP DCM 4 eq., 16 h, 22°C	$Ni(acac)_2$ DMF 4 eq., 4 h, 22°C	Wilkinson's Cat. DMF 4 eq., 4 h, 80°C	$[Rh(OAc)_2]_2$ DMF 4 eq., 4 h, 80°C	H_2PtCl_6 DMF 4 eq., 4 h, 80°C	$Pb(OAc)_2.3H_2O$ DMF 4 eq., 4 h, 22°C	$Zn(OAc)_2.2H_2O$ DMF 4 eq., 4 h, 22°C	Silia*MetS*
	96 [4 eq.]		> 99 [16h]	97	80 [16 h]	97	> 99	Thiol
	> 99		99	97			97 [80°C]	Thiourea
not screened	not screened	92	88	not screened	99		> 99	Cysteine
99 [4 eq.]	> 99 [4 eq.]	97	> 99	> 99	> 99	99	94	DMT
	> 99		> 99	> 99			> 99	Amine
90	97 [4 eq.]	99	> 99	> 99 [22°C]	> 99	81	> 99	Diamine
95	> 99	93	97	97 [22°C]	97	> 99 [80°C]	> 99	Triamine
	not screened	91 [80°C]	90	97 [22°C]	not screened		> 99	Imidazole
	> 99 [4 eq.]	> 99	97	96 [16 h]				TAAcOH
	> 99 [4 eq.]	> 99	88	> 99 [16 h]		90	> 99	TAAcONa

Catalyst, Solvent, Condition & Reaction				
CuCN (in DMF)  10 eq., 4 h, 22°C Rosemund von-Braun Cyanation	ridium Crabtree's Cat. (in DCM)  4 eq., 4 h, 22°C Alkene Hydrogenation	$LaCl_3.LiCl$ (in DMF)  1 eq., 4 h, 22°C 1,2-Addition on Ketone	$PhCH_2ZnCl$ (in THF)  4 eq., 4 h, 80°C Negishi Coupling	Silia*MetS*
94				Thiol
> 99				Thiourea
> 99	86	Li: 75, La: > 99	91	Cysteine
> 99			84	DMT
98			94	Amine
> 99			95	Diamine
> 99			91	Triamine
95			94	Imidazole
80				TAAcOH
> 99	80	Li: 95, La: > 99	94	TAAcONa

Silia*MetS* - A GlaxoSmithKline Case Study[1]

A metal scavenging study was performed following the synthesis of a key synthetic intermediate obtained by the Suzuki-Miyaura coupling presented below. Various parameters were investigated including the efficiency of Silia*MetS* in different formats, scavenging kinetics, intermediate recovery and purity.



ONE REACTION ALL PARAMETERS INVESTIGATED

Scavenging Efficiency, Recovery & Purity

Small-Scale Scavenging (*Synthesis Scale ~ 5 g*)

Table below shows the most efficient Silia*MetS* Metal Scavenger products for the treatment of the reaction mixture after work-up in both bulk and fixed mode bed (*pre-packed SPE cartridges*).

Silia*MetS* Scavenging Efficiency & Intermediate Recovery Results

Silia*MetS*	Batch Reactor Mode (*Bulk*)		Fixed Mode (*SPE*)	Intermediate Recovery
	5 eq., 4 h, 22°C	5 eq., 4 h, 40°C	6 mL / 1 g	
Silia*MetS* Thiol	95%	> 99%	98%	> 99%
Silia*MetS* Thiourea	83%	93%	99%	98%
Silia*MetS* Cysteine	84%	91%	97%	> 99%
Silia*MetS* DMT	97%	> 99%	> 99%	98%
Initial Pd Concentration:	179 ppm in MTBE		76 ppm in Toluene	-

Scavenging Conclusion

Addition of only 5 equivalents of Silia*MetS* products for 4 hours at the end of the reaction reduces the residual metal concentration to single digit ppm.

Recovery & Purity Conclusion

Palladium was completely removed, while the organic compound was not sequestrated by Silia*MetS* products. No impurities were released.

[1] *Org. Proc. Res. & Dev.*, **2008**, *12*, 896

Larger Scale Scavenging (*Synthesis Scale ~ 55 g*)

Silia*MetS* Metal Scavengers in pre-packed Silia*Sep* Flash Cartridges are a great alternative for metal removal at process development scale. These cartridges offer excellent scavenging efficiency as shown by results in t below. After the first run, almost all the palladium is captured. After three runs, less than 1 ppm remained in solution.

Silia*Sep* Scavenging Results

Run #	Scavenging
1	97%
2	99%
3	> 99%

Initial Pd Concentration: 700 ppm in AcOEt

Experimental Conditions:

Cartridge Size: 120 g of Silia*MetS* Thiol
Nb. Equivalent of Silia*MetS* Thiol: 25 eq.
Solution Volume: 1 liter
Flow Rate: 40 mL / min

Metal Scavenging in Flow Chemistry (*Preliminary Results*)

Flow chemistry is a relatively new technique that is gaining in popularity for large scale manufacturing because of the small investment needed to be able to produce large quantities in a short time. Silia*MetS* Metal Scavengers can also be used in flow chemistry to scavenge metals. A crude reaction mixture purified using a Syrris ASIA® Flow Chemistry System is presented below.

Silia*MetS* Thiol Scavenging Results in Flow Chemistry

Flow Rate	Solution Volume	Contact Time with Silia*MetS* Thiol	Time Needed to Treat the Solution	Scavenging Results
1.50 mL/min	100 mL	16 min	1h10	94.0%
1.00 mL/min	100 mL	24 min	1h40	94.3%
0.75 mL/min	50 mL	32 min	1h10	94.5%
0.50 mLmin	50 mL	48 min	1h40	95.0%

Initial Pd Concentration: 547 ppm in EtOAc

Experimental Conditions:

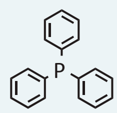
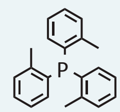
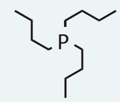
Scavenger Used: Silia*MetS* Thiol
Silia*MetS* Nb. Equivalent: 13.5 eq.
Reactors: 2 x 12 mL
Reactors in Series

Total Solution Volume: 100 mL
Purification Scale: 12.5 g
Temperature: 22°C

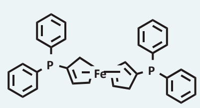
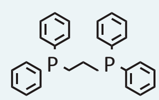
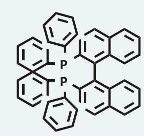
Variation of Phosphorous Ligand Nature & Scavenging

Even for the same metal, a variation in the scavenging efficiency can be observed depending on the nature of the products present in the solution to be treated. For example, the steric hindrance of a catalyst and the electronic effects of the phosphorous ligands, are factors influencing the removal of the metal. The same suzuki coupling shown on page 27 was performed using different phosphorous ligands; three monodentate and three bidentate ligands. For comparison purposes, scavenging screening was done by using the same two sets of conditions. No optimization was done to increase Silia*MetS* performance. By experience, using longer reaction times or higher temperatures will allow for better results.

Silia*MetS* Scavenging Results with Monodentate Ligands

Silia*MetS*	Triphenylphosphine [PPh_3]		Tri(o-tolyl)phosphine [$P(otol)_3$]		Tri-n-butylphosphine [$PnBu_3$]	
						
	4 eq., 4 h, 22°C	4 eq., 4 h, 60°C	4 eq., 4 h, 22°C	4 eq., 4 h, 60°C	4 eq., 4 h, 22°C	4 eq., 4 h, 60°C
Silia*MetS* Thiol	70%	97%	87%	96%	26%	85%
Silia*MetS* Thiourea	55%	86%	54%	82%	18%	41%
Silia*MetS* Cysteine	69%	76%	77%	90%	17%	44%
Silia*MetS* DMT	95%	97%	95%	> 99%	36%	87%
Initial Pd Concentration:	27 ppm in EtOAc		84 ppm in EtOAc		90 ppm in EtOAc	

Silia*MetS* Scavenging Results with Bidentate Ligands

Silia*MetS*	1,1'-bis(diphenylphosphino)ferrocene [dppf]		1,3-bis(diphenylphosphino)propane [dppp]		(+/-) BINAP	
						
	4 eq., 4 h, 22°C	4 eq., 4 h, 60°C	4 eq., 4 h, 22°C	4 eq., 4 h, 60°C	4 eq., 4 h, 22°C	4 eq., 4 h, 60°C
Silia*MetS* Thiol	50%	69%	75%	90%	31%	56%
Silia*MetS* Thiourea	3%	23%	40%	60%	33%	21%
Silia*MetS* Cysteine	29%	36%	47%	55%	19%	29%
Silia*MetS* DMT	14%	22%	95%	98%	41%	64%
Initial Pd Concentration:	63 ppm in EtOAc		93 ppm in EtOAc		16 ppm in EtOAc	

Scavenging Conclusion

In all cases, Silia*MetS* DMT and Thiol remained the better scavengers throughout the study, even though there is a variation in the nature of the ligand.

Ruthenium Scavenging with Silia*MetS*

Ruthenium-based catalysts are commonly used in organic synthesis, mainly in olefin metathesis reactions [ROM(P) and RCM]. Grubbs and Hoveyda-Grubbs catalysts are the most popular ruthenium-based complexes in this field of applications. Complete ruthenium removal can be tedious using conventional methods.

Silia*MetS* allow the maximal tolerated concentration of the residual ruthenium to be reached. A ruthenium scavenging study was conducted and various parameters were investigated in order to learn more about their influence on the scavengers' robustness as well as to establish the best experimental conditions.

Ruthenium Scavenging Results using Silia*MetS*

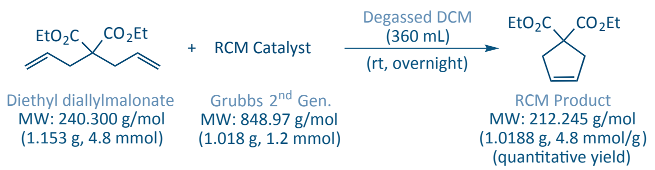
Silia*MetS*	Grubbs 1st Gen.		Grubbs 2nd Gen.		Hoveyda-Grubbs 1st Gen.		Hoveyda-Grubbs 2nd Gen.	
	Toluene[1]	DMF[2]	Toluene[1]	DMF[2]	Toluene[1]	DMF[2]	Toluene[1]	DMF[2]
Silia*MetS* Thiol	90%	96%	-	99%	97%	93%	-	-
Silia*MetS* Thiourea	-	98%	-	96%	97%	98%	-	-
Silia*MetS* DMT	95%	99%[2]	> 99%	99%[2]	> 99%[2]	98%[2]	98%[2]	99%[2]
Silia*Bond* Amine	95%	97%	92%	-	-	-	-	-
Silia*MetS* Diamine	99%	99%	91%	94%	> 99%	98%	-	90%
Silia*MetS* Triamine	-	95%	-	-	93%	95%	-	95%
Silia*MetS* TAAcOH	93%	-	-	-	-	-	-	-
Silia*MetS* TAAcONa	96%	-	96%	-	98%	-	-	-

Exp. Conditions: [1] 8 eq. of Silia*MetS*, 16 h, 80°C; [2] Only 4 eq. of Silia*MetS*. Initial concentration: 500 ppm for all ruthenium-based catalysts.

Note: **Silia*MetS* Cysteine** and **Imidazole** were not screened in this study (*and are not currently available for this application*). Only **Silia*MetS*** results higher than 90% are presented in this table.

Silia*MetS* vs Other Purification Methods

The use of Silia*MetS* to remove ruthenium catalyst after a ring-closing metathesis (*RCM*) reaction is the most effective purification method. As demonstrated below, the main advantage is that no product is lost during the purification step.



Scavenging Results for Various Purification Methods*

Scavenging	Scavenger	Filtration over packed bed of ...[2]			Flash Purification	
	Silia*MetS* DMT[1]	Act. Carbon	Celite	Silica	Manual	Silia*Sep* Cart.
Ruthenium captation	93%	73%	24%	58%	70%	73%

[1] Using 4 eq., 16h, 22°C. [2] Solution is passed directly on a packed bed of various adsorbents, which was then washed with the same quantity of solvent.

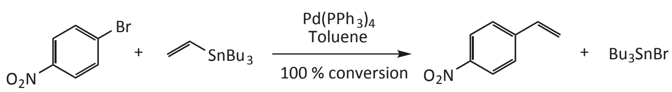
*Quantitative yield obtained for each purification method (*adjusted in function of the residual concentration of catalyst*). No impurities were generated in all cases using the different methods (*determined by NMR*).

Tin Scavenging with Silia*MetS*

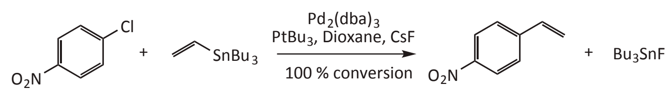
Organotin compounds are versatile reagents commonly used in organic synthesis. The two main applications are in Stille couplings or radical reactions. The removal of tin residues can often be an issue due to the high toxicity of this metal.

Traditional removal methods for this impurity are treatment with an aqueous solution of KF, NH_4OH or NaOH, or with bases such as DBU. However, the efficiency of these methods can vary and may be inapplicable for particular compounds.

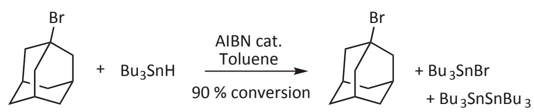
Silia*MetS* Cysteine & TAAcONa can be used to efficiently remove tin residues from organic mixtures as demonstrated by the exemples below.



Stille Coupling #1



Stille Coupling #2



Radical Reduction

Tin Scavenging using Silia*MetS* Cysteine & TAAcONa

Reactions	Inital Concentration	Silia***MetS*** Cysteine		Silia***MetS*** TAAcONa		
		4 eq., 4 h, 22°C [2 treatments]	8 eq., 4 h, 22°C	4 eq., 4 h, 22°C [2 treatments]	8 eq., 4 h, 22°C	4 eq., 16 h, 22°C
Stille coupling #1[1]	3,385 ppm	99%	64%	96%	62%	-
Stille coupling #2[1]	981 ppm	90%	66%	66%	50%	-
Radical Reduction	4,090 ppm	92%	88%	90%	90%	90%

[1] Pd residues were completely removed after only one treatment with **Silia*MetS* Cysteine**.

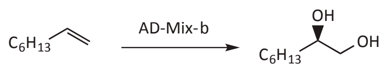
Osmium Scavenging with Silia*MetS*

Osmium products are very useful in organic synthesis. One of the most commonly used is osmium tetroxide (OsO_4), which is a very reliable and powerful reagent for the cis-dihydroxylation of alkenes. However, osmium compounds, in particular OsO_4, are highly poisonous, even at low exposure levels, and must be handled with appropriate precautions. Therefore, it is important to efficiently remove residual osmium from products of interest.

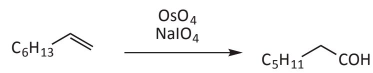
A scavenging study on three organic reactions involving osmium reactants were performed. The metal scavenging efficiency of Silia*MetS* is highlighted in the table on the following page.

Osmium Scavenging with Silia*MetS* (*con't*)

Dihydroxylation Reaction
[OsO_4]



Sharpless Dihydroxylation
[Potassium osmate ($K_2OsO_2(OH)_4$)]



Lemieux-Johnson Oxidation
[OsO_4]

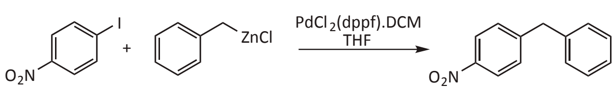
Osmium Scavenging using Silia*MetS*

Silia*MetS*	Dihydroxylation	Sharpless Dihydroxylation		Lemieux-Johnson Oxidation	
	4 eq., 4 h, 22°C	8 eq., 4 h, 22°C	8 eq., 16 h, 22°C	8 eq., 4 h, 22°C	8 eq., 16 h, 22°C
Silia*MetS* Thiol	87%	> 98%	> 98%	87%	92%
Silia*MetS* Cysteine	89%	> 98%	> 98%	87%	91%
Silia*MetS* DMT	92%	97%	> 98%	87%	91%
Silia*MetS* Imidazole	87%	> 98%	> 98%	89%	91 %
Initial Os Concentration:	132 ppm in EtOAc	25 ppm in EtOAc		21 ppm in EtOAc	

Note: > 98 % of scavenging means < 0.5 ppm of osmium.

Multiple Metal Scavenging with Silia*MetS*

Silia*MetS* can be used to remove multiple metals in the same reaction with excellent efficiency. The Negishi coupling presented below was performed to show that Silia*MetS* can be used to simultaneously remove residual zinc, palladium, and iron present after the reaction.



Negishi Coupling

Multiple Removal Scavenging Results

Silia*MetS*	Palladium	Iron	Zinc
Silia*MetS* Cysteine	95%	> 99%	98%
Silia*MetS* DMT	83%	93%	99%
Silia*MetS* Imidazole	84%	91%	97%
Silia*MetS* TAAcONa	97%	> 99%	> 99%
Initial Concentration:	188 ppm in THF	110 ppm in THF	6 ppm in THF

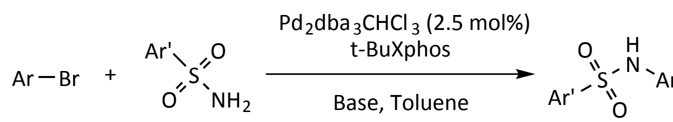
Conditions: 4 eq. of Silia*MetS* (*relative to palladium*), 4 h, 22°C.

Silia*MetS* Success Stories Published by Customers

Silia*MetS* Metal Scavengers are being used by many pharmaceutical companies, several of which are now using them in pilot plants. In the literature, you can find a number of success stories published by customers highlighting the ease of use and reliable performance of **Silia*MetS***. Some examples are presented in the following pages.

An Amgen Case Study[1]

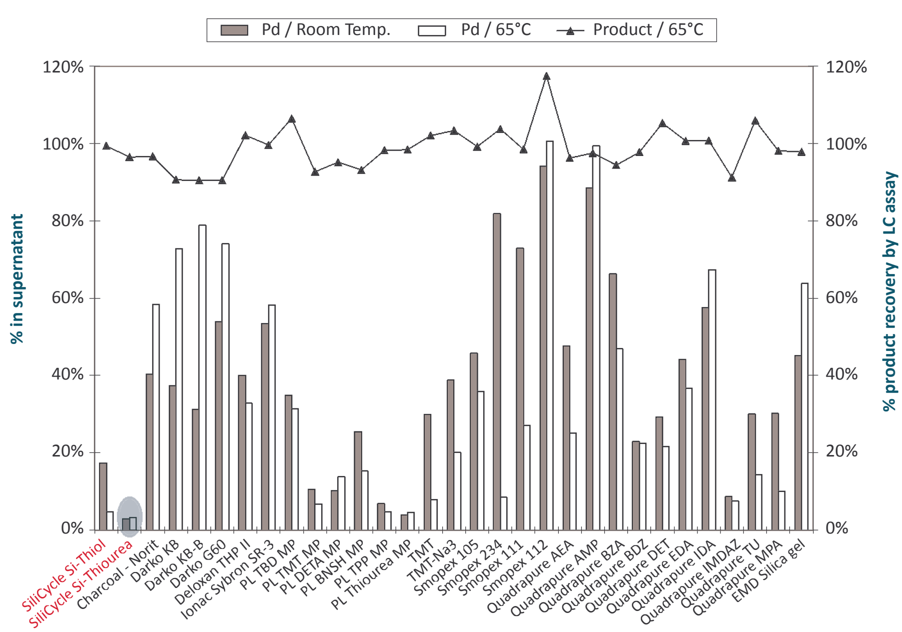
In 2009, Amgen published a chapter in "Catalysis of Organic Reactions" related to the use of scavengers for the removal of palladium in small to multi-kilogram production scale. In their study, they evaluated various parameters such as the scavenging efficiency, the influence of the scavenger loading and the loss of product to adsorption (*recovery*). The study was based on a palladium-catalyzed sulfonamide coupling and scavenger screening was performed at both room temperature and 65°C using 31 different scavengers.

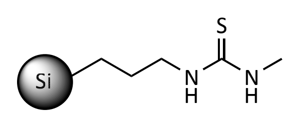


Amgen Scavenger Screening Results

Condition: 20 mg of each scavenger (*20% w/w*) in 2 mL HPLC vial that contains 1 mL of crude reaction mixture containing 100 mg of product. Each vial was sealed and agitated overnight. Initial palladium concentration was 423 ppm.

The **BEST** scavenger identified during their study was the Silia*MetS* Thiourea providing the lowest Pd content (*residual palladium concentration: 3% or < 14 ppm*) without product sequestration. They mentioned that Silia*MetS* Thiourea was used extensively in early process development work.





Silia*MetS* Thiourea

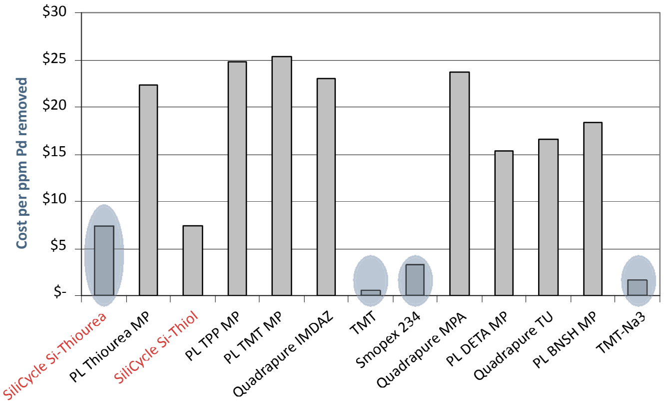
[1] Catalysis of Organic Reactions, Chapter 5. Application of Scavengers for the Removal of Palladium in Small Lot Manufacturing

Allgeier & al., Amgen Inc., Thousand Oaks (*California*)

Cost Comparison for Most Efficient Scavengers (≥ *80%*)

At pilot-plant scale, the optimal compromise between the cost per ppm removed and the scavenging efficiency is crucial. The histogram at right shows a cost comparison on best scavengers identified.

Results highlighted by the graph reduced the number of options to only 4 candidates for further evaluation: in pole position the Silia*MetS* Thiourea , and then the TMT, TMT-Na3, and the Smopex 234.



Top 4 Scavengers Overview

A screening validation was conducted on 1 g scale purification (*10 mL of solution*) with 20% w/w of each top 4 scavengers at 65°C overnight. After filtration, residual metal concentration was analyzed by ICP-MS and product recovery was determined by HPLC (*see below*). Silia*MetS* Thiourea was chosen for the large scale purification. See Amgen's paper for further details.

Screening Validation Results on Top 4 Scavengers

Scavengers	Residual Metal Concentration (*ppm*)			Product Recovery	Commentary
	Screening Exp. in Solution	Validation Exp. in Solution	Validation Exp. in Solid Product[1]		
SiliCycle Thiourea	14	11	158	102%	Best performance but also most expensive.
TMT	33	15	264	104%	Fine in suspension, filterability concerns on scale.
Smopex 234	36	38	496	84%	Favorable cost but product recovery inadequate
TMT-Na3	85	81	1 555	78%	Very basic compounds (*not effective with base-sensitive groups*). Low recovery.
Purification Scale:	100 mg	1 g	1 g	1 g	
Initial Concentration:	423 ppm	381 ppm	3,577 ppm		

Note: [1]Solid product is obtained by dividing the metal concentration in ppm by the amount of product in the test (*1g*).

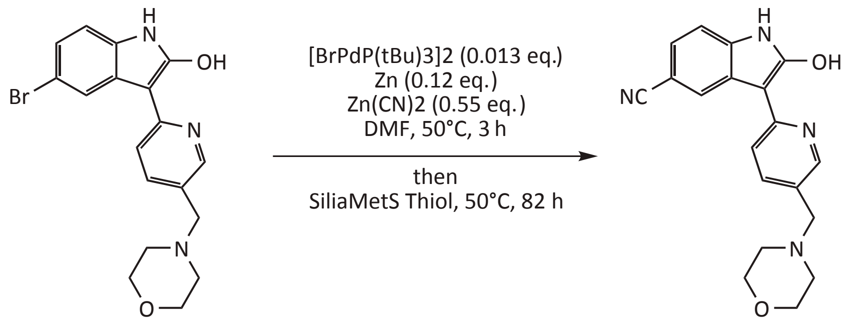
Amgen's Conclusion

"Scavengers offer a practical and expedient option for removal of palladium from process streams to ensure quality of organic products... The screening protocol involves treatment of a candidate process stream with 20% w/w scavenger on product at both room temperature and 65°C followed by analysis of Pd and product adsorption. High-temperature treatment increased the efficiency of Pd removal... Evaluation of process costs is key to identifying Pd removal solutions. While scavengers add cost to a process, their use is often justified by the speed to production in early phase development."

An AstraZeneca Case Study

Publication: Ryberg, P., *Organic Process Research & Development, 12,* **2008**, *540*
Process Chemistry, AstraZeneca PR&D, Sweden.

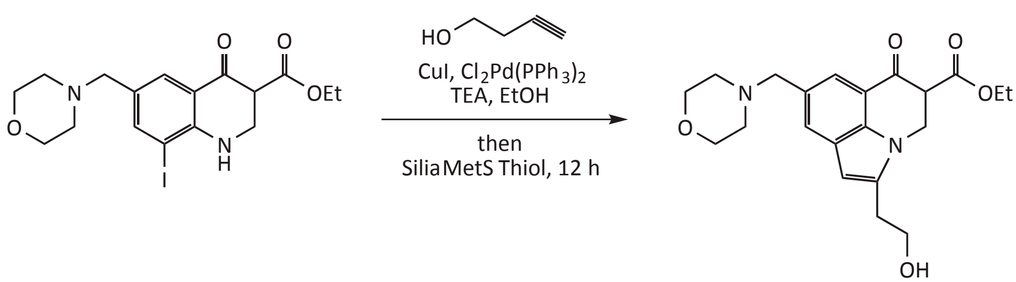
In 2008, AstraZeneca published a paper in which they removed palladium impurities in a large-scale process. The workup method found to work the best was a treatment with Silia*MetS* Thiol (*25% w/w or ~1.4 kg*) at 50°C to purify more than 6.7 kg of material. Final residual palladium concentration was as low as 1-2 ppm.



A Pfizer Global R&D Case Study

Publication: Dorow, R.L. & all, *Organic Process Research & Development, 10,* **2006**, *493*
Pfizer Global Research and Development, Kalamazoo, Michigan (*USA*)

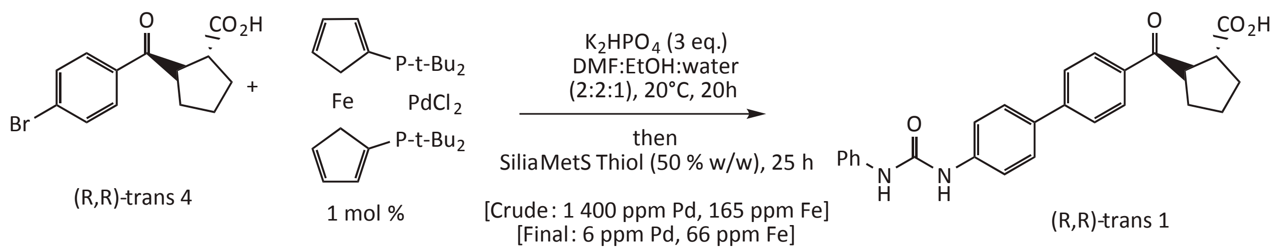
In 2006, Pfizer published a paper in which they removed palladium & copper impurities in a 20 kg pilot plant scale. They made two subsequent treatments using Silia*MetS* Thiol (*20% + 7% w/w*) at room temperature for 12 hours. After scavenging with Silia*MetS* Thiol, the desired product was obtained with a yield of 76% containing only 17 ppm Pd and 1 ppm Cu. An alternative method was also tried using 80% w/w of Deloxan THP (*Degussa AG*) overnight followed by basification with Na_2CO_3. Residual metal concentration with this method was higher compared to that of Silia*MetS* and the yield was lower (*about 60%-70%*). Silia*MetS* allows lower residual metal concentration & higher yield with fewer manipulations!



An Abbott Laboratories Case Study

Publication: Ravn, M.M. & all, P., *Organic Process Research & Development*, *14*, **2010**, *417*
Global Pharmaceutical R&D, Process Research & Development and Discovery, Abbott Laboratories, Chicago, Illinois (*USA*)

In 2010, Abbott Laboratories published a paper in which they removed palladium and iron impurities using Silia*MetS* Thiol (*50% w/w relative to **1***). Thus, palladium and iron levels were respectively 6 ppm and 66 ppm. Refer to Abbott's publication for more details.

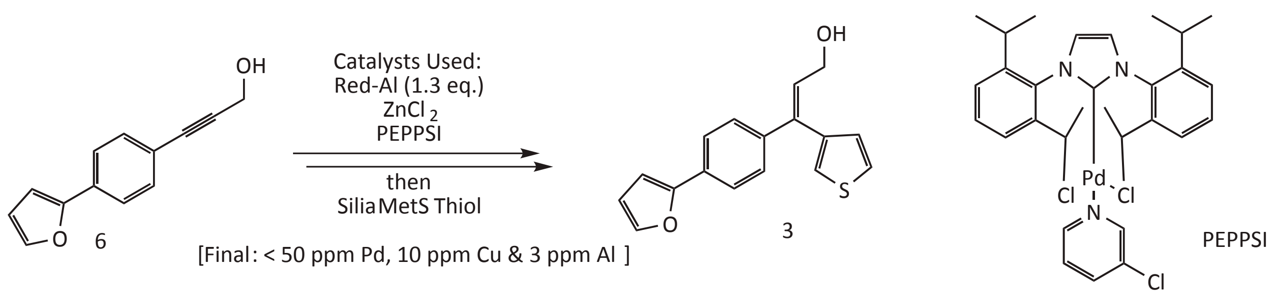


A Johnson & Johnson Case Study

Publication: Houpis I.N. & all, *Organic Process Research & Development*, *13*, **2009**, *598*
Johnson & Johnson PRD, API Development, Belgium, and Solvias A.G., Synthesis and Catalysis, Switzerland

In 2009, Johnson & Johnson (*J&J*) in collaboration with Solvias published a paper in which they developed a mild Sonogashira reaction using various metal catalysts. Treatment with Silia*MetS* Thiol simultaneously removed Pd, Cu & Al. Residual concentrations were below 50, 10, and 3 ppm, respectively, in the isolated product **3**. Refer to J&J's publication for more details.

Note: copper comes from a previous synthesis step.



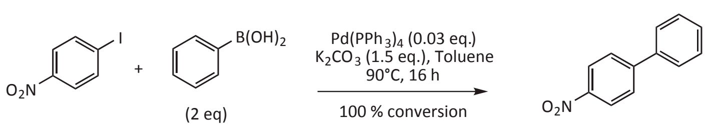
Silia*MetS* Leaching & Stability Studies

Silia*MetS* Metal Scavengers are being used by many pharmaceutical and biotechnological companies. Each **Silia*MetS*** manufactured by SiliCycle is submitted to an extensive washing procedure to ensure the product exhibits extremely low levels of extractables and leachables.

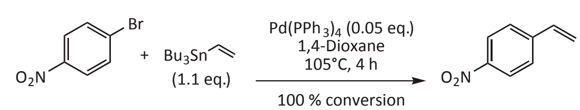
SiliCycle has implemented a quality control procedure to prevent leaching that includes loading and reactivity determination, as well as leachables and extractables analysis (*silica gel purity ≥ 99.995%*). The solution must be free of contaminants for the product to successfully pass the rigorous quality control tests.

To address the end users concerns for potential leaching of impurities into reaction mixtures using Silia*MetS*, we have performed three typical metal containing reactions. We then investigated the detection, identification, and quantification of possible impurities resulting from the scavengers used.

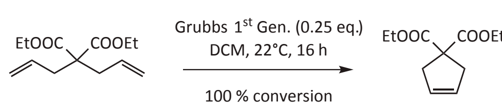
The following three transition metal catalyzed reactions were performed:



Suzuki Coupling



Stille Coupling



Ring-Closing Metathesis

Experimental Procedure

Crude reaction mixtures (*8 mL*) were placed in a standard polypropylene tube equipped with a 20 µm frit, filled with 1 g of the appropriate Silia*MetS* Metal Scavenger, and mixed for 4 h at either room temperature or 80°C. Solutions were then filtered through a 0.02 µm filter prior to analysis.

Leaching Analysis

For each Silia*MetS*, silane leaching was analyzed by ICP-OES, which has proven to be very sensitive for silicon quantification (*detection limit in solution is 0.125 ppm*). Traces of non-silicon containing impurities were also analyzed by GC-MS and ^{1}H NMR Analysis. Only results for Silia*MetS* Thiol and DMT are shown. However, no evidence of impurities was found for all Silia*MetS*. Contact us for the complete study results.

Gel Purity Calculation Example

Impurity % : $\dfrac{\text{2 mg of silicon}}{\text{1,000,000 mg of SiliaMetS}}$ x 100 => 0.0002% impurity

Gel purity = 100 - (*Impurity %*) => 99.9998% purity

Silane Leaching Analysis by ICP-OES

Results shown in the table below for Silia*MetS* Thiol & DMT confirm that minimal leaching occurs with SiliCycle Silia*MetS*.

Note: concentration given are in ppm and represent mg of silicon leached per kg of SiliaMetS.

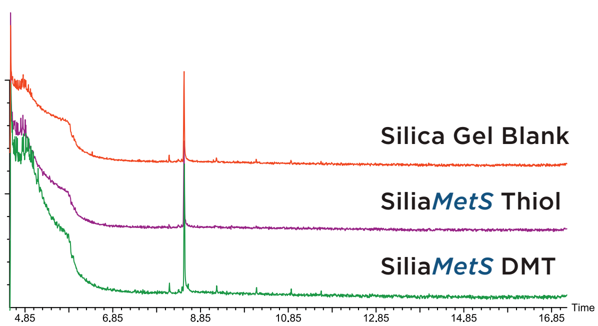
Stability of Silia*MetS* in Suzuki, Stille and Ring-Closing Metathesis reactions

Reaction (*solvent*)	Temperature	Silia*MetS* Thiol		Silia*MetS* DMT	
		[Silicon]	Gel Purity	[Silicon]	Gel Purity
Suzuki (*Toluene*)	22°C	2 ppm	99.9998%	1 ppm	99.9999%
	80°C	2 ppm	99.9998%	2 ppm	99.9998%
Stille (*1,4-Dioxane*)	22°C	2 ppm	99.9998%	1 ppm	99.9999%
	80°C	1 ppm	99.9999%	3 ppm	99.9997%
Ring-Closing Met. (*DCM*)	22°C	2 ppm	99.9998%	2 ppm	99.9998%

Note: Very low levels of silicon were detected in most experiments, giving product purities higher than 99.995%.

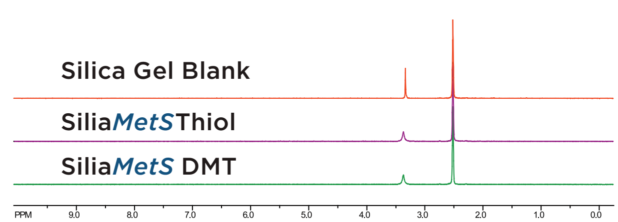
Non-Silicon Leaching Analysis

Gas chromatography-mass spectrometry (*GC-MS*)



Compared to the silica blank spectrum (*bare silica in solvent*), neither experiment showed evidence of any impurities for either Silia*MetS* Thiol or DMT.

1H NMR Analysis (*d6-dmso*)



Note: each experiment was run on a 1 g aliquote of Silia*MetS* and was shaken for one hour at room temperature. In GC-MS spectrum, peak at 8.5 minutes is the internal standard (*1-fluoronaphthalene, 100 ppm*). In NMR spectrum, peaks at 2.4 and 3.4 ppm are, respectively, d6-dmso and water contained in deuterated solvent.

Stability Study (*Shelf Life*)

SiliCycle certifies that Silia*MetS* Metal Scavengers stored under recommended conditions in an undamaged container are guaranteed to perform for over two years from the manufacturing date without loss of performance (*results at right*).

Silia*MetS* Thiol after Two Years

Lot #	QC Date	Scavenging
11577	January 2008	> 99.9%
	October 2010	99.6%
12218	February 2008	99.9%
	October 2010	99.1%

Scavenging: 1 000 ppm of $Pd(OAc)_2$ in DMF.

Conditions: 2 eq. of Silia*MetS* Thiol, 1 h, 22°C.

Silia*MetS* Metal Scavengers Ordering Information

Silia*MetS* Bulk Ordering Information

Metal Scavenger	Part Number	Metal Scavenger	Part Number
Silia*MetS* Thiol	R51030B	**Silia*MetS*** Diamine	R49030B
Silia*MetS* Thiourea	R69530B	**Silia*MetS*** Triamine	R48030B
Silia*MetS* Cysteine	R80530B	**Silia*MetS*** Imidazole	R79230B
Silia*MetS* DMT	R79030B	**Silia*MetS*** TAAcOH	R69030B
Silia*Bond* Amine	R52030B	**Silia*MetS*** TAAcONa	R69230B

Formats: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 5kg, 10kg, 25kg, ... up to multi-ton scale. Contact us for details.

Silia*Sep* Metal Scavenger Cartridges Ordering Information (*see SiliaSep's section at page 157*)

Silia*Sep* Type Quantity per box	Silia*Sep* 4 g 2/box	Silia*Sep* 12 g 1/box	Silia*Sep* 25 g 1/box	Silia*Sep* 40 g 1/box	Silia*Sep* 80 g 1/box
Silia*Sep* Thiol	FLH-R51030B-ISO04	FLH-R51030B-ISO12	FLH-R51030B-ISO25	FLH-R51030B-ISO40	FLH-R51030B-ISO80
Silia*Sep* Thiourea	FLH-R69530B-ISO04	FLH-R69530B-ISO12	FLH-R69530B-ISO25	FLH-R69530B-ISO40	FLH-R69530B-ISO80
Silia*Sep* Cysteine	FLH-R80530B-ISO04	FLH-R80530B-ISO12	FLH-R80530B-ISO25	FLH-R80530B-ISO40	FLH-R80530B-ISO80
Silia*Sep* DMT	FLH-R79030B-ISO04	FLH-R79030B-ISO12	FLH-R79030B-ISO25	FLH-R79030B-ISO40	FLH-R79030B-ISO80
Silia*Sep* Amine	FLH-R52030B-ISO04	FLH-R52030B-ISO12	FLH-R52030B-ISO25	FLH-R52030B-ISO40	FLH-R52030B-ISO80
Silia*Sep* Diamine	FLH-R49030B-ISO04	FLH-R49030B-ISO12	FLH-R49030B-ISO25	FLH-R49030B-ISO40	FLH-R49030B-ISO80
Silia*Sep* Triamine	FLH-R48030B-ISO04	FLH-R48030B-ISO12	FLH-R48030B-ISO25	FLH-R48030B-ISO40	FLH-R48030B-ISO80
Silia*Sep* Imidazole	FLH-R79230B-ISO04	FLH-R79230B-ISO12	FLH-R79230B-ISO25	FLH-R79230B-ISO40	FLH-R79230B-ISO80
Silia*Sep* TAAcOH	FLH-R69030B-ISO04	FLH-R69030B-ISO12	FLH-R69030B-ISO25	FLH-R69030B-ISO25	FLH-R69030B-ISO80
Silia*Sep* TAAcONa	FLH-R69230B-ISO04	FLH-R69230B-ISO12	FLH-R69230B-ISO25	FLH-R69230B-ISO25	FLH-R69230B-ISO80

Silia*Sep* Metal Scavenger Cartridges Ordering Information

Silia*Sep* Type Quantity per box	Silia*Sep* 120 g 2/box	Silia*Sep* 220 g 1/box	Silia*Sep* 330 g 1/box	Silia*Sep* XL 800 g 1/box	Silia*Sep* XL 1600 g 1/box
Silia*Sep* Thiol	FLH-R51030B-IS120	FLH-R51030B-IS220	FLH-R51030B-IS330	FLH-R51030B-IS750	FLH-R51030B-I1500
Silia*Sep* Thiourea	FLH-R69530B-IS120	FLH-R69530B-IS220	FLH-R69530B-IS330	FLH-R69530B-IS750	FLH-R69530B-I1500
Silia*Sep* Cysteine	FLH-R80530B-IS120	FLH-R80530B-IS220	FLH-R80530B-IS330	FLH-R80530B-IS750	FLH-R80530B-I1500
Silia*Sep* DMT	FLH-R79030B-IS120	FLH-R79030B-IS220	FLH-R79030B-IS330	FLH-R79030B-IS750	FLH-R79030B-I1500
Silia*Sep* Amine	FLH-R52030B-IS120	FLH-R52030B-IS220	FLH-R52030B-IS330	FLH-R52030B-IS750	FLH-R52030B-I1500
Silia*Sep* Diamine	FLH-R49030B-IS120	FLH-R49030B-IS220	FLH-R49030B-IS330	FLH-R49030B-IS750	FLH-R49030B-I1500
Silia*Sep* Triamine	FLH-R48030B-IS120	FLH-R48030B-IS220	FLH-R48030B-IS330	FLH-R48030B-IS750	FLH-R48030B-I1500
Silia*Sep* Imidazole	FLH-R79230B-IS120	FLH-R79230B-IS220	FLH-R79230B-IS330	FLH-R79230B-IS750	FLH-R79230B-I1500
Silia*Sep* TAAcOH	FLH-R69030B-IS120	FLH-R69030B-IS220	FLH-R69030B-IS330	FLH-R69030B-IS750	FLH-R69030B-I1500
Silia*Sep* TAAcONa	FLH-R69230B-IS120	FLH-R69230B-IS220	FLH-R69230B-IS330	FLH-R69230B-IS750	FLH-R69230B-I1500

Silia*MetS* Metal Scavengers Ordering Information (*con't*)

Silia*Sep* OT Metal Scavenger Cartridges (*rated 60 psi*)

Silica Weight Quantity per box	2 g 20/box	5 g 20/box	10 g 16/box	15 g 16/box	20 g 16/box
Silia*Sep* OT Thiol	SPE-R51030B-12U	SPE-R51030B-20X	FLH-R51030B-70Y	FLH-R51030B-70i	FLH-R51030B-70Z
Silia*Sep* OT Thiourea	SPE-R69530B-12U	SPE-R69530B-20X	FLH-R69530B-70Y	FLH-R69530B-70i	FLH-R69530B-70Z
Silia*Sep* OT Cysteine	SPE-R80530B-12U	SPE-R80530B-20X	FLH-R80530B-70Y	FLH-R80530B-70i	FLH-R80530B-70Z
Silia*Sep* OT DMT	SPE-R79030B-12U	SPE-R79030B-20X	FLH-R79030B-70Y	FLH-R79030B-70i	FLH-R79030B-70Z
Silia*Sep* OT Amine	SPE-R52030B-12U	SPE-R52030B-20X	FLH-R52030B-70Y	FLH-R52030B-70i	FLH-R52030B-70Z
Silia*Sep* OT Diamine	SPE-R49030B-12U	SPE-R49030B-20X	FLH-R49030B-70Y	FLH-R49030B-70i	FLH-R49030B-70Z
Silia*Sep* OT Triamine	SPE-R48030B-12U	SPE-R48030B-20X	FLH-R48030B-70Y	FLH-R48030B-70i	FLH-R48030B-70Z
Silia*Sep* OT Imidazole	SPE-R79230B-12U	SPE-R79230B-20X	FLH-R79230B-70Y	FLH-R79230B-70i	FLH-R79230B-70Z
Silia*Sep* OT TAAcOH	SPE-R69030B-12U	SPE-R69030B-20X	FLH-R69030B-70Y	FLH-R69030B-70i	FLH-R69030B-70Z
Silia*Sep* OT TAAcONa	SPE-R69230B-12U	SPE-R69230B-20X	FLH-R69230B-70Y	FLH-R69230B-70i	FLH-R69230B-70Z

Silia*Sep* OT Metal Scavenger Cartridges (*rated 60 psi*)

Silica Weight Quantity per box	25 g 10/box	50 g 10/box	70 g 10/box	100 g 12/box
Silia*Sep* OT Thiol	FLH-R51030B-95K	FLH-R51030B-95M	FLH-R51030B-95N	FLH-R51030B-276F
Silia*Sep* OT Thiourea	FLH-R69530B-95K	FLH-R69530B-95M	FLH-R69530B-95N	FLH-R69530B-276F
Silia*Sep* OT Cysteine	FLH-R80530B-95K	FLH-R80530B-95M	FLH-R80530B-95N	FLH-R80530B-276F
Silia*Sep* OT DMT	FLH-R79030B-95K	FLH-R79030B-95M	FLH-R79030B-95N	FLH-R79030B-276F
Silia*Sep* OT Amine	FLH-R52030B-95K	FLH-R52030B-95M	FLH-R52030B-95N	FLH-R52030B-276F
Silia*Sep* OT Diamine	FLH-R49030B-95K	FLH-R49030B-95M	FLH-R49030B-95N	FLH-R49030B-276F
Silia*Sep* OT Triamine	FLH-R48030B-95K	FLH-R48030B-95M	FLH-R48030B-95N	FLH-R48030B-276F
Silia*Sep* OT Imidazole	FLH-R79230B-95K	FLH-R79230B-95M	FLH-R79230B-95N	FLH-R79230B-276F
Silia*Sep* OT TAAcOH	FLH-R69030B-95K	FLH-R69030B-95M	FLH-R69030B-95N	FLH-R69030B-276F
Silia*Sep* OT TAAcONa	FLH-R69230B-95K	FLH-R69230B-95M	FLH-R69230B-95N	FLH-R69230B-276F

Silia*Prep* Metal Scavenger Cartridges (*see SiliaPrep's section at page 173*)

Formats Quantity per box	200 mg / 3 mL 50 / box	500 mg / 3 mL 50 / box	500 mg / 6 mL 50 / box	1 g / 6 mL 50 / box	2 g / 6 mL 50 / box
Silia*Prep* OT Thiol	SPE-R51030B-03G	SPE-R51030B-03P	SPE-R51030B-06P	SPE-R51030B-06S	SPE-R51030B-06U
Silia*Prep* OT Thiourea	SPE-R69530B-03G	SPE-R69530B-03P	SPE-R69530B-06P	SPE-R69530B-06S	SPE-R69530B-06U
Silia*Prep* OT Cysteine	SPE-R80530B-03G	SPE-R80530B-03P	SPE-R80530B-06P	SPE-R80530B-06S	SPE-R80530B-06U
Silia*Prep* OT DMT	SPE-R79030B-03G	SPE-R79030B-03P	SPE-R79030B-06P	SPE-R79030B-06S	SPE-R79030B-06U
Silia*Prep* OT Amine	SPE-R52030B-03G	SPE-R52030B-03P	SPE-R52030B-06P	SPE-R52030B-06S	SPE-R52030B-06U
Silia*Prep* OT Diamine	SPE-R49030B-03G	SPE-R49030B-03P	SPE-R49030B-06P	SPE-R49030B-06S	SPE-R49030B-06U
Silia*Prep* OT Triamine	SPE-R48030B-03G	SPE-R48030B-03P	SPE-R48030B-06P	SPE-R48030B-06S	SPE-R48030B-06U
Silia*Prep* OT Imidazole	SPE-R79230B-03G	SPE-R79230B-03P	SPE-R79230B-06P	SPE-R79230B-06S	SPE-R79230B-06U
Silia*Prep* OT TAAcOH	SPE-R69030B-03G	SPE-R69030B-03P	SPE-R69030B-06P	SPE-R69030B-06S	SPE-R69030B-06U
Silia*Prep* OT TAAcONa	SPE-R69230B-03G	SPE-R69230B-03P	SPE-R69230B-06P	SPE-R69230B-06S	SPE-R69230B-06U