Scavenging Solutions

Silia*MetS*® Metal Scavengers
Silia*Bond*® Organic Scavengers

Metal and Organic Scavengers Overview

Scavenging Technologies: Creativity for Utmost Benefits

- Technology innovated by SiliCycle researchers
- Increased R&D and manufacturing productivity
- Amazingly versatile (*solvents, pH, compatible in batch flow, microwave, etc.*)
- Green and environmentally friendly technology
- Broadest scope of metals & organics to be scavenged

Since ancient times, chemists have been searching for techniques and tools to separate, isolate and purify chemical substances from one another to improve the quality of life. It's been a long road since the alchemists of the Middle-Ages understood that their search for the philosophers' stone would depend, at least in part, on good separation of elements.

SiliCycle grafted technology enables more powerful purification processes to help reach new purity standards. Our solutions are extremely versatile and customizable, hence suitable for a use in a vast array of industries, facing different contamination issues.

Discover what the scavenging technology from SiliCycle has to offer and how it can assist you in these times of environmental changes, tighter quality control and regulatory compliance.

Easier, Cleaner, Faster, Efficient Purification Processes Using Metal & Organic Scavengers

- Almost two decades of know-how in silica-grafting and scavenging technology
- Broadest portfolio of scavengers with associated applications
- Great variety of formats for all purifications scales: from laboratory to plant scale
- Successful technology for a variety of fields, such as pharmaceuticals, organic chemistry labs, agrochemicals, mining, fine chemicals, water and waste treatment
- Great compatibility with a myriad of experimental conditions, solvents, pH and temperatures
- Strong chemical, physical, thermal and mechanical stability

SiliCycle Has Pioneered the Field of Functionalized Silica, So You Can Benefit From Our Scavenging Expertise

Challenging purifications in chemistry can be overcome creatively and elegantly.

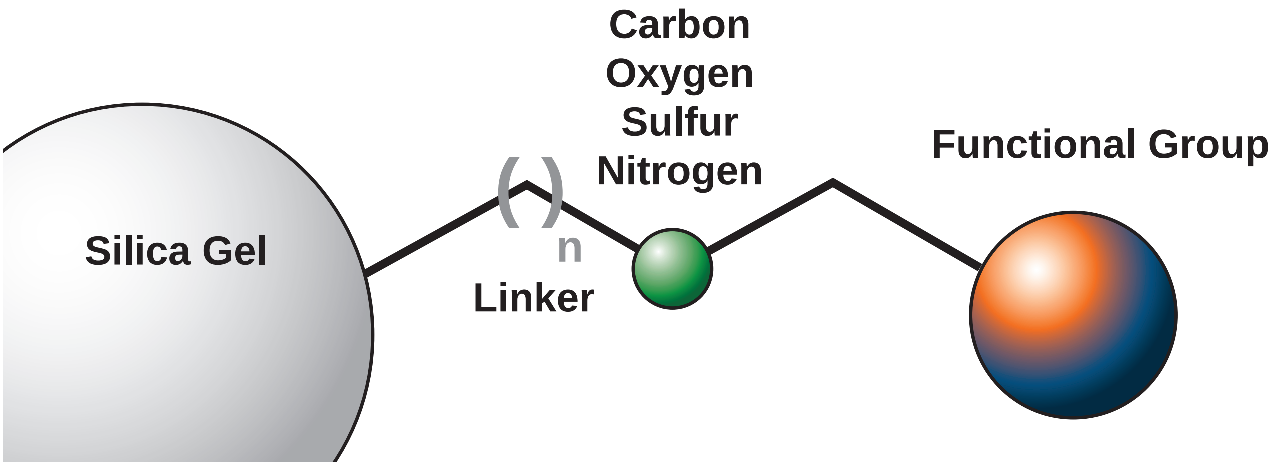
At SiliCycle, silica gels are functionalized with various molecules featuring scavenging properties toward different metals and / or organics.

We name our metal scavengers Silia*MetS* and our organic scavengers Silia*Bond*.

This technology combines the benefits of classical, century-old purification techniques, while integrating new assets that are becoming more and more critical in modern industries. New purification procedures need to be more selective, more efficient, quicker and greener.

It is because of today's strive for greater performance while respecting environmental concerns that silica-based scavengers were developed; they are a powerful tool with an eco-friendly twist:

- Reduced purification steps
- No swelling
- No cross-contamination
- Less solvent needed
- Efficient precious metal recovery



Typical Structure of our Functionalized Silicas with Various Organic Groups

Why Choose Silica-Based vs Polymer-Based Scavengers

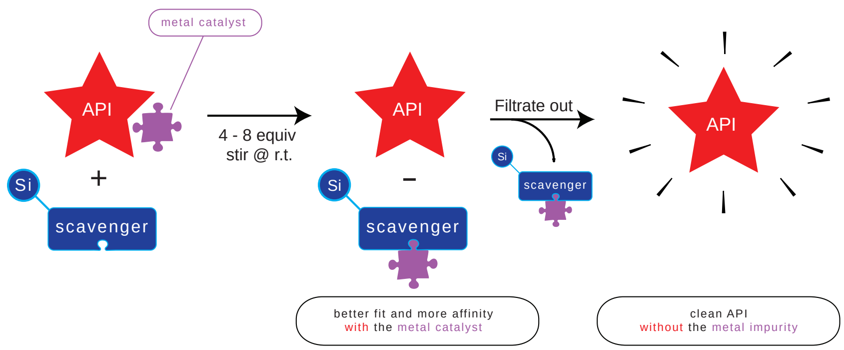
Silica-based scavengers have been proven to be the purification solution of choice over all. Silica matrices show strong advantages over polymeric resins in purification, such as:

- No swelling
- Faster kinetics
- Solvent independence
- Ease of use
- Mechanical stability
- Thermal stability
- Format flexibility
- Controlled & precise loading

New Pharmaceutical Challenges in Purification

SiliCycle Helps You Achieve Your Goals

In recent years, the time pressure associated with quickly bringing drug candidates to market has increased the number of transition metal-catalysed reactions progressing from lead optimisation to early scale-up. The removal of post-reaction metal residues has become a major issue in the pharmaceutical industry. Purification of APIs (*Active Pharmaceutical Ingredients*), or Product of Interest 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's Scavenger Solutions have significantly changed how chemists can purify APIs. Here is the scavenging mechanism:

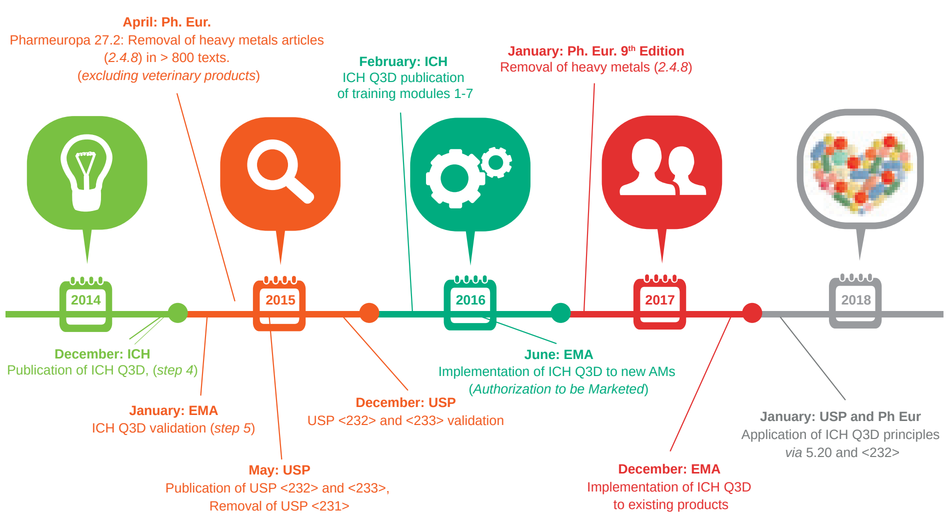


Scavengers for Metal Impurities (*SiliaMetS*)

New ICH-Q3D Heavy Metal Regulation Ready for Implementation in the Pharmaceutical Industry

Since June 2013, the International Conference on Harmonisation (*ICH*) has been working on its Q3D guidelines on metal elemental impurities in new drugs and new formulations containing known ingredients. After many revisions and improvements, the final version of the Q3D guidelines was finally accepted and signed off by the ICH Steering Committee in December 2014, hence requiring the entire manufacturing industry and supply chain to meet more stringent regulations.

Since December 2015, twenty-four (*24*) metals - well-known to act as catalysts or present in solvents - have been indicted and associated with great health risks, and have been assigned distinctive PDE (*Permitted Daily Exposure*) limits. For example, now that ICH Q3D contains Lithium and Barium, we no longer talk of heavy metals impurities but elemental impurities.



There is no doubt that these new guidelines will be one of the next major challenges to address for production plants and QC labs of the pharmaceutical industry. Take advantage of SiliCycle's expertise and knowledge in the field of grafting technologies to efficiently address this new regulation.

Scavengers for Organic Impurities (*SiliaBond*)

The Importance of Organic Contaminant Removal From APIs

Using excess reagents in organic synthesis is a very common strategy to maximise conversion and product yield. But the benefits of this approach can rapidly be outshined when comes the need to purify the final reaction mixture from excess reagents.

In addition, even reagents used in stoechiometric amounts can lead to an uncomplete reaction, and this is far more common than the other way around.

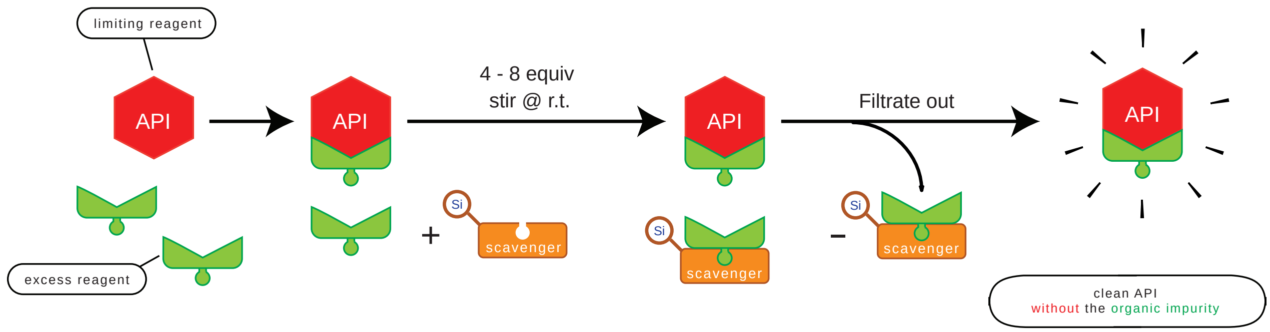
These reagents can either contaminate the API with potentially genotoxic impurities or environmental hazards, or jeopardize subsequent reactions by their reactivity. Indeed, such reagents usually bear nucleophilic, electrophilic, acidic or basic functional groups.

There is a very strong need in organic chemistry and high-throughput screening for simpler work-up and purification processes. Our range of organic scavengers have been widely acknowledged and adopted by early R&D teams up to manufacturing.

Two Ways Silia*Bond* Organic Scavengers Can Help You Purify Your API From Organic Contaminants

Method 1: Direct scavenging of the undesired compound to isolate the API

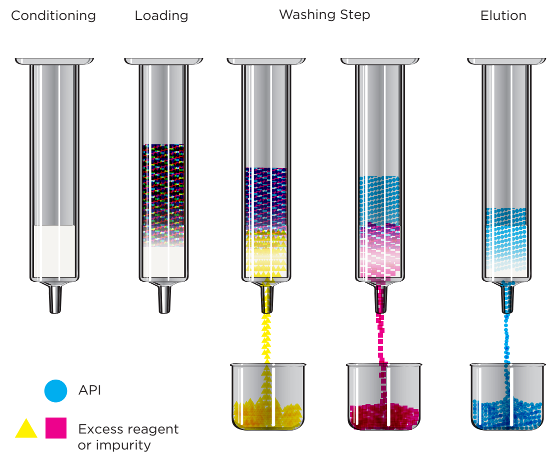
- Silica is bound with a functional group, that will specifically react with a product: either excess reagents (*unreacted*) or impurities.
- The API is recovered by simple filtration as demonstrated on the following scheme:



Method 2: Catch and release of the API

Silia*Bond* scavenger is packed in a SPE cartridge:

- **Conditioning step:** with six to ten hold-up volumes of solvent
- **Loading step:** API is loaded and trapped onto the cartridge bed
- **Washing step:** cartridge is washed to filter excess reagents and / or other impurities
- **Elution step:** API is eluted, recovered and purified

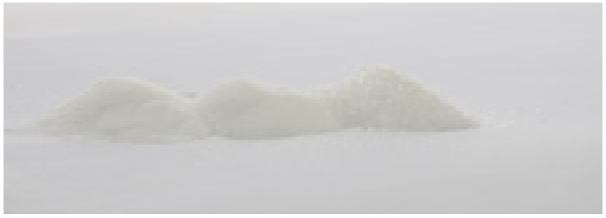


Different Formats for Different Applications

Scavengers as Bulk Silica

All our scavengers can be used in bulk directly in your reaction flask or reactor.

- All scavengers are available in the following format size: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc. Up to multi-ton scale!
- All our scavengers have, by default, the same silica backbone: our Silia*Flash* R10030B.
  - Particle Size: 40 - 63 µm
  - Pore Size: 60 Å
- All our Silia*Flash* silica gels of various particle sizes and pore sizes are available as silica backbones upon request. Please visit our Silia*Flash* chapter p. 213 for all details.



Scavengers in Silia*Prep* SPE Cartridges

All our scavengers are available in pre-packed SPE cartridges. Please refer to our Silia*Prep* Ordering Information p. 208 to learn about the different formats available.

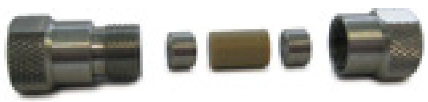
Scavengers in Silia*Sep* Flash Cartridges

All our scavengers are available pre-packed in Flash cartridges (*please see p. 208*). Please take a look at our Silia*Sep* chapter p. 205 for more information on small-scale cartridges (*research or discovery labs*); and to p. 253 to learn about large-scale purifications on the kilo-scale cartridges (*up to 2.7 kg of crude reaction material applicable to cartridges*).

Packings can also be tailored to your available equipment & scales.

Scavengers as Guard Columns (*for HPLC*)

Silia*Chrom* HPLC Guard Columns are designed to effectively protect both analytical and preparative HPLC columns. The usage of this shorter column is highly recommended to prolong column lifetime and does not alter chromatography. All metals can be prejudicial and very damaging to your column and detector, complicating purification steps, often making them longer, more laborious and less effective.



Crude reaction mixtures can now directly be injected without further metal removal, which will save precious time for the chemist. Another great benefit is that there is much less risk of corroding the equipment by injecting dirty samples.

Silia*Chrom* Guard Columns are cost effective and easy to use as a pre-filter to remove contaminants prior to injection. In liquid chromatography, contaminants introduced into the column can cause:

- Higher backpressure
- Resolution loss
- Baseline noise or drift
- Peak shape changes
- Irreversible damages (*column + system*)

SiliCycle is the only one on the market to offer protective guard cartridges filled with metal scavengers to protect your HPLC columns and system from damageable metallic impurities.

Silia*Chrom* Guard Column Dimensions

Silia*Chrom* Guard Columns are available in lengths of 10 - 20 mm and three internal diameters (*ID: 4.0, 10 and 21.2 mm*). The Guard Column internal diameter should be the same as the HPLC column or one size smaller. Never use a guard column with a larger ID than the HPLC column (*risk of efficiency loss*).

Silia*Chrom* Scavenger Guard Columns

Guard Column Name	Palladium's Favorite Metal Guard Column	Universal Metal Guard Column
Scavenger Packing #	K346	K307
Effective Scavenger Can also Remove these Metals	**Pd** **Ag, Cr, Hg, Ir, Ni, Os, Pt, Rh, Ru** Cd, Co, Cu, Fe, Pb, Sc, Sn, W, Zn	**Ca, Cd, Cs, Co, Cr, Cu, Fe, Ir, La, Li, Mg, Mn, Ni, Os, Pd, Pt, Rh, Ru, Sc, Sn, W, Zn** Ag

Silia*Chrom* Scavenger Guard Column Formats

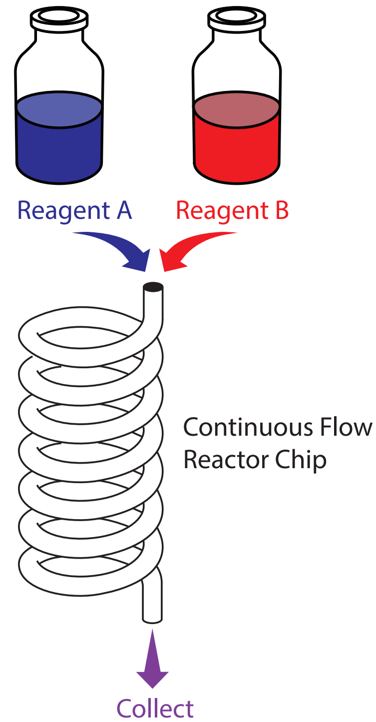
Particle Size of Sorbent (*µm*)	Formats Available (*internal diameter x length in mm*)			
	4.0 x 10	4.0 x 20	10 x 10	21.2 x 10
5	05E-A-N010	05E-A-N020	05E-A-Q010	05E-A-T010
10	07E-A-N010	07E-A-N020	07E-A-Q010	07E-A-T010

Please visit our Ordering Information section p. 209 to learn about the different formats that are available and how to build your own part number.

Compatibility with Different Technologies

Functionalized Scavengers in Flow Chemistry

Flow chemistry is a relatively new technique that is being used more and more for large scale manufacturing because it only requires a small investment but enables the production of large quantities in a short time. The use of supported scavengers in flow chemistry is even more recent, but is generally more reliable and safer than batch procedures.



Supported scavengers are available on different supports such as silica, polymers, charcoal and alumina. They offer many advantages over the traditional homogeneous scavengers, including ease of handling and purification. Silica presents no swelling, much higher mechanical and thermal stability and ease of scalability than polymer.

Scavenging can be achieved using Silia*MetS* or Silia*Bond* in flow chemistry applications. Simply place the silica-based scavenger inside the solid-phase reactors provided with your flow system (*such as the 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.

In this catalog, all application notes and case studies using flow chemistry technology are identified by this logo:

Can be packed with any of our scavengers

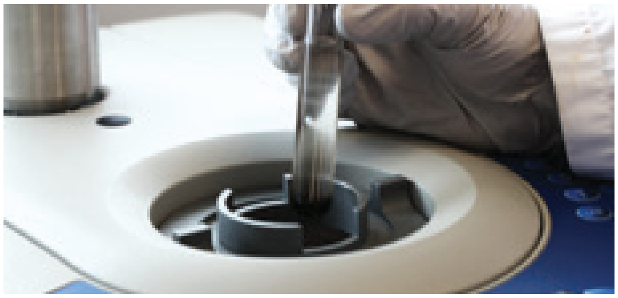
Scavengers in Microwave-Assisted Chemistry

Fast kinetics, higher yields, excellent purity, wide compatibility of solvents and their applicability to a variety of reactions and applications are just some of the advantages that make scavengers very important tools in the laboratory.

After their introduction, chemists started to use supported reagents for solution-phase synthesis, and later on heterogeneous scavengers for post-reaction purification.

Commonly used polymer-supported reagents, although very useful, have drawbacks when used in microwave synthesizers, namely swelling and heat instability. The high temperatures generated put stress on the resins. Also, because of the small reaction volumes, the swelling of the resins can be problematic. ***Silica-based products, on the other hand, do not suffer from such shortcomings. They are heat resistant and they do not swell.***

Metal and organic removal impurity using Silia*MetS* and Silia*Bond* can also be done under microwave irradiation to provide excellent scavenging efficiency in just minutes. Simply mix into a microwave tube the scavenger, the API dissolved in a suitable solvent, and set-up the system with chosen parameters. Usually, five minutes are sufficient for complete scavenging.

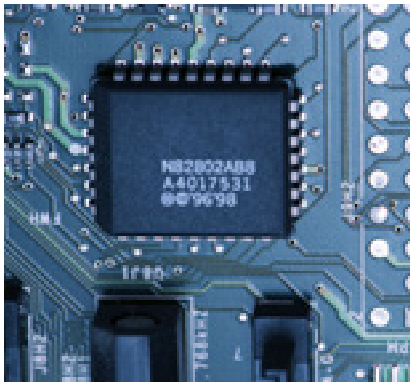


In this catalog, all application notes and case studies using microwave technology are identified by this logo:

Scavengers in Industry

Because our technology is flexible, versatile and customizable to suit your particular needs, these are some of the markets we have been helping over the years:

- Pharmaceutical
- Chemistry
- Electronics
- Mining
- Semi-conductors
- Optical fibers
- Metal recycling
- Universities & Research centers
- Natural extracts



Metal & Organic Scavenging Screening Services

CONFIDENTIALITY GUARANTEED

This service was specially designed for scientists that are either confronted with a residual impurity that needs to be discarded, or in lower in concentration.

With increasing regulatory requirements (*FDA, ICH*) for residual levels of metal catalysts and organic potentially genotoxic impurities (*PGI compounds*), the removal of post-reaction metal residues has become a major issue in the industry. SiliCycle offers an unparalleled range of metal scavengers with its Silia*MetS* line, which significantly facilitates this purification process.

Our scavenging screening services are innovative as they provide solutions to 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 transfers are guaranteed.

1. NDA signed for confidentiality purpose
2. Scavenging questionnaire completed by customer and revised by our experts
3. Communications to determine the objectives of the service
4. Customer's sample sent to SiliCycle
5. Initial lab-scale screening to select the most efficient scavengers and generate data
6. Optimization of the conditions
7. Scale-up trials and purity evaluation
8. Preparation of the report and wrap up meeting to present results to customer
9. Detailed experimental procedure for easy technology transfer & plant trials

Full Process Scale

We can also offer an exclusive partnership program designed to run on Full Process Scale. We will be working with you, in function of your needs. This process optimization work can be carried out and optimized as a slurry in your reactor followed by filtration (*bulk mode*), or via a cartridge in a flow design.

Please discover our full range of R&D Services in pages 287 to 303

Over the years, SiliCycle has developed a number of screening services to assist customers in their project and help identify solutions for purification problems, at all stages & scales, from R&D to production.

Regulatory Information

Regulatory Documents & Information

The SiliCycle scavengers have been used for over a decade in pilot plants and production units under cGMP conditions by the pharmaceutical industry as well as CMOs and CROs. They have ran their own analysis proving that silica-based scavengers can safely be used, both in reactors or cartridges, without leaching that would compromize the purity of their precious compound.

SiliCycle is committed to high quality standards and always strives to provide superior quality products. In doing so, all products are manufactured in an ISO 9001:2008 compliant facility and subjected to stringent quality control.

SiliCycle provides a Certificate of Analysis with all its products, certifying that every lot has been manufactured and tested in accordance with SiliCycle specifications. Moreover, samples from every lot are kept for subsequent analysis.

All products are shipped with the following information:

- Certificate of Analysis (*molecular loading, surface coverage, volatile content, etc.*)
- Material Safety Data Sheet (*MSDS*)
- Technical information

All products can be shipped with the following information, under request:

- BSE / TSE declaration (*non animal-derived*)
- GMO-Free Certificate
- Melamine-Free Certificate

Regulatory Support File

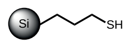
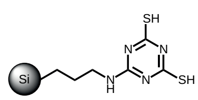
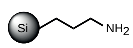
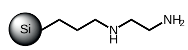
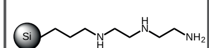
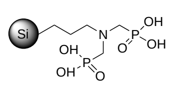
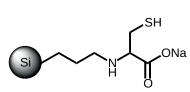
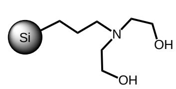
SiliCycle can work with you to fill and provide customized regulatory documents, including specific analytical tests in line with your needs.

Our Regulatory Support Files (*RSF*) are documents that include both proprietary and non-proprietary information on performance, chemical / thermal / mechanical stability, extractable & leachable compounds, SOPs, scale-up procedures, batch history, analytical methods and more. RSF documentation can be obtained through a Non-Disclosure Agreement (*NDA*).

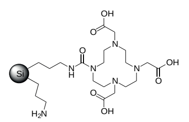
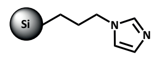
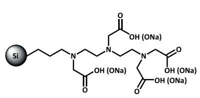
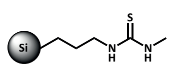
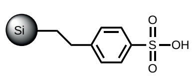
For any inquiries, please contact regulatorysupport@silicycle.com

Silia*MetS* Metal Scavengers Portfolio

Silia*MetS* Metal Scavengers Technical Information

Scavengers	Structure	Brief Description	Metals Removed[1]	Typical Characteristics [2, 3]
Silia*MetS* Thiol **PN: R51030B** Loading: ≥ 1.20 mmol/g Endcapping: Yes		Silia*MetS* Thiol is our most versatile and robust metal scavenger for a variety of metals under a wide range of conditions.	**Ag, Hg, Os, Pd & Ru** Cu, Ir, Pb, Rh & Sn	Color: White Density: 0.682 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* DMT **PN: R79030B** Loading: ≥ 0.50 mmol/g Endcapping: Yes		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*).	**Ir, Ni, Os, Pd, Pt, Rh & Ru** Cd, Co, Cu, Fe, Sc & Zn	Color: Light brown Density: 0.732 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Amine **PN: R52030B** Loading: ≥ 1.20 mmol/g Endcapping: Yes		Also known for their electrophile scavenging efficiencies and their base reagent qualities, Silia*MetS* Amine, Diamine and Triamine have also proven to be very useful for the scavenging of the following metals: Pd, Pt, Cr, W and Zn.	**Cd, Cr, Pd, Pt, Rh & Ru** Co, Cu, Fe, Hg, Pb, W & Zn	Color: Off-white Density: 0.700 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* Diamine **PN: R49030B** Loading: ≥ 1.28 mmol/g Endcapping: Yes			**Cr, Pd, Pt, W & Zn** Cd, Co, Cu, Fe, Hg, Ni, Pb, Ru & Sc	Color: Off-white Density: 0.728 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* Triamine **PN: R48030B** Loading: ≥ 1.11 mmol/g Endcapping: Yes			**Cr, Pd, Pt, W & Zn** Ag, Cd, Co, Cu, Fe, Hg, Ni, Os, Pb, Rh, Ru & Sc	Color: Off-white Density: 0.736 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* AMPA **PN: R85130B** Loading: ≥ 0.80 mmol/g Endcapping: Yes		Silia*MetS* AMPA is an aminomethyl-alkylphosphonic acid ligand known for its excellent metal-bonding properties. It is particularly efficient to remove Al, Sb, Ni, La, and also very effective for Co, Cu, Fe, Mg and Zn scavenging from reaction intermediates or final APIs.	**Al, Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Mg, Nd, Ni, Pm, Pr, Sb, Sm, Tb, Tm, V & Yb** Co, Cu, Fe, Mg & Zn	Color: Yellow Density: 0.707 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 1 Year
Silia*MetS* Cysteine **PN: R80530B** Loading: ≥ 0.30 mmol/g Endcapping: Yes		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.	**Cd, Fe, Ir, Os, Ru, Sc & Sn** Ca, Cr, Cs, Cu, La, Mg, Pd, Pt, Rh & Zn	Color: Orange Density: 0.665 g/mL Solvent Compatibility: 2 Prolonged Storage: 1 Shelf Life: 1 Year
Silia*MetS* DEAM **PN: R54430B** Loading: ≥ 0.85 mmol/g Endcapping: Yes		Silia*MetS* DEAM is a versatile scavenger designed to remove trace metal of Ti, Zn, Fe and Ag as well as boronic acids from reaction intermediates or final APIs.	**Ag, Fe, Sn, Ti & Zn**	Color: Off-white Density: 0.691 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years

Silia*MetS* Metal Scavengers Technical Information

Scavengers	Structure	Brief Description	Metals Removed[1]	Typical Characteristics[2, 3]
Silia*MetS* DOTA **PN: R91030B** Loading: ≥ 0.38 mmol/g Endcapping: Yes		Silia*MetS* DOTA is a silica-supported tetracarboxylic acid and its various conjugate bases. DOTA molecule is a well-adopted complexing agent. Linked to various metals, so formed-complexes are used as contrast agents in cancer treatments or other medical applications.	**Ca, Cu, Gd, La, Ni & Zn** Co, Fe, Mg, Pd, Pt & Rh	Color: Light yellow Density: 0.681 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 1 Year
Silia*MetS* Imidazole **PN: R79230B** Loading: ≥ 0.96 mmol/g Endcapping: Yes		Silia*MetS* Imidazole is a versatile metal scavenger for a variety of metals including Cd, Co, Cu, Fe, Ni, Os, Pd and Rh.	**Cd, Co, Cu, Fe, Ir, Li, Mg, Ni, Os, W & Zn** Cr, Pd & Rh	Color: Off-white Density: 0.681 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* TAAcOH **PN: R69030B** Loading: ≥ 0.41 mmol/g Endcapping: No		Silia*MetS* TAAcOH & TAAcONa are supported versions of EDTA in their acid 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 oxidation states, compared to Silia*MetS* TAAcONa which is useful for metals in higher oxidation states (≥ *2*).	**Ca, Co, Ir, Li, Mg, Ni, Os, Ru & Sc** Cr, Cs, Fe, Pd, Rh & Sn	Color: Off-white Density: 0.635 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* TAAcONa **PN: R69230B** Loading: ≥ 0.41 mmol/g Endcapping: No			**Ca, Cd, Cs, Cu, Fe, Ir, La, Li, Mg, Ni, Os, Rh, Sc & Sn** Cr, Pd, Ru & Zn	Color: Off-white Density: 0.712 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* Thiourea **PN: R69530B** Loading: ≥ 1.07 mmol/g Endcapping: Yes		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.	**Pd & Ru** Ag, Cu, Fe, Os, Rh, Sc & Sn	Color: Off-white Density: 0.767 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Tosic Acid **PN: R60530B** Capacity: ≥ 0.54 meq/g Endcapping: Yes		Silia*Bond* Tosic Acid is in a class of strong acids used in different fields of synthetic organic chemistry. The aromatic ring makes it slightly more acidic than other supported sulfonic acids.	**Fe, Rh & Sn** Ag, Cu, Ni, Pd, Pt, Ru & Zn	Color: Off-white Density: 0.698 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years

[1] **Scavenging Efficiency:** Best scavenger for the removal of a particular metal is indicated in **Navy Blue**
Good scavenger indicated in **Pale Blue**

[2] **Solvent Compatibility**: 1- All solvents, aqueous and organic
2- All organic solvents

[3] **Prolonged Storage**: 1- Keep dry
2- Keep cool (< *8°C*) and dry
3- Keep cool (< *8°C*), dry and under inert atmosphere

Potentially Genotoxic Impurities (PGI) Scavenger
Contact Us for More Information

Silia*MetS* Metal Scavengers Selection Table

Best scavenger: ■ | Good scavenger: ●

Silia*MetS* Metal Scavengers Selection Table								
Scavenger		Silia*MetS* Thiol (*Si-Thiol*) PN: R51030B	Silia*MetS* DMT (*Si-DMT*) PN: R79030B	Silia*Bond* Amine (*Si-WAX*) PN: R52030B	Silia*MetS* AMPA (*Si-AMPA*) PN: R85130B	Silia*MetS* Cysteine (*Si-CYS*) PN: R80530B	Silia*MetS* DEAM (*Si-DEAM*) PN: R54430B	Silia*MetS* Diamine (*Si-DIA*) PN: R49030B
Loading (*mmol/g*)		≥ 1.20	≥ 0.50	≥ 1.20	≥ 0.80	≥ 0.30	≥ 0.85	≥ 1.28
Typical Tap Density (*g/mL*)		0.682	0.732	0.700	0.707	0.665	0.691	0.728
Metals to be scavenged	**Ag**	■					■	
	Al				■			
	Ca					●		
	Cd		●	■		■		●
	Ce				■			
	Co		●	●	●			●
	Cr			■		●		■
	Cs					●		
	Cu	●	●	●	●	●		●
	Fe		●	●	●	■	■	●
	Gd				■			
	Hg	■		●				●
	Ir	●	■			■		
	La				■	●		
	Li							
	Mg				●	●		
	Ni		■		■			●
	Os	■	■			■		
	Pb	●		●				●
	Pd	■	■	■		●		■
	Pt		■	■		●		■
	Rh	●	■	■		●		
	Ru	■	■	■		■		●
	Sc		●			■		●
	Sn	●				■	■	
	Ti						■	
	W			●				■
	Zn		●	●	●	●	■	■

Silia*MetS* Metal Scavengers Selection Table

Silia*MetS* DOTA (*Si-DOTA*) PN: R91030B	Silia*MetS* Imidazole (*Si-IMI*) PN: R79230B	Silia*MetS* TAAcOH (*Si-TAAcOH*) PN: R69030B	Silia*MetS* TAAcONa (*Si-TAAcONa*) PN: R69230B	Silia*MetS* Thiourea (*Si-THU*) PN: R69530B	Silia*MetS* Triamine (*Si-TRI*) PN: R48030B	Silia*Bond* Tosic Acid (*Si-SCX*) PN: R60530B	Scavenger
≥ 0.38	≥ 0.96	≥ 0.41	≥ 0.41	≥ 1.07	≥ 1.11	≥ 0.54 meq/g	**Loading (*mmol/g*)**
0.681	0.681	0.635	0.712	0.767	0.736	0.698	**Typical Tap Density (*g/mL*)**
							Metals to be scavenged
				●	●	●	Ag
							Al
■		■	■				Ca
	■		■		●		Cd
							Ce
●	■	■			●		Co
	●	●	●		■		Cr
		●	■				Cs
■	■		■	●	●	●	Cu
●	■	●	■	●	●	■	Fe
■							Gd
					●		Hg
	■	■	■				Ir
■			■				La
	■	■	■				Li
●	■	■	■				Mg
■	■	■	■		●	●	Ni
	■	■	■	●	●		Os
					●		Pb
●	●	●	●	■	■	●	Pd
●					■	●	Pt
●	●	●	■	●	●	■	Rh
		■	●	■	●	●	Ru
		■	■	●	●		Sc
		●	■	●		■	Sn
							Ti
	■				■		W
■	■		●		■	●	Zn

Silia*MetS* Metal Scavengers 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 tables, shown below, will help 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 Scavenger Screening Service. Contact us to take advantage of our expertise in metal removal.

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

Silia*MetS*	Catalyst, Solvent & Conditions (*% of catalyst scavenged*)							
	$Pd(OAc)_2$	$Pd_2(allyl)_2Cl_2$	$Pd_2(dba)_3$	$Pd(PPh_3)_4$	$PdCl_2(dppf)$	Grubbs 1st Gen.	Grubbs 2nd Gen.	Hoveyda-Grubbs 1st
	DMF	DMF	DMF	DMF	DMF	DMF	DMF	DMF
	4 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 22°C	8 equiv, 16 h, 80°C	8 equiv, 16 h, 80°C	8 equiv, 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 equiv]	99 [4 equiv]	98 [4 equiv]
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, Conditions & Reaction			
	$PdCl_2(PPh_3)_2$, CuI (*in DME*)	$Pd(OAc)_2$, P(o-tol)$_3$ (*in i-PrOH, H_2O*)	$RhCl(PPh_3)_3$ (*in Toluene*)	$FeCl_3.6H_2O$ (*in THF*)
	8 equiv, 4 h, 22°C	5 equiv, 4 h, 40°C	65 equiv, 4 h, 22°C	5 equiv, 4 h, 22°C
	Sonogashira Coupling	Suzuki Coupling	Wilkinson Hydrogenation	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	TPAP	$Ni(acac)_2$	Wilkinson's Cat.	$[Rh(OAc)_2]_2$	H_2PtCl_6	$Pb(OAc)_2.3H_2O$	$Zn(OAc)_2.2H_2O$
DMF	DCM	DMF	DMF	DMF	DMF	DMF	DMF
8 equiv, 16 h, 80°C	4 equiv, 16 h, 22°C	4 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 22°C	4 equiv, 4 h, 22°C
	96		> 99 [16 h]	97	80 [16 h]	97	> 99
	> 99		99	97			97 [80°C]
not screened	not screened	92	88	not screened	99		> 99
99 [4 equiv]	> 99	97	> 99	> 99	> 99	99	94
	> 99		> 99	> 99			> 99
90	97	99	> 99	> 99 [22°C]	> 99	81	> 99
95	> 99	93	97	97 [22°C]	97	> 99 [80°C]	> 99
	not screened	91 [80°C]	90	97 [22°C]	not screened		> 99
	> 99	> 99	97	96 [16 h]			
	> 99	> 99	88	> 99 [16 h]		90	> 99

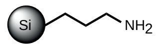
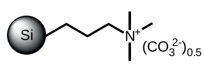
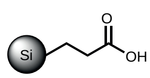
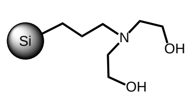
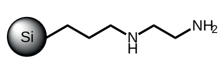
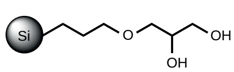
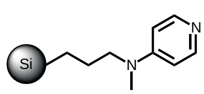
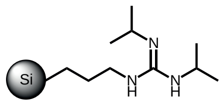
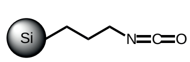
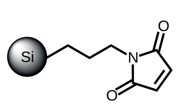
Catalyst, Solvent, Conditions & Reaction			
CuCN (*in DMF*)	Iridium Crabtree's Cat. (*in DCM*)	$LaCl_3.LiCl$ (*in DMF*)	$PhCH_2ZnCl$ (*in THF*)
10 equiv, 4 h, 22°C	4 equiv, 4 h, 22°C	1 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C
Rosemund von-Braun Cyanation	Alkene Hydrogenation	1,2-Addition on Ketone	Negishi Coupling
94			
> 99			
> 99	86	Li: 75, La: > 99	91
> 99			84
98			94
> 99			95
> 99			91
95			94
80			
> 99	80	Li: 95, La: > 99	94

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

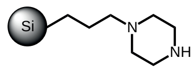
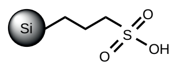
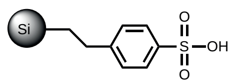
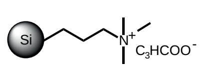
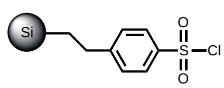
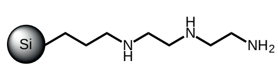
Scavenging Solutions

Silia*Bond* Organic Scavengers Portfolio

Silia*Bond* Organic Scavengers Technical Information

Scavengers	Structure	Nature	Molecules Removed	Typical Characteristics [1,2]
Silia*Bond* Amine **PN: R52030B** Loading: ≥ 1.20 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.700 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic Phenols	
Silia*Bond* Carbonate **PN: R66030B** Loading: ≥ 0.46 mmol/g Endcapping: Yes		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids, Acidic Phenols & Boronic Acids	Color: Off-white Density: 0.608 g/mL Solvent Compatibility: 3 Prolonged Storage: 1 Shelf Life: 1 Years
Silia*Bond* Carboxylic Acid **PN: R70030B** Loading: ≥ 0.92 mmol/g Endcapping: Yes		Scavenger for Bases (*Ionic Bonding*) Catch & Release	Primary / Secondary Amines & Anilines	Color: Off-white Density: 0.687 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* DEAM PGI-S **PN: R54430B** Loading: ≥ 0.85 mmol/g Endcapping: Yes		Scavenger for Electrophiles & Lewis Acids (*Covalent & Ionic Bonding*) Catch & Release	Boronic Acids	Color: Off-white Density: 0.691 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* Diamine **PN: R49030B** Loading: ≥ 1.28 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.728 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic phenols	
Silia*Bond* Diol **PN: R35030B** Loading: ≥ 0.97 mmol/g Endcapping: No		Scavenger for Electrophiles & Lewis Acids (*Covalent & Ionic Bonding*) Catch & Release	Boronic Acids	Color: Off-white Density: 0.687 g/mL Solvent Compatibility: 2 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* DMAP **PN: R75630B** Loading: ≥ 0.53 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides & Sulfonyl Chlorides	Color: Light brown to brown Density: 0.674 g/mL Solvent Compatibility: 1 Prolonged Storage: 3 Shelf Life: 1 Years
Silia*Bond* Guanidine **PN: R68230B** Loading: ≥ 0.80 mmol/g Endcapping: Yes		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids, Acidic Phenols & Boronic Acids	Color: Light yellow Density: 0.732 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Isocyanate **PN: R50030B** Loading: ≥ 1.16 mmol/g Endcapping: Yes		Scavenger for Nucleophiles (*Covalent Bonding*)	Alcohols, Alkoxides, Amines, Anilines, Hydrazines, Organometallics, Thiols & Thiolates	Color: Off-white Density: 0.741 g/mL Solvent Compatibility: 3 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*Bond* Maleimide **PN: R71030B** Loading: ≥ 0.64 mmol/g Endcapping: Yes		Scavenger for Nucleophiles (*Covalent Bonding*)	Thiols & Thiolates	Color: Off-white Density: 0.644 g/mL Solvent Compatibility: 5 Prolonged Storage: 3 Shelf Life: 2 Years

Silia*Bond* Organic Scavengers Technical Information

Scavengers	Structure	Nature	Molecules Removed	Typical Characteristics [2, 3]
Silia*Bond* Piperazine **PN: R60030B** Loading: ≥ 0.83 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.671 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic Phenols	
Silia*Bond* Propylsulfonic Acid **PN: R51230B** Loading: ≥ 0.63 mmol/g Endcapping: Yes		Scavenger for Bases (*Ionic Bonding*) Catch & Release	Amines & Anilines	Color: Off-white Density: 0.728 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Tosic Acid **PN: R60530B** Loading: ≥ 0.54 meq/g Endcapping: Yes				Color: Off-white Density: 0.698 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* TMA Acetate **PN: R66430B** Loading: ≥ 0.71 mmol/g Endcapping: No		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Carboxylic Acids	Color: Off-white Density: 0.665 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Tosyl Chloride **PN: R44030B** Loading: ≥ 0.63 mmol/g Endcapping: Yes		Scavenger for Nucleophiles (*Covalent Bonding*)	Alcohols, Alkoxides, Amines, Anilines, Hydrazines, Organometallics, Thiols & Thiolates	Color: Off-white Density: 0.761 g/mL Solvent Compatibility: 4 Prolonged Storage: 3 Shelf Life: 6 months
Silia*MetS* Triamine **PN: R48030B** Loading: ≥ 1.11 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.736 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic Phenols	

[1] **Solvent Compatibility**:
1- All solvents, aqueous and organic
2- All organic solvents
3- Anhydrous aprotic solvents
4- Anhydrous aprotic solvents, unstable in DMF
5- Polar solvents (*DMF, MeOH, H_2O*)

[2] **Prolonged Storage**:
1- Keep dry
2- Keep cool (< *8°C*) and dry
3- Keep cool (< *8°C*), dry and under inert atmosphere

Potentially Genotoxic Impurities (PGI) Scavenger
Contact Us for More Information

Scavenging Solutions

Silia*Bond* Organic Scavengers Selection Table

Silia*Bond* Organic Scavengers can help you purify your API. Functional group is bound to silica, that will specifically react with a given product. Use the double-entry chart below to choose the best match between the impurity you are dealing with or the scavenger your already have in hand.

Electrophile scavenger (*Covalent Bonding*): ◆ | **Nucleophile scavenger (*Covalent Bonding*):** ▼

Ionic bonding: ● | **Catch & release:** ⬢

Silia*Bond* Organic Scavengers Selection Table

Scavenger	Silia*Bond* Amine (*Si-WAX*) PN: R52030B	Silia*MetS* Diamine (*Si-DIA*) PN: R49030B	Silia*MetS* Triamine (*Si-TRI*) PN: R48030B	Silia*Bond* Carbonate (*Si-CO3*) PN: R66030B	Silia*Bond* Carboxylic Acid (*Si-WCX*) PN: R70030B	Silia*MetS* DEAM (*Si-DEAM*) PN: R54430B	Silia*Bond* Diol (*Si-Diol*) PN: R35030B	Silia*Bond* DMAP (*Si-DMAP*) PN: R75630B
Loading (*mmol/g*)	≥ 1.20	≥ 1.28	≥ 1.11	≥ 0.46	≥ 0.92	≥ 0.85	≥ 0.97	≥ 0.53
Typical Tap Density (*g/mL*)	0.700	0.728	0.736	0.608	0.687	0.691	0.687	0.674
Electrophiles & Nucleophiles to be scavenged								
Acid *Carboxylic acid*		● ⬢		● ⬢				
Acyl chloride		◆						◆
Acidic phenol		● ⬢		● ⬢				
Alcohol								
Aldehyde		◆						
Alkoxide								
Amine					● ⬢			
Anhydride		◆						
Aniline					● ⬢			
Boronic acid				● ⬢		◆ ⬢	◆ ⬢	
Chloroformate		◆						
Hydrazine								
Isocyanate		◆						
Ketone		◆						
Organometallic								
Sulfonyl chloride		◆						◆
Thiol / Thiolate								

Silia*Bond* Organic Scavengers Selection Table

Silia*Bond* Guanidine (*Si-GUA*) PN: R68230B	Silia*Bond* Isocyanate (*Si-ISO*) PN: R50030B	Silia*Bond* Maleimide (*Si-MAL*) PN: R71030B	Silia*Bond* Piperazine (*Si-PPZ*) PN: R60030B	Silia*Bond* Propylsulfonic Acid (*Si-SCX-2*) PN: R51230B Tosic Acid (*Si-SCX*) PN: R60530B	Silia*Bond* TMA Acetate (*Si-SAX-2*) PN: R66430B	Silia*Bond* Tosyl Chloride (*Si-TsCl*) PN: R44030B	Scavenger
≥ 0.80	≥ 1.16	≥ 0.64	≥ 0.83	SCX-2: ≥ 0.63 SCX: ≥ 0.54 meq/g	≥ 0.71	≥ 0.63	**Loading (*mmol/g*)**
0.732	0.741	0.644	0.671	SCX-2: 0.728 SCX: 0.698	0.665	0.761	**Typical Tap Density (*g/mL*)**
● ⬢			● ⬢		● ⬢		**Acid** *Carboxylic acid*
			◆				**Acyl chloride**
● ⬢			● ⬢				**Acidic phenol**
	▼					▼	**Alcohol**
			◆				**Aldehyde**
	▼					▼	**Alkoxide**
	▼			● ⬢		▼	**Amine**
			◆				**Anhydride**
	▼			● ⬢		▼	**Aniline**
● ⬢							**Boronic acid**
			◆				**Chloroformate**
	▼					▼	**Hydrazine**
			◆				**Isocyanate**
			◆				**Ketone**
	▼					▼	**Organometallic**
			◆				**Sulfonyl chloride**
	▼	▼				▼	**Thiol / Thiolate**

Typical Experimental Procedures in Batch Mode Reactor (*Bulk*)

STEP	For Silia*MetS* Metal Scavengers	For Silia*Bond* Organic Scavengers
	For initial screening, start with 4 - 8 molar equivalents of Silia***MetS*** in respect to the residual metal concentration.	For initial test, start with 2 - 4 molar equivalents of Silia***Bond*** in respect to the impurity.
1	Dissolve the crude product to be treated in a suitable solvent (*or directly use the crude reaction mixture*) and prepare vials containing the same solution volume. Directly add your chosen Silia*MetS* / Silia*Bond* to these vials. **Note**: *no pre-wetting / pre-activation is required.*	
2	For initial tests, stir the solution for at least one hour at room temperature.	
3	Scavenging progress can be followed by normal analytical techniques. The scavenging progress can also be estimated by looking at the color of the solution, as depicted herein:  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 colored, 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. Keep in mind that colors can come from other factors unrelated to the impurities.	Scavenging progress can be followed by normal analytical techniques. If scavenging seems incomplete or very slow, reaction time or temperature can be increased, or more equivalents of the scavenger can be added.
4	At the end of the scavenging, filter off the scavenger using a fritted funnel or filtration device.	
5	Wash the Silia*MetS* with additional solvent for total recovery of the API (*or compound of interest*) and concentrate the solution under vacuum.	Wash thoroughly with solvent to afford impurity-free solution. Concentrate under vaccum.
6	Analyze the residual metal or organic impurity concentration of each vial to identify the most efficient scavenger.	
7	Direct scale-up is now possible. Otherwise, scavenging optimization can be examined.	

Please keep in mind that the above procedures are standard and introductory, but optimization of conditions is key to optimal scavenging efficiency.

Due to it's ease of operation & how swiftly it can handle different sets of conditions, we use the SiliCycle MiniBlock to run our scavenging screenings & optimisations.

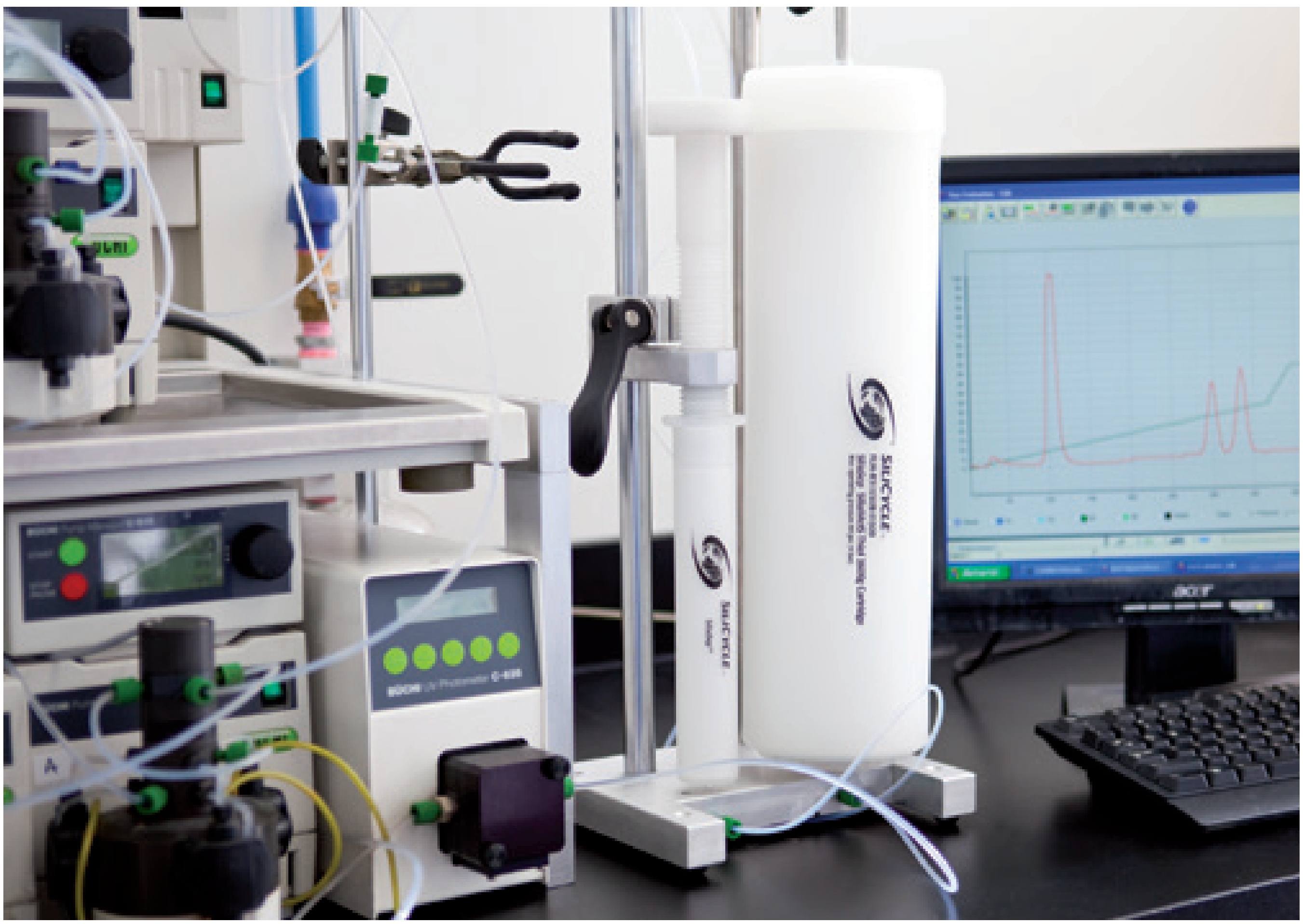
Typical Experimental Procedures in Fixed-Bed Mode (*SPE or Flash cartridges*)

Fixed-bed formats are a great alternative for metal or organic removal and are directly scalable.

We suggest initial screening investigations to be done using Silia*Prep* 2 g / 6 mL SPE cartridges.

Typical Experimental Procecures

STEP	Description
1	Condition the cartridge with 3 - 4 column volumes using the same solvent as the solution to be treated.
2	Add the solution containing the API and the metal or organic impurity 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 at the bottom can be applied to speed up the flow rate.
3	For most Silia*MetS* metal scavengers, a dark colored band will be observed on the top of the silica bed (*right*). ***Note**: if the residual solution is still colored, multiple passes through the same cartridge can be done.*
4	Once the scavenging is completed, wash the cartridge using at least three column volumes of solvent to ensure total API recovery.



Experimental Optimization for Scavengers

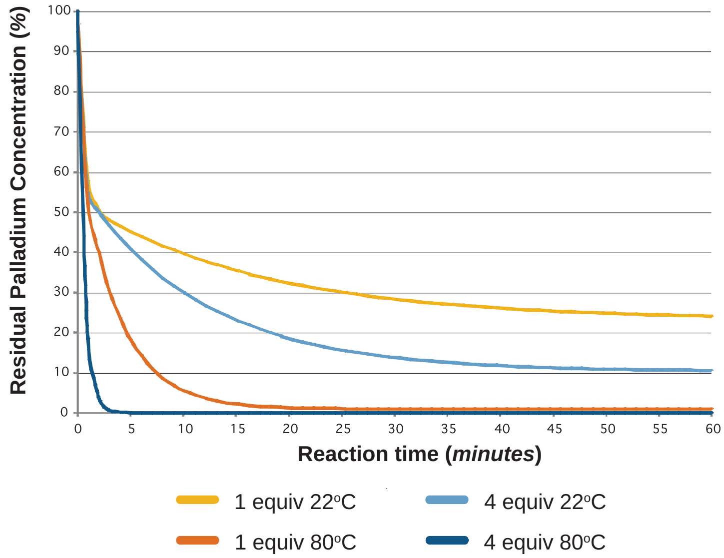
If the scavenging is incomplete or if you wish to optimize the reaction, you can try the steps below. Various parameters can be changed one at a time or simultaneously to improve removal efficiency.

***Note**: you can mix multiple scavengers to get superior efficiency for example when multiple species are suspected or when there's more than one catalyst present.*

Number of Silia*MetS* or Silia*Bond* Equivalents

For initial screening experiments we suggest using 4 - 8 molar equivalents for Silia*MetS* and 2 - 4 molar equivalents for Silia*Bond* relative to the residual impurities concentration. Once the preferred scavenger is identified, further optimization can be done to reduce the number of equivalents used (*typically down to 2 - 4 equivalents, although some cases might require a higher ratio*).

Residual Concentration (%) of $Pd(OAc)_2$ with Silia*MetS* Thiol in DMF



Subsequent Treatments

In some cases (*equilibrium process or the presence of multiple species*), multiple treatments with our scavengers are desirable over a single treatment with a larger amount.

For optimal results, filtration between each treatment can enable higher scavenging efficiency.

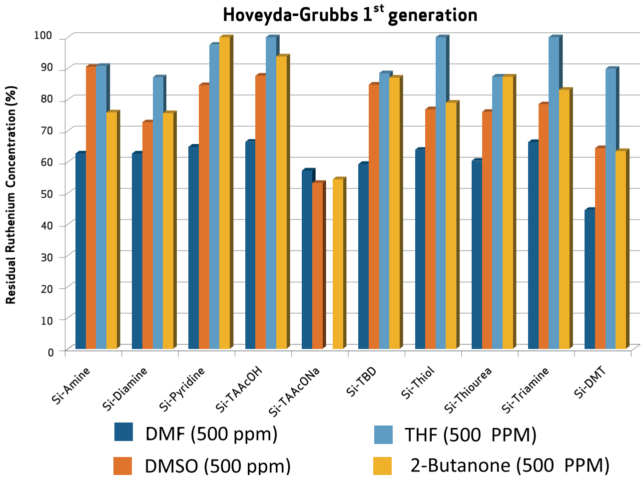
Temperature

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

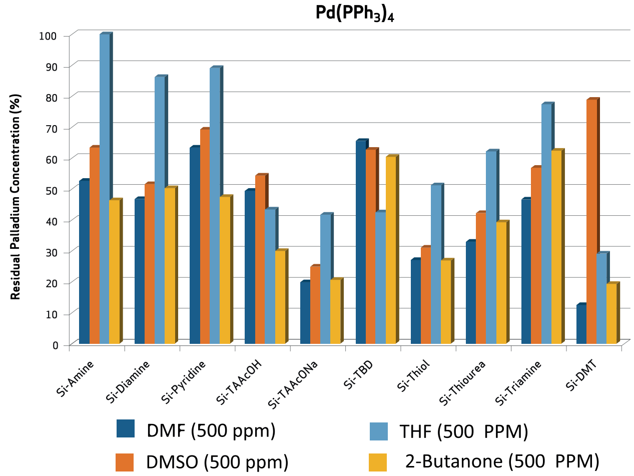
Solvent

Silia*MetS* and Silia*Bond* 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 figures 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.

Hoveyda-Grubbs 1st generation



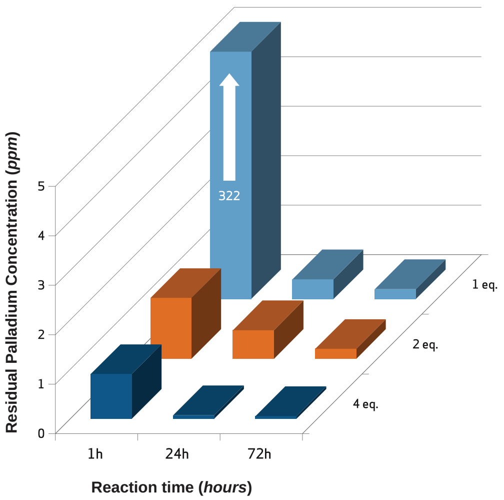
$Pd(PPh_3)_4$



Mixing Rate

Our scavengers are mechanically stable and offer excellent scavenging efficiency in batch processes agitated by overhead 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, scavenger dispersion in solution is improved.



Conditions: $Pd(OAc)_2$, THF, Silia*MetS* Thiol, r.t.
Initial concentration: 1,000 ppm

Reaction Time

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

pH of the Aqueous Solution

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

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

One advantage of our scavengers 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.

Determining the Optimal Amount of Scavenger to be Used

From Residual Metal Concentration

Example: knowing that the palladium (*Pd*) concentration in 800 g of material is 500 ppm (*the oxidation state does not affect the calculation*).

Data needed:

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

1. Determine the amount of palladium to be scavenged

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

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

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

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

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

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

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

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

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

If you have any doubt, please go to our online calculator to have all the work automatically done for you !
http://www.silicycle.com/web-tools/scavengers-calculator

From Amount of Metal Catalyst Used

Data needed:

Amount of metal catalyst used: e.g.: 10 g of $Pd(PPh_3)_4$

Metal catalyst molecular weight: $Pd(PPh_3)_4$ = 1,155.56 g/mol

Determine the amount of palladium to be scavenged

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

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

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.

From Residual Organic Residue Concentration

Data needed:

Loading of organic scavenger: e.g.: Silia*Bond* Guanidine = 0.74 mmol/g

Estimated amount of impurity to be removed (*in mmol*): e.g.: 5 mmol

Calculate the amount of scavenger (*SiliaBond Guanidine*) to use (*1 equivalent*)

$$\text{Amount of SiliaBond Guanidine to use} = \frac{\text{Number of mmol of impurity}}{\text{SiliaBond Guanidine loading}}$$

$$\text{Amount of SiliaBond Guanidine to use} = \frac{5\text{ mmol}}{0.74\text{ mmol/g}} = 6.76\text{ g of SiliaBond Guanidine for 1 equiv}$$

To scavenge 5 mmol of impurity, 6.76 g of Silia*Bond* Guanidine are needed if using only one equivalent. However, keep in mind that it is highly recommended that a minimum of two equivalents be used at first.

In this case, the amount (*g*) of Silia*Bond* Guanidine will be two times higher (*2 x 6.76 g = 13.52 g*).

Scavenging Solutions

Silia*MetS* / Silia*Bond* Stability & Leaching Studies

Because our Metal and Organic Scavengers are being used by many pharmaceutical companies, each Silia*MetS* and Silia*Bond* 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 that includes loading and reactivity determination, as well as leachables and extractables analysis. The solution must be free of contaminants for the product to successfully pass the rigorous quality control tests.

Chemical Resistance In Acidic Medium

Silia*MetS* Thiol (*0.4 g*) was added to several acidic solutions for chemical resistance testing (*4 mL*). Methanol (*0.4 mL*) was added to each vial in order to ensure the silica was well impregnated with the aqueous medium. The solution was stirred mechanically for 1 to 16 hours at 22°C, and 1 hour at 60°C. Si-Thiol was then filtered and rinsed thoroughly with water and methanol, dried and subjected to CNS analysis.

Chemical Resistance of Silia*MetS* Thiol in Acidic Media

Experimental Conditions	1 M, 1h 22°C	5 M, 1h 22°C	5 M, 16h 22°C	5 M, 1h 60°C	5 M, 16h 60°C
H_3PO_4 (*phosphoric acid*)	No Significant Change	No Significant Change	No Significant Change	No Significant Change	Substantial Loss
H_2SO_4 (*sulfuric acid*)	No Significant Change	No Significant Change	No Significant Change	No Significant Change	Substantial Loss
HCl (*hydrochloric acid*)	No Significant Change	No Significant Change	No Significant Change	No Significant Change [1]	Substantial Loss
HNO_3 (*nitric acid*)	No Significant Change	No Significant Change	No Significant Change	No Significant Change	Substantial Loss
AcOH (*acetic acid*)	No Significant Change	No Significant Change	No Significant Change	No Significant Change	Substantial Loss
TFA (*trifluoroacetic acid*)	No Significant Change	No Significant Change	No Significant Change	No Significant Change	Substantial Loss
HCO_2H (*formic acid*)	N/A	N/A	No Significant Change	No Significant Change	Substantial Loss

[1]: reaction was stirred at 40°C.

Chemical Resistance In Basic Medium

Silia*MetS* Thiol (*0.4 g*) was added to several basic media in water, methanol or dichloromethane (*4 mL*). In the case where water was the solvent, methanol (*0.4 mL*) was added to each vial in order to ensure the silica was well impregnated with the aqueous medium. The solution was stirred mechanically for 1 to 16 hours at 22°C. Si-Thiol was then filtered and rinsed thoroughly with water and methanol, dried and subjected to CNS analysis.

Chemical Resistance of Silia*MetS* Thiol in Basic Media

Experimental Conditions	1 M, 1h, 22°C *in protic solvent (water)*	5 M, 1h, 22°C *in protic solvent (water)*	5 M, 16h, 22°C *in protic solvent (methanol)*	5 M, 1h, 22°C *in aprotic solvent (dichloromethane)*
NaOH (*sodium hydroxide*)	Substantial Loss	Silica was dissolved	N/A	N/A
NH_4OH (*ammonium hydroxide*)	No Significant Change	No Significant Change	N/A	N/A
Na_2CO_3 (*sodium carbonate*)	No Significant Change	No Significant Change	N/A	N/A
$NaHCO_3$ (*sodium bicarbonate*)	No Significant Change	No Significant Change	N/A	N/A
TEA (*triethylamine*)	No Significant Change	No Significant Change	No Significant Change	No Significant Change
DEA (*diethanolamine*)	Substantial Loss	Substantial Loss	No Significant Change	No Significant Change
Pyridine	No Significant Change	No Significant Change	No Significant Change	No Significant Change
NH_3 (*ammonia*)	N/A	N/A	No Significant Change	No Significant Change

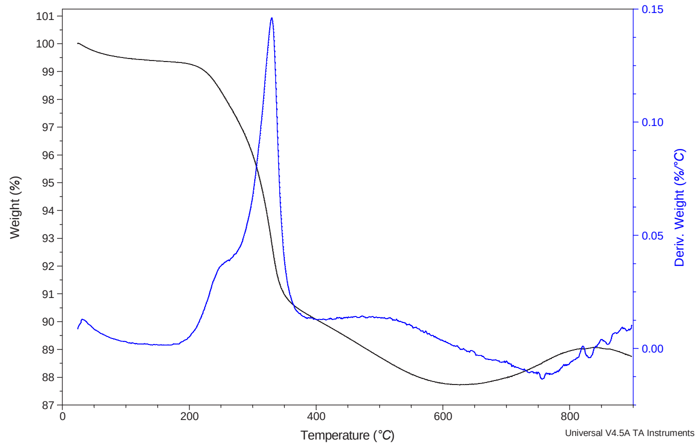
No Significant Change (*0 - 0.7 % difference*)
Light Loss (*0.8 - 1.0 % difference*)
Fair Loss (*1.0 - 1.5 % difference*)
Substantial Loss (> *1.5 % difference*)
Silica was dissolved

No change in color was observed in the supernatant after filtration and washing steps.
Silia*MetS* Thiol is resistant to most basic and acidic conditions.

Thermal Stability

Thermogravimetric analysis, or TGA, is our method to determine any mass loss on Si-Thiol due to decomposition, oxidation, or loss of volatiles (*such as moisture*).
Based on TGA Analysis, Silia*MetS* Thiol is considered to be stable up to 220ºC, but we suggest not to go over 150ºC.

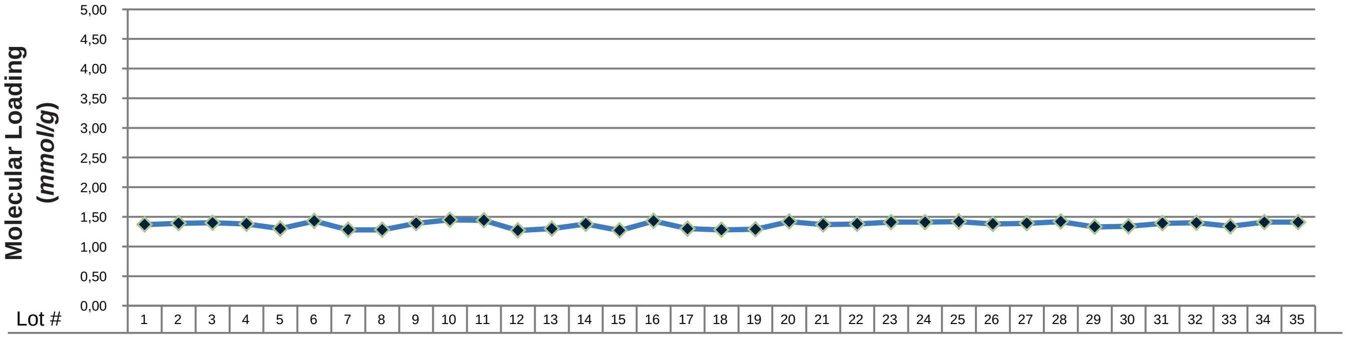
Zoom on important mass loss
(*TGA from 0 - 400°C*)

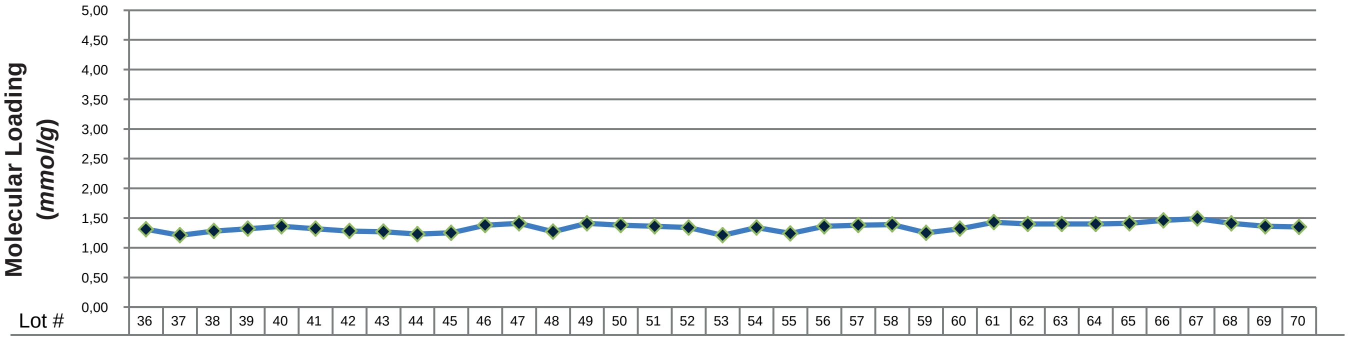


Silia*MetS* Thiol Batch History - Lot-to-lot Reproducibility

The manufacture of functionalized silica gels is both a complex and controlled process. SiliCycle maintains extensive records of each batch manufactured, and retains these for a minimum of 7 years. Such records contain the production history of finished and released products. They provide objective evidence that the functionalized gels were manufactured in accordance to our quality standards and minimal requirements, and act as a record of traceability information for all units or lots.

SiliCycle's loadings of functionalized gels are always extremely constant from batch-to-batch. As an example, here is an overview of lot-to-lot reproducibility over seventy consecutive lots of Silia*MetS* Thiol of same batch size manufactured.



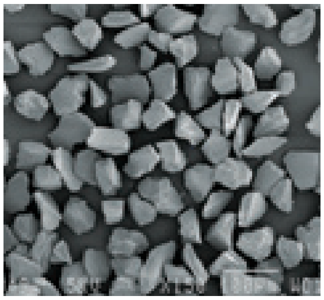


Mechanical Stability

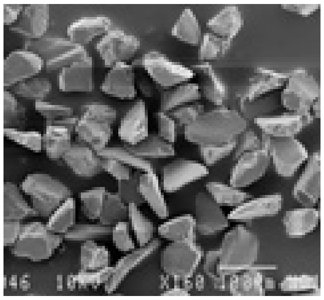
The mechanical resistance of silica gel is roughly 10,000 psi. This value depends on pore diameter and particle size.

In the following experiment, a comparison of mechanical resistance between silica gel and polymer was conducted:

SEM of Silia*MetS* Thiol

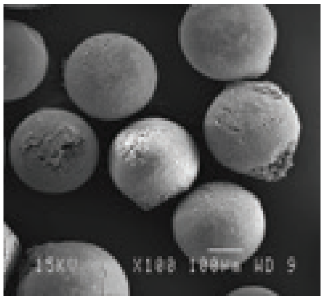


After 4 hours
under mechanical stirring

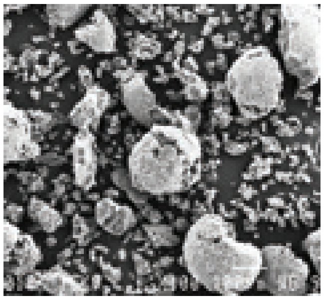


After 16 hours
under mechanical stirring

SEM of Polymer-Support



After 4 hours
under mechanical stirring

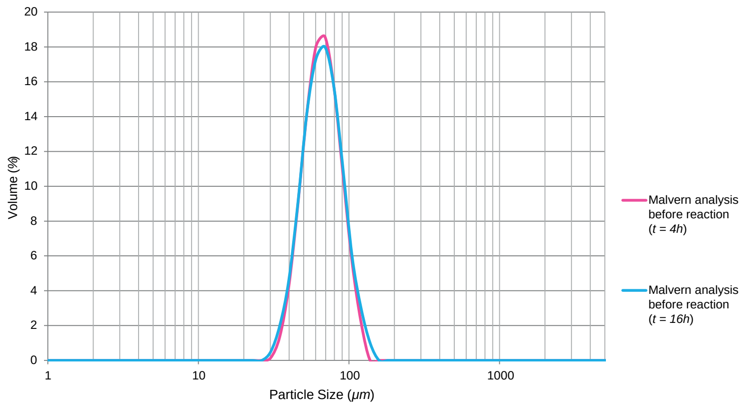


After 16 hours
under mechanical stirring

- Stirring speed: 500 RPM
- Solvent: DMF
- Temperature: 22°C

After 16 hours, there was hardly no difference in the silica particles on which our scavengers are functionalized. In comparison, the polymer support was completely destroyed.

SEM & Malvern Analysis are a safe and clear demonstration that almost no mechanical grinding nor crushing of the silica occurs after stirring, which is not the case for polymeric support, for which drastic grinding appears.



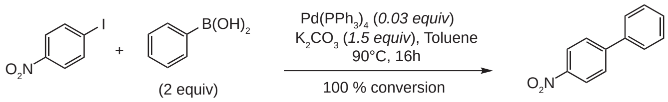
Mechanical Stirrer in Reactor

This picture was taken in one of SiliCycle's medium-sized reactors.

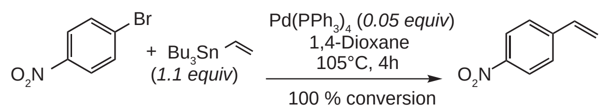
Silia*MetS* Thiol has been produced for more than 20 years in SiliCycle's reactors without any damage.

Leaching and Extractable Studies

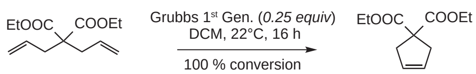
To address the concerns for potential leaching of impurities into reaction mixtures using Silia*MetS* Thiol & DMT, four typical metal-containing reactions were performed. Detection, identification and quantification of possible impurities resulting from the scavenging action was then performed.



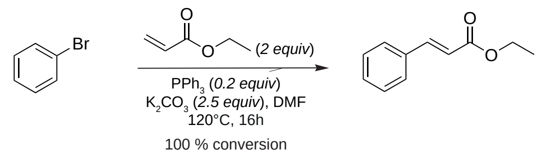
Suzuki Coupling



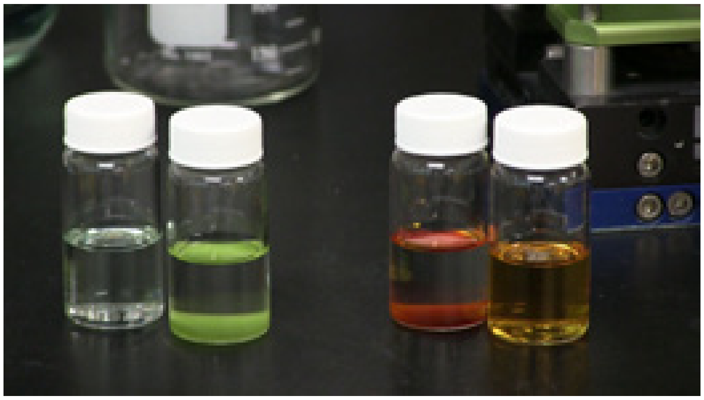
Stille Coupling



Grubbs Ring-Closing Metathesis



Heck Coupling



Experimental Procedure

Crude reaction mixtures (*8 mL*) were placed in a standard polypropylene tube equipped with a 20 µm frit, loaded 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 0.2 µm filter prior to analysis.

Leaching Analysis

Silane leaching was analyzed by Inductively-Coupled Plasma-Optical Emission Spectroscopy (*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 Gas Chromatography-Mass Spectrometry (*GC-MS*), Liquid chromatography-tandem mass spectrometry (*LC-MS*) and ^{1}H NMR Analysis.

Gel Purity Calculation

Here is an example of how gel purity can be calculated:

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

$$\text{Gel purity} = 100 - (\textit{Impurity \%}) \Rightarrow \text{99.9998 \% purity}$$

Silane Leaching Analysis by ICP-OES

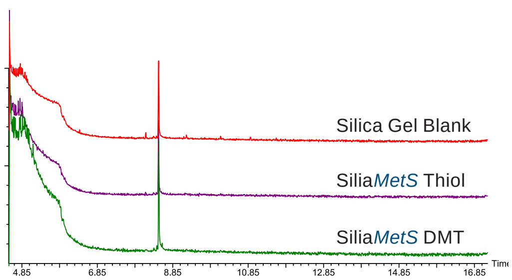
Results shown in the table below for Silia*MetS* Thiol & DMT confirm that minimal leaching occurs with SiliCycle Silia*MetS*.

Stability of Silia*MetS* in Suzuki, Stille, Heck and Grubbs Ring-Closing Metathesis Reactions

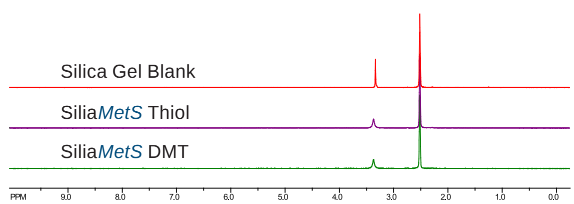
Reaction (*solvent*)	Temperature	Silia***MetS*** Thiol		Silia***MetS*** DMT	
		[*Silicon*]	Gel Purity (%)	[*Silicon*]	Gel Purity (%)
Suzuki (*Toluene*)	22°C	2 ppm	99.9998	1 ppm	99.9999
	80°C	2 ppm	99.9998	2 ppm	99.9998
Stille (*1,4-Dioxane*)	22°C	2 ppm	99.9998	1 ppm	99.9999
	80°C	1 ppm	99.9999	3 ppm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

Non-Silicon Leaching Analysis

Each experiment was run on a 1 g aliquote of Silia*MetS* and was shaken for 1 hour at room temperature. Leaching examination was performed through both GC-MS and ^{1}H NMR analysis, comparing leaching profiles of bare silica, Silia*MetS* Thiol and Silia*MetS* DMT.



Gas Chromatography-Mass Spectrometry (*GC-MS*)



^{1}H NMR Analysis (d_6-*DMSO*)

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

Note*: 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, d_6-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 two years from the manufacturing date without significant loss of performance.

Silia*MetS* Thiol after Two Years

Lot #	QC Date	Scavenging (%)
11577	Year 0	> 99.9
	Year 1	99.5
	Year 2	99.6
12218	Year 0	99.9
	Year 1	99.5
	Year 2	99.1
64215	Year 0	99.2
	Year 1	99.3
	Year 2	99.5

Scavenging: 1,000 ppm of $Pd(OAc)_2$ in DMF.
Conditions: 2 equiv of Silia*MetS* Thiol, 1 h, 22°C.

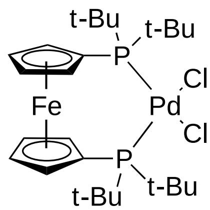
SiliaMetS Metal Scavengers Application Examples & Case Studies

Scavenging of Pd-118 Using SiliaMetS Metal Scavengers

(*More experimental details avalaible in Application Note #AN-001. Please check our Website*)

Some of Silia*MetS* Metal Scavengers have a particularly powerful scavenging behavior toward reagent Pd-118.

Pd-118, or Pd(d*t*bpf)Cl_2 is a strong, homogeneous catalyst that has been shown to be very stable and active for all coupling reactions, especially aminations, reductive carbonylations and Suzuki couplings. Nevertheless, metals from this active catalyst can act as severe contaminants and be tricky to get rid of.



Pd-118 Complex

Behavior of our SiliaMetS Metal Scavengers Toward this Specific Complex (*catalyst only in solvent*)

Scavengers	DMF, 22°C		DMF, 60°C		Methyl-THF, 22°C		Methyl-THF, 60°C		DCM, 22°C	
	Scavenging Efficiency of Preliminary Screening (*in %*)									
	Pd	Fe	Pd	Fe	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* DMT	76	45	**97**	51	85	63	**97**	47	**96**	83
Silia*MetS* Diamine	76	27	54	18	51	25	80	0	38	29
Silia*MetS* Thiol	51	28	72	34	50	50	88	64	36	48
Silia*MetS* Cysteine	59	49	67	49	70	60	**93**	52	53	50
Silia*MetS* Tosic Acid	25	47	8	54	70	69	85	**83**	80	**78**

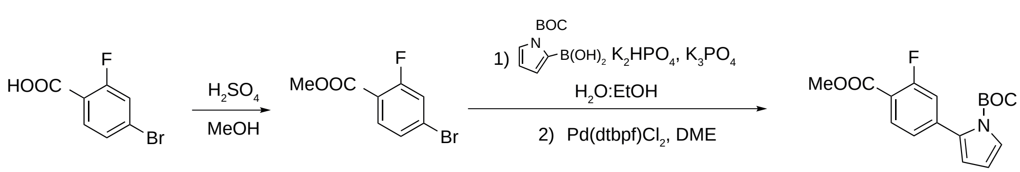
Conditions: Palladium complex solutions were made in DMF, methyl-THF and dichloromethane, and shaken with four molar equivalents of metal scavengers for four hours, at room temperature or 60°C.

Scavenging Conclusion

Silia*MetS* DMT and Cysteine proved to be the preferred scavengers for Palladium (*Pd*) in this application. As for Iron (*Fe*), Silia*Bond* Tosic Acid (*SCX*) was the best scavenger. Furthermore, very good removal of both metals could be achieved through a combination of scavengers.

Scavenging of Pd(d*t*bpf)Cl_2 in Suzuki Coupling for the Preparation of Arylpyrrolidines

Abbott Laboratories has recently used Pd(d*t*bpf)Cl_2 for the preparation of arylpyrrolidines resulting in a final mixture contaminated with Pd and Fe.



SiliCycle has used this latter synthesis as a control reaction to study the effect of our Metal Scavengers on such contamination. The final crude mixtures were treated with the most promising metal scavengers and further optimization was carried out.

Overview of Metal Residues Scavenging Efficiency (*in %*) in Various Experimental Conditions of a Suzuki Coupling for the Preparation of Arylpyrrolidines

Effect of Time in the Scavenging Efficiency with 4 equiv at 22°C (*in %*)

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* DMT	78	44	**89**	51	**98**	35
Silia*Bond* Tosic Acid	34	65	34	70	36	**86**

Effect of Time in the Scavenging Efficiency with 8 equiv at 22°C (*in %*)

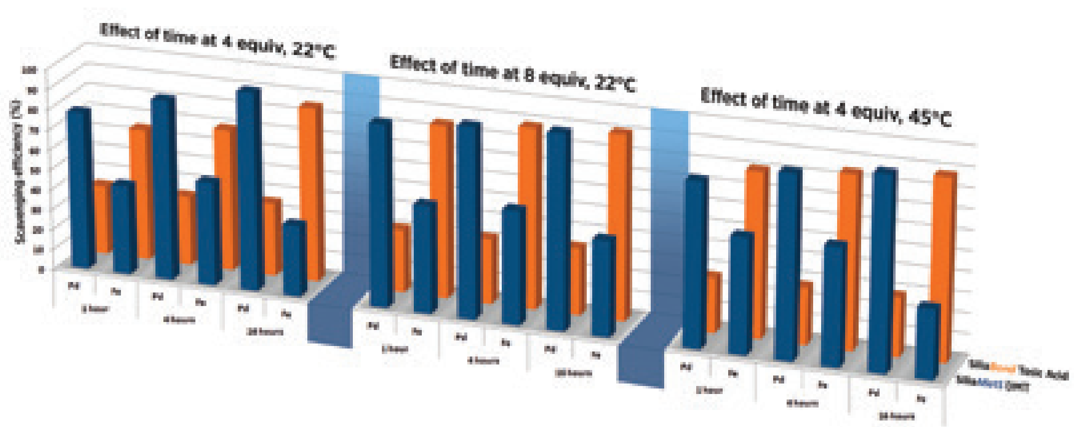
Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* DMT	**90**	53	**94**	56	**96**	47
Silia*Bond* Tosic Acid	31	**85**	32	**89**	33	**91**

Effect of Time in the Scavenging Efficiency with 4 equiv at 45°C (*in %*)

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* DMT	81	57	**90**	58	**95**	34
Silia*Bond* Tosic Acid	27	81	28	**85**	29	**89**

Scavenging Conclusion

Clearly, Silia*MetS* DMT proves to be the preferred scavenger for palladium. As for iron, Silia*Bond* Tosic Acid was by far, the best reagent. A combination of scavengers can achieve, in some cases, very good removal of both metals. The best results were obtained using 8 equiv of each scavenger at 22°C for 16h.



M. Ravn *et al.*, *Org. Proc. Res. Dev.*, **2010**, *14*, 417-424
D. Barnes *et al.*, *Org. Proc. Res. Dev.*, **2009**, *13*, 225-229
Abbott Laboratories, North Chicago, Illinois, United States

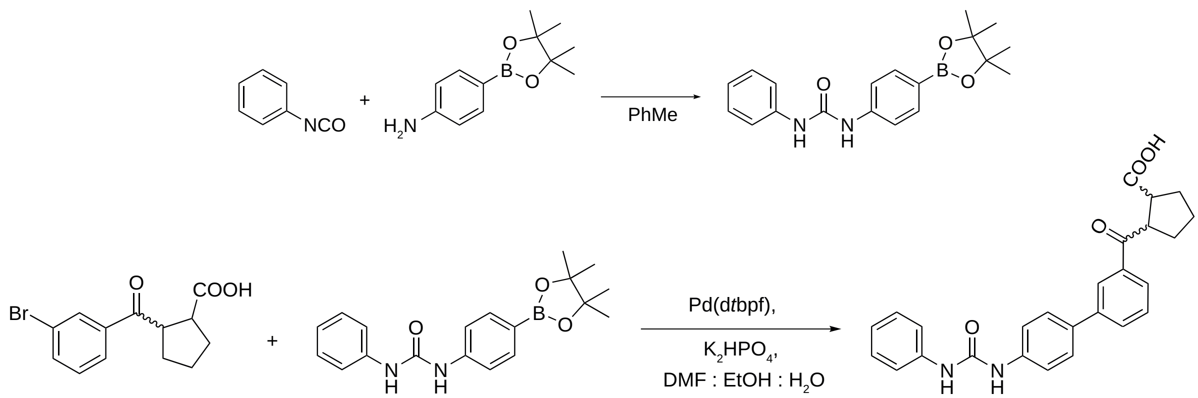
Scavenging of $Pd(dtbpf)Cl_2$ in Suzuki Coupling for the Synthesis of a DGAT-1 Inhibitor

Diacyl glycerolacyltransferase-1 (*DGAT-1*) is one of two known isoforms that catalyse the final step of triglyceride biosynthesis and hence could play a role in the development of obesity and insulin resistance. In a DGAT-1 inhibitor synthesis project, a kilogram-scale Suzuki-Miyaura reaction was described by Abbott researchers in 2010.

Pd

Fe

This synthesis was reproduced in SiliCycle's labs and the resulting contaminated mixtures were treated with our most promising scavengers.



Effect of Time in the Scavenging Efficiency with 4 Equivalents at 22°C (*in %*)

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* Thiol	53	19	72	31	**90**	67
Silia*Bond* Tosic Acid	11	54	24	**92**	22	**95**

Effect of Time in the Scavenging Efficiency with 8 Equivalents at 22°C (*in %*)

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* Thiol	69	12	**86**	37	**96**	69
Silia*Bond* Tosic Acid	24	**91**	33	**91**	17	**92**

Effect of Time in the Scavenging Efficiency with 4 Equivalents at 45°C (*in %*)
Treatment with 2 Scavengers Simultaneously: Silia*MetS* Thiol & Silia*Bond* Tosic Acid

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* Thiol & Silia*Bond* Tosic Acid	78	81	91	81	**96**	81

Conclusion

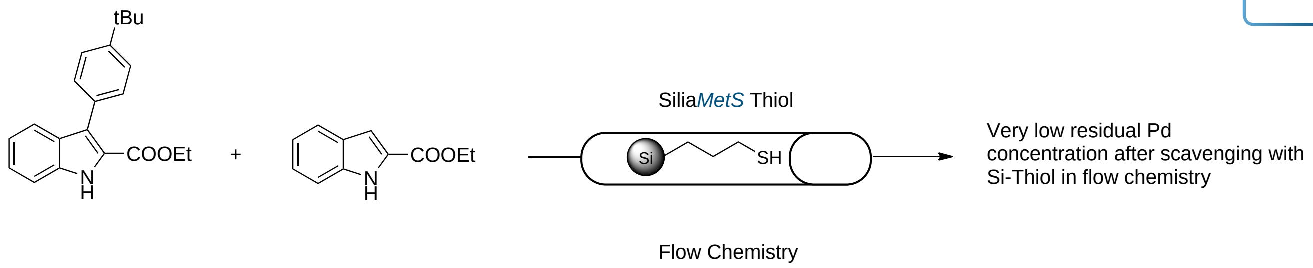
In this case again, it was Silia*MetS* Thiol that proved to be the preferred scavenger for palladium under any conditions. As for iron, Silia*Bond* Tosic Acid was, again and by far, the most effective.

Scavenger combinations can achieve, in some cases, even higher removal of both metals. The best conditions were using 4 or 8 equiv at 22ºC for 16h.

M. Ravn *et al.*, *Org. Proc. Res. Dev.*, **2010**, *14*, 417-424
D. Barnes *et al.*, *Org. Proc. Res. Dev.*, **2009**, *13*, 225-229
Abbott Laboratories, North Chicago, Illinois, United States

Metal Scavenging in Flow Chemistry (*Preliminary Results in Suzuki Coupling Reaction*)

Silia*MetS* Metal Scavengers can also be used in flow chemistry. A crude reaction mixture purified using a Syrris ASIA® Flow Chemistry System is presented in the table 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 (*in* %)
1.50 mL/min	100 mL	16 min	1h10	94
1.00 mL/min		24 min	1h40	94
0.75 mL/min	50 mL	32 min	1h10	94
0.50 mL/min		48 min	1h40	**95**

Initial Pd Concentration: 547 ppm in EtOAc

Experimental Conditions:

Scavenger Used: Silia*MetS* Thiol
Palladium Complex $Pd(OAc)_2/P(o\text{-}Tolyl)_3$ homogeneous catalyst
Nb. Equivalent: 13.5 equiv
Reactors: 2 x 12 mL Reactors in Series
Total Solution Volume: 50 or 100 mL
Purification Scale: 12.5 g
Temperature: 22°C

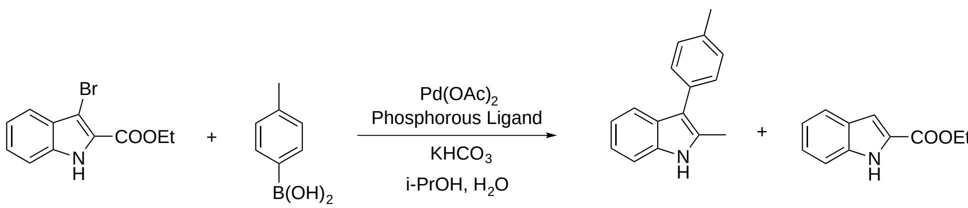
Conclusion

Although top scavenging result reached 95 % at a flow rate of 0.50 mL/min (*using a solution volume of 50 mL and with a contact time of 48 min*, *1h40 of treatment*), all flow conditions appeared to yield excellent level of scavenging.

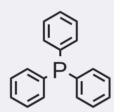
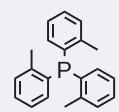
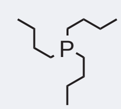
The Effect of Variation of Phosphorous Ligand Nature On Scavenging

Pd

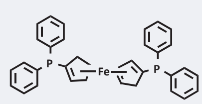
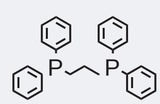
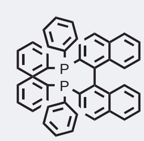
Even for the same metal, a variation in the scavenging efficiency can be observed depending on the nature of the products present in the solution to be treated. For example, steric hindrance and the electronic effects of the phosphorous ligands are factors influencing the removal of the metal. The same Suzuki coupling 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 (*in* %) with 4 equiv, 4 h

Silia***MetS***	Triphenylphosphine [PPh_3] 		Tri(o-tolyl)phosphine [$P(otol)_3$] 		Tri-n-butylphosphine [$PnBu_3$] 	
	22°C	60°C	22°C	60°C	22°C	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 (*in* %) with 4 equiv, 4 h

Silia***MetS***	1,1'-bis(diphenylphosphino) ferrocene [dppf] 		1,3-bis(diphenylphosphino) propane [dppp] 		(+/-) BINAP 	
	22°C	60°C	22°C	60°C	22°C	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	

Conclusion

In all cases, Silia*MetS* DMT and Thiol remained the best scavengers throughout the study, even though there is a variation in the nature of the ligand. As expected, scavenging was more difficult with bidentate, more basic phosphine ligands. The best conditions were using 4 equiv for 4 h, at 60°C.

Ruthenium Scavenging

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 application. Complete ruthenium removal can be tedious using conventional methods.

Under various conditions, several Silia*MetS* are known to be excellent scavengers to obtain minimal tolerated concentrations of residual ruthenium.

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* (*in %*)

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**	**> 99**	**99**	**> 99**	**98**	**98**	**99**
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**	-	-	-

Notes: Silia*MetS* Cysteine and Imidazole were not screened in this study.
Only Silia*MetS* results higher than 90 % are presented in this table.

Experimental Conditions:

Nb. Equivalent: [1] 8 equiv of Silia*MetS*, 16 h, 80°C
[2] 4 equiv of Silia*MetS*, 16 h, 80°C

Initial Concentration: 500 ppm for all ruthenium-based catalysts.

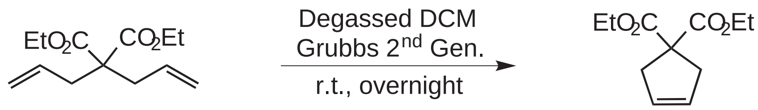
Conclusion

For all Ru-catalyzed reactions, the best scavenging was achieved using Silia*MetS* DMT. For most experiments, little or no differences was observed when using toluene or DMF.

Scavenging Solutions

Silia*MetS* vs Other Purification Methods

The use of Silia*MetS* to remove ruthenium catalysts after a ring-closing metathesis (*RCM*) reaction is a very effective purification method. One of its main advantages is that no product is lost during the purification step.



quantitative yield

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

Table: Scavenging Results for Various Purification Methods* (*in %*)

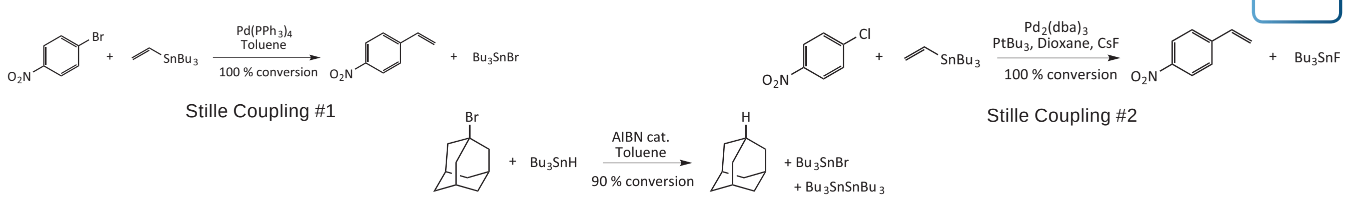
[1] Using 4 equiv, 16 h, 22°C. [2] Solution is passed directly on a packed bed of various adsorbents, which was then washed with the same quantity of solvent.

*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 Using Silia*MetS* Cysteine & TAAcONa

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.

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



Radical Reduction

Reactions	Initial Concentration	Silia*MetS* Cysteine		Silia*MetS* TAAcONa		
		4 equiv, 4 h, 22°C [*2 treatments*]	8 equiv, 4 h, 22°C	4 equiv, 4 h, 22°C [*2 treatments*]	8 equiv, 4 h, 22°C	4 equiv, 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

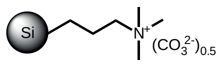
Table: Tin Scavenging using Silia*MetS* Cysteine & TAAcONa (*in %*)

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

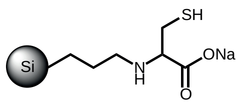
Comparison of Tin Scavenging Using Silia*Bond* Carbonate vs Silia*MetS* Cysteine

Sn

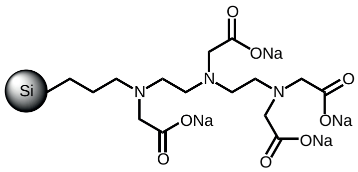
SiliCycle also provides a quaternary ammonium salt grafted on silica to which a carbonate group is ionically bounded. The latter has shown to be an excellent alternative for tin retrieval from organic mixtures.



Silia*Bond* Carbonate



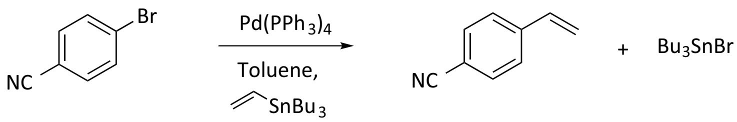
Silia*MetS* Cysteine



Silia*MetS* TAAcONa

Stille Reaction

Tin scavenging was demonstrated on a Stille coupling in which Bu_3SnBr is the major tin by-product. In each test, residual Pd was scavenged in its entirety (*from 24 mg/L to < 0.1 mg/L*).



Tin Scavenging (*in %*)				
	4 h, 8 equiv, 22°C	4 h, 16 equiv, 22°C	16 h, 8 equiv, 80°C	4 h, 8 equiv, 22°C [*2 treatments*]
Silia*Bond* Carbonate	91	**99**	**96**	**99**
Silia*MetS* Cysteine	77	**99**	84	94

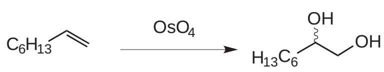
Conclusion

Scavenging yields were excellent with both scavengers. Hence, Silia*Bond* Carbonate was found to be of the same high efficiency as Silia*MetS* Cysteine to scavenge tin compounds of R_3SnX type.

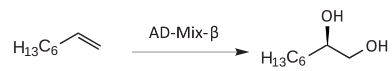
Osmium Scavenging with Silia*MetS*

Osmium tetroxide (*OsO_4*), 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.

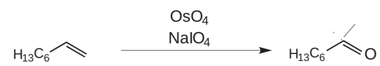
Therefore, it is important to efficiently remove residual osmium from products of interest. A scavenging study on three organic reactions involving osmium reactants were performed. The metal scavenging efficiency of Silia*MetS* is highlighted in the following table.



Dihydroxylation Reaction
[*OsO_4*]



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



Lemieux-Johnson Oxidation
[$NaIO_4$, OsO_4]

Osmium Scavenging using Silia*MetS* (*in %*) at 22°C

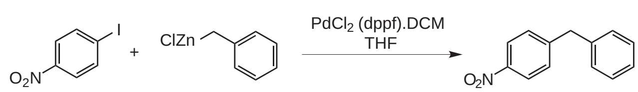
Silia*MetS*	Dihydroxylation	Sharpless Dihydroxylation		Lemieux-Johnson Oxidation	
	4 equiv, 4 h	8 equiv, 4 h	8 equiv, 16 h	8 equiv, 4 h	8 equiv, 16 h
Silia*MetS* Thiol	87	**> 98**	**> 98**	87	92
Silia*MetS* Cysteine	89	**> 98**	**> 98**	87	91
Silia*MetS* DMT	92	**97**	**> 98**	87	91
Silia*MetS* Imidazole	87	**> 98**	**> 98**	89	91
Initial Os Concentration (*in EtOAc*)	132 ppm	25 ppm		21 ppm	

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

All scavengers were equally effective for Sharpless dihydroxylation or Lemieux-Johnson oxidation. As for simple dihydroxylation, Silia*MetS* DMT was slightly more efficient.

Multiple Metal Scavenging

Silia*MetS* can be used to remove multiple metals in the same reaction with excellent efficiency.



The Negishi coupling presented in scheme above was performed to show that Silia*MetS* can be used to simultaneously remove residual palladium, iron and zinc present after the reaction.

Multiple Removal Scavenging Results (*in %*)

Silia*MetS*	Pd	Fe	Zn
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 (*in THF*)	188 ppm	110 ppm	6 ppm

For Zinc removal, all tested scavengers gave excellent results. Overall, for multiple removal scavenging results, Silia*MetS* Cysteine and TAacONa showed to be the most versatile scavengers.

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

Silia*MetS* in Aqueous Conditions

Along with growing importance of sustainable chemistry and catalysis, Silia*MetS* compatibility in aqueous conditions needed to be evaluated. As a preliminary exploration, palladium nitrate scavenging was tested at four (*4*) different pH in various acidic medias.

Zn Pd Ru Pt Fe Rh Ag Ni Sn Cu

Scavenging (*in %*) of $Pd(NO_3)_2$ in Various Aqueous Conditions, 4 equiv at 22°C, 4 h

Scavengers	H_2SO_4 (*1 M*)	HNO_3 (*1 M*)	AcOH (*1 M*)	H_2O
Silia*MetS* Cysteine	**> 99**	**> 99**	**> 99**	76
Silia*MetS* Diamine	43	23	**> 99**	5
Silia*MetS* DMT	**> 99**	**> 99**	**> 99**	15
Silia*MetS* Imidazole	**> 99**	**> 99**	**> 99**	36
Silia*MetS* TAAcOH	**98**	**98**	**98**	**98**
Silia*MetS* Thiol	**> 99**	**> 99**	**> 99**	77
Silia*MetS* Thiourea	**> 99**	**> 99**	**> 99**	35
Silia*Bond* Tosic Acid	19	6	76	28
Silia*MetS* Triamine	55	49	**96**	10

Experimental Conditions: an aqueous 250 ppm solution of $Pd(NO_3)_3$ was prepared in a volumetric flask. 8 mL of this solution was introduced in 10 mL polypropylene tube charged with four molar equivalents of a metal scavenger. All scavengers were treated identically. The tubes were shaken on the SiliCycle MiniBlock orbital shaker for four hours. All solutions were filtered on separate tubes, and the remaining palladium was measured.

In purely aqueous conditions, Silia*MetS* TAAcOH was the most compatible and efficient scavenger. However, in acidic conditions, apart from Silia*Bond* Tosic Acid, all scavengers showed good to excellent removal capability.

Scavenging activity can either be driven by H_3O^+ concentration (*pH*), or its counter-ion. Results illustrate well that the counter-anion (*and counter-cation*) plays a determinant role in the affinity of the resin toward palladium.

Other complexes were tested using the same method described as above for scavenging of $Pd(NO_3)_3$.

Various Metallic Complexes Scavenging (*in %*) & Concentrations in Aqueous Conditions, 4 Equiv at 22°C, 4 h

Scavenger	$RuCl_3$ [*150 ppm*]	K_3PtCl_6 [*250 ppm*]	$FeCl_3$ [*250 ppm*]	$RhCl_3$ [*250 ppm*]	$Pd(NO_3)_2$ [*250 ppm*]
Silia*MetS* Cysteine	**94**	**96**	**> 99**	14	76
Silia*MetS* Diamine	11	71	25	94	5
Silia*MetS* DMT	0	**97**	6	68	15
Silia*MetS* Imidazole	0	91	6	59	36
Silia*MetS* TAAcOH	63	0	**> 99**	5	**98**
Silia*MetS* TAAcONa	47	87	**98**	7	77
Silia*MetS* Thiol	0	57	7	0	35
Silia*MetS* Thiourea	0	92	9	34	28
Silia*Bond* Tosic Acid	52	87	**> 99**	**98**	**99**
Silia*MetS* Triamine	14	61	13	92	10

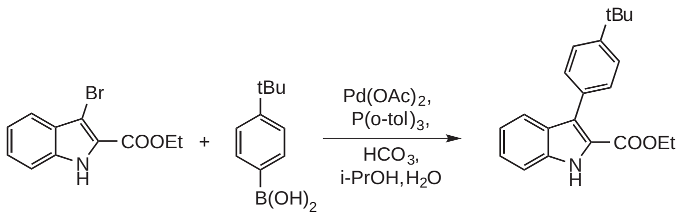
Scavenger	$AgNO_3$ [*250 ppm*]	$Ni(NO_3)_2$ [*250 ppm*]	$Sn(OTf)_2$ [*250 ppm*]	$CuSO_4$ [*250 ppm*]	$ZnSO_4$ [*250 ppm*]
Various Metallic Complexes Scavenging (*in %*) & Concentrations in Aqueous Conditions, 4 Equiv at 22°C, 4 h					
Silia*MetS* Cysteine	92	70	**97**	**97**	**98**
Silia*MetS* Diamine	74	43	47	93	58
Silia*MetS* DMT	**> 99**	40	60	86	51
Silia*MetS* Imidazole	90	25	39	64	39
Silia*MetS* TAAcOH	**> 99**	84	93	**99**	86
Silia*MetS* TAAcONa	**97**	**96**	73	94	**95**
Silia*MetS* Thiol	**96**	6	6	0	0
Silia*MetS* Thiourea	79	1	17	14	3
Silia*Bond* Tosic Acid	86	90	**95**	88	81
Silia*MetS* Triamine	76	33	58	44	58

Conclusion

Scavengers such as Silia*MetS* Cysteine and Silia*MetS* TAAcONa were shown to have very good scavenging efficiency in aqueous media. Silia*MetS* TAAcOH and Silia*Bond* Tosic Acid were also efficient. Generally speaking, many metal scavengers have demonstrated excellent performance in aqueous environment, even when bearing hydrophobic moieties.

Pd scavenging after a Suzuki-Miyaura Coupling using a GlaxoSmithKline Published Reaction

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



Scavenging Efficiency, Recovery & Purity

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

The 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-bed mode bed (*pre-packed SPE cartridges*).

Silia*MetS* Scavenging Efficiency & Intermediate Recovery Results (*in %*)

Scavengers	Batch Reactor Mode (*Bulk*) 5 equiv, 4 h, 22°C	Batch Reactor Mode (*Bulk*) 5 equiv, 4 h, 40°C	Fixed-Bed Mode (*SPE*) 6 mL / 1 g	Intermediate Recovery
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 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.

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 the results in associated table. After the first run, almost all the palladium was captured. After three runs, less than 1 ppm remained in solution.

Silia*Sep* Scavenging Results (*in %*)

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

Initial Pd Concentration: 700 ppm in AcOEt

Experimental Conditions:

Scavenger Used: Silia*MetS* Thiol
Cartridge Size: 120 g
Nb. Equivalent: 25 equiv
Solution Volume: 1 L
Flow Rate: 40 mL/min

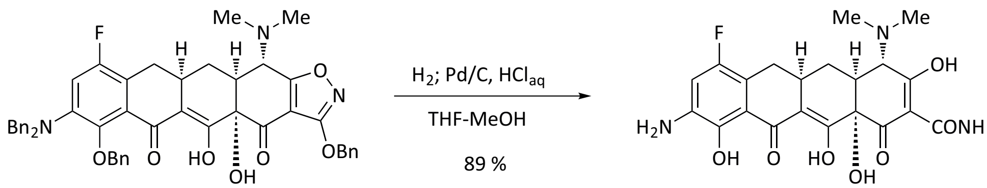
J. F. Toczko *et al.*, *Org. Proc. Res. Dev.*, **2008**, *12*, 896-899
Chemical Development, GlaxoSmithKline, North Carolina, United States

Scavenging Solutions

A Tetraphase Case Study: Palladium Scavenging in the Development of the First Fully Synthetic Fluorocycline Using Silia*MetS* DMT

Process research and development of the first fully synthetic broad spectrum fluorotetracycline in clinical development was reported by Tetraphase Pharmaceuticals. The key reaction was a Dieckmann condensation between a suitable substituted aromatic moiety and a cyclohexanone derivative. Subsequent hydrogenolysis was extensively studied, using a Pd/C catalyst. **Without any treatment, residual palladium levels as high as 2,000 ppm were detected.**

Silia*MetS* DMT was found to be an excellent metal scavenger to reduce the residual Pd content to more than acceptable levels.



Scale-Up of Hydrogenation and Pd Scavenging Results				
Entry[1]	Hydrogenation Time (*h*)	Time for Slurry in EtOH / H_2O (*h*)	Yield (%)	Pd Content (*ppm*) (*after treatment*)
1	12	2	82	0.4
2	4	17	73	2
3	7	2	77	0.39
4	10	2.5	79	1.11
5	11	4	85	**< 0.2**

[1] 6.2 to 10 wt % Pd/C was used

Conclusion

The reaction was run in THF / MeOH (*3.3/10 v/v*) under nitrogen with 10 wt % Pd/C. Without any treatment, residual palladium levels were as high as 2,000 ppm, but after stirring with 50 or 100 wt % Silia*MetS* DMT in MeOH for 2 - 3 h, residual levels were consistently below 1.5 ppm.

Another strategy to avoid subsequent purification by Silia*MetS* DMT can be to use an heterogeneous palladium-based catalyst, namely Silia*Cat* DPP-Pd. See p. 18-19 for more information on our catalysts.

M. Ronn *et al.*, *Org. Proc. Res. Dev.*, **2013**, *17*, 838-845
Tetraphase Pharmaceuticals Inc., Massachusetts, United States

A Genentech Case Study: Palladium and Ruthenium Removal in the Synthesis of Akt Inhibitor Ipatasertib using Silia*MetS* Thiol (*Multi-kilogram Scale*)

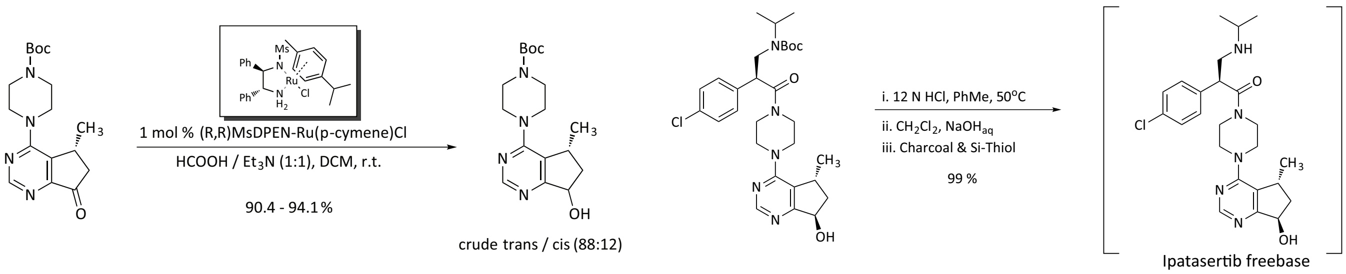
The first-generation process to manufacture Akt inhibitor Ipatasertib through a late-stage convergent coupling of two challenging chiral components on a multi-kilogram scale was reported by Array BioPharma.

A carbonylative esterification and subsequent Dieckmann cyclization sequence was developed to forge a cyclopentane ring in the target. A second key chiral component, a β^2-amino acid, was produced using an asymmetric aminomethylation (*Mannich*) reaction.

Upon scale-up, the deprotection of the Boc-API for the preparation of the Ipatasertib mono-HCl salt was easily completed in toluene in 12 N HCl.

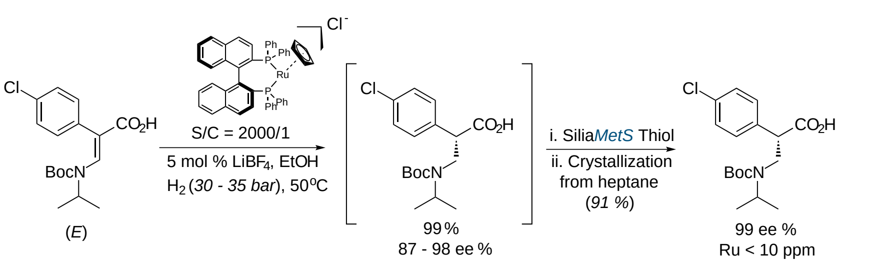
The aqueous layer was then basified to pH ≥ 12 with aqueous NaOH in order to extract the Ipatasertib free-base with DCM. The DCM solution was subsequently treated with charcoal and Silia*MetS* Thiol to remove colored impurities and trace heavy metals resulting from previous synthetic steps.

These metals consisted in Palladium (*Pd/C catalyst in a Noyori Asymetric Transfer Hydrogenation of ketone*), Ruthenium [*(R,R) MsDPEN-Ru(p-cymene)Cl) catalyst for asymmetric ketone reduction*] and Titanium (*$TiCl_4$ catalyst in asymmetric Aldol addition*).

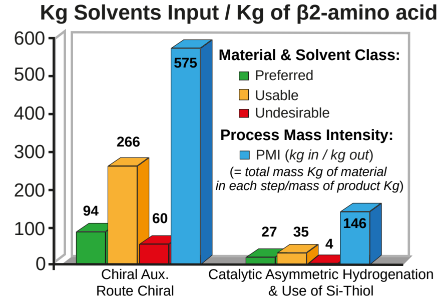


In Akt inhibitor synthesis, Genentech describes a scalable catalytic asymmetric hydrogenation process for the multi-kilogram scale production of a β^2-amino acid, the last building block. An extensive catalysis screening and optimization study was done and identified a simple Ru-BINAP catalyst system to directly afford the *S* product in high enantiomeric excess and yield was reported.

The final process enabled the multi-kilogram production in > 99 % ee to be used as a key component for one of their clinical candidates.



Process Mass Intensity & Kg Solvents Input / Kg of β2-amino acid



Conclusion

For 138 Kg of the crude amino acid, 8.3 Kg of Silia*MetS* Thiol were necessary. Filtration of the DCM solution over Celite® resulted in a 99 % yield of Ipatasertib free-base with a ruthenium content of less than 5 ppm (*ICP-OES*).

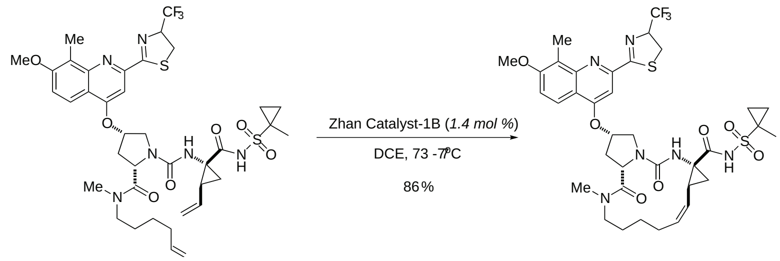
J. Lane, T. Remarchuk *et al.*, *Org. Proc. Res. Dev.*, **2014**, *18*, 1641-1651
Small Molecule Process Chemistry, Genentech, Inc., a member of the Roche Group, California, United States
Array BioPharma Inc., Colorado, United States

T. Remarchuk *et al.*, *Org. Proc. Res. Dev.*, **2014**, *18*, 1652-1666
Small Molecule Process Chemistry, Genentech, Inc., a member of the Roche Group, California, United States
Array BioPharma Inc., Colorado, United States

T. Remarchuk *et al., Org. Proc. Res. Dev.*, **2014**, *18*, 135-141
Small Molecule Process Chemistry, Genentech Inc., A member of the Roche Group, California, United States
Catalysis and Chiral Technologies, Johnson Matthey, Cambridge United Kingdom
WuXi AppTec Co., Ltd., Shanghai, China

An Idenix Case Study: Ruthenium Removal in the Macrocyclization of Dienyl-ureas Via RCM, using Silia*MetS* DMT

A novel assembly of two structurally related 14-membered ring macrocyclic hepatitis C virus protease inhibitors was reported by Idenix Pharmaceuticals. Key to their successful construction was an ultimate ring-closing metathesis step on the highly functionalized dienyl-urea via Zhan Catalyst-1B (*Ru-based catalyst*).



Several methods have been reported to remove Ru by-products, and were investigated in this study with some variations, including the use of tris(*hydroxymethyl*)phosphine, lead tetraacetate, TPPO, DMSO followed by silica gel filtration, adsorption onto silica gel, activated carbon and silica gel chromatography, treatment with mercaptonicotinic acid (*MNA*) and washing with aqueous $NaHCO_3$, and the use of supercritical fluid extraction. Resulting Ru levels of those methods vs Silia*MetS* DMT treatment were analyzed by ICP-OES and are listed below.

Effect of Reaction Conditions and Purification on Ru Content and Yield of Protease Inhibitor

Entry	Reaction Conditions	Ru Reduction Operation	Ru content (*ppm*)	Yield (*%*)
1	250 mL/g diene 4.9 mM 1.5 wt % catalyst	MNA / $NaHCO_3$ wash; charcoal; silica gel filtration	14 (*initial*)	-
		1st MeOH trituration	12	63
		2nd MeOH trituration	7.5	58
2	250 mL/g diene 4.9 mM 1.5 wt % catalyst	charcoal; silica gel filtration	120 (*initial*)	-
		1st MeOH trituration	34	81
		2nd MeOH trituration	20	75
3	250 mL/g diene 4.9 mM 1.5 wt % catalyst	charcoal; silica gel filtration	120 (*initial*)	-
		1st MeOH trituration	48	79
		5/4 v/v DCE / MeOH crystallization	4.6	61
4	80 mL/g diene 15.2 mM 1.1 wt % catalyst	charcoal; silica gel filtration	880 (*initial*)	-
		1st MeOH trituration	300	84
		Toluene crystallization	22	45
5	80 mL/g diene 15.2 mM 1.1 wt % catalyst	charcoal; silica gel filtration	880 (*initial*)	-
		1st MeOH trituration 2:1 v/v	300	84
		EtOAc / n-heptane crystallization	19	51
6	80 mL/g diene 15.2 mM 1.25 wt % catalyst	Silia*MetS* DMT 16 h treatment + filtration	380 (*initial*)	-
			66	75
7	160 mL/g diene 7.6 mM 1.25 wt % catalyst	Silia*MetS* DMT 16 h treatment + filtration	200 (*initial*)	-
			3.6	86
8	250 mL/g diene 4.9 mM 1.25 wt % catalyst	Silia*MetS* DMT 16 h treatment + filtration	180 (*initial*)	-
			7.7	89

Conclusion

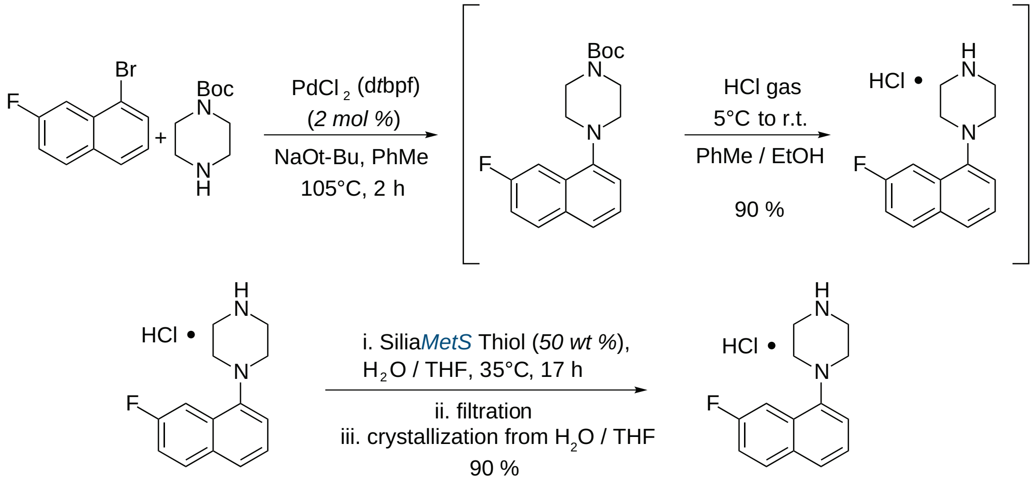
As one can easily note, treatment with Silia*MetS* DMT gave a much lower Ru residual content conjointly with the highest final yields. Hence, low yield losses (*11 - 14 %*) and high purities (*98 %*) were achieved, together with excellent Ru levels observed (*as low as 3.6 ppm*), indicating the strong utility of this approach in Ru removal in the synthesis of macrocycle HCV PIs IDX316.

B. A. Mayes *et al.*, *Org. Proc. Res. Dev.*, **2013**, *17*, 811-828
Idenix Pharmaceuticals Inc., Massachusetts, United States

A Pfizer Case Study: Palladium Removal Using Silia*MetS* Thiol After a Buchwald-Hartwig Amination

Silia*MetS* Thiol was employed by researchers at Pfizer for Pd removal during the preparation of a naphthalenopiperazine HCl salt. The product from the Buchwald-Hartwig amination of naphthyl bromide with Boc-piperazine was telescoped as a toluene solution and the Boc protecting group was subsequently cleaved with HCl gas to afford the HCl salt containing over 1,300 ppm Pd.

A water / THF solution of this material was then treated with Silia*MetS* Thiol (*50 wt %*) at 35°C for 17 h and, following crystallization from water / THF.



107 g
1,325 ppm Pd

97 g
2 ppm Pd

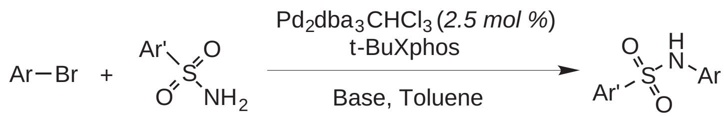
Conclusion

The HCl salt was obtained with a 90 % yield and with only 2 ppm Pd. This chemistry was demonstrated on a kilogram scale.

J. Magano *et al.*, *J. Synth. Commun.*, **2008**, *38*, 3631-3639
Research API, Pfizer Global Research and Development, Connecticut, United States
Separation Sciences, Pfizer Global Research and Development, Connecticut, United States
Research API, Pfizer Global Research and Development, Michigan, United States
Supply Chain API, Pfizer Global Research and Development, Michigan, United States

An Amgen Case Study: Palladium Removal using Various Resins

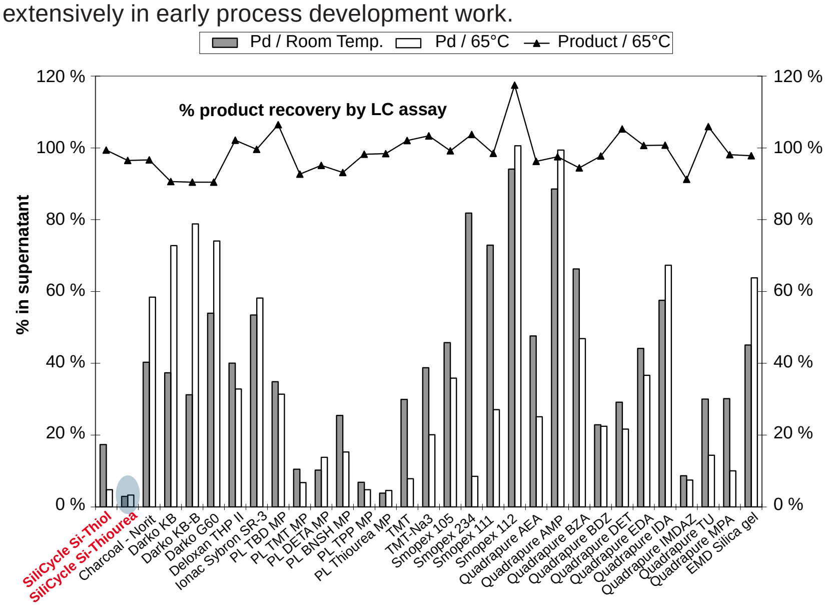
In 2009, Amgen published a chapter in "*Catalysis of Organic Reactions*" related to the use of scavengers for the removal of palladium in small to multi-kilogram production scales. In this study, several parameters were evaluated, such as scavenging efficiency, influence of the scavenger loading and 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.

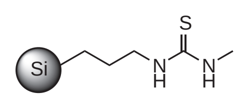


Amgen Scavenger Screening Results

Conditions: 20 mg of each scavenger (*20 % w/w*) were placed in 2 mL HPLC vials each containing 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.



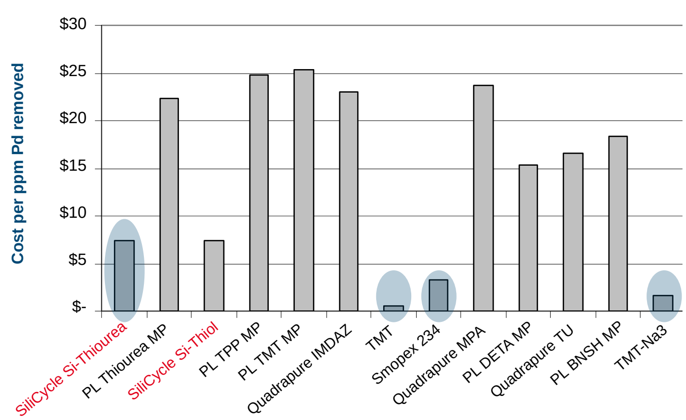


Silia*MetS* Thiourea

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.

Results highlighted by the graph reduced the number of options to only four candidates for further evaluation: in pole position Silia*MetS* Thiourea, followed by TMT, TMT-Na_3 and Smopex 234.



Note: Silia*MetS* DMT does not appear in this study because it had not been commercialized yet at the time of the study.

Top 4 Scavengers Overview

A screening validation was conducted on 1-g scale purification (*10 mL of solution*) with 20 % w/w of the four best scavengers at 65°C overnight. After filtration, residual metal concentration was analyzed by ICP-MS and product recovery was determined by HPLC. Silia*MetS* Thiourea was chosen for the large scale purification.

Screening Validation Results on Top 4 Scavengers

Scavengers	Residual Metal Concentration (*ppm*)			Product Recovery	Commentary from Amgen
	Screening Exp. in Solution	Validation Exp. in Solution	Validation Exp. in Solid Product		
SiliCycle Thiourea	14	11	158	102 %	Best performance
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*) and low recovery
Initial Concentration	423 ppm	381 ppm	3,577 ppm	-	-
Purification Scale	100 mg	1 g	1 g	1 g	-

Please see Amgen's chapter for further details *(see reference below*).

Amgen's Conclusion

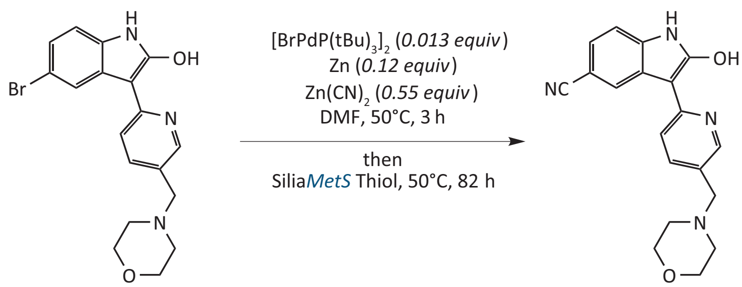
"*Scavengers offer a practical and expedient option for removal of palladium from process streams to ensure quality of organic products... The screening protocol involves treatment of a candidate process stream with 20 % w/w scavenger on product at both room temperature and 65°C followed by analysis 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.*"

J. Allgeier *et al.*, *Catalysis of Organic Reactions*, Chapter 5. Application of Scavengers for the Removal of Palladiumin Small Lot Manufacturing, Amgen Inc., Thousand Oaks, California

Scavenging Solutions

An AstraZeneca Case Study: Palladium Removal using Silia*MetS* Thiol

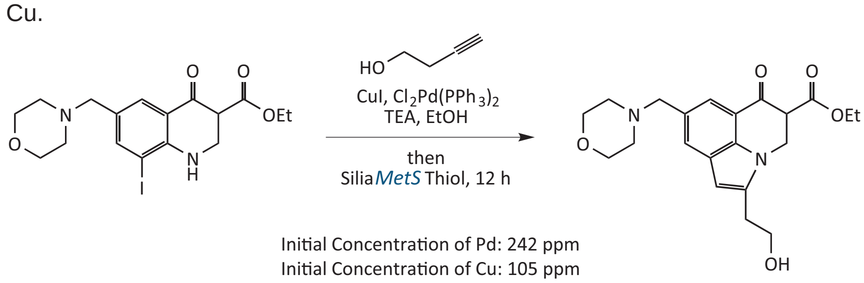
In 2008, AstraZeneca published a paper on removal of palladium impurities in a pilot-scale process. The work-up method found to work the best was a treatment with Silia*MetS* Thiol (*25 % w/w or ~1.4 kg*) at 50°C to purify more than 6.7 kg of material. Final residual palladium concentration was as low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



P. Ryberg *et al.*, *Org. Proc. Res. Dev.*, **2008**, *12*, 540-543
Process Chemistry, AstraZeneca PR&D, Sweden

A Pfizer Global R&D Case Study: Palladium and Copper Removal on a Large Scale Batch using Silia*MetS* Thiol

In 2006, Pfizer published a paper on removal of palladium & copper impurities in a 20 kg pilot-plant batch. 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.

Screening Validation Results on Top 4 Scavengers

Scavengers	Residual Metal Concentration (*ppm*) Pd	Residual Metal Concentration (*ppm*) Cu	Yield (%)
Degussa Deloxan THP	20	2	60 - 70
SiliCycle SIlia*MetS* Thiol	**17**	**1**	**76**

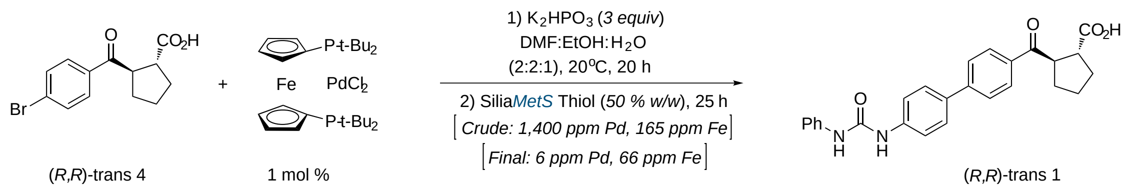
Silia*MetS* allows lower residual metal concentration & higher yield with fewer manipulations!

R. L. Dorow *et al.*, *Org. Proc. Res. Dev.*, **2006**, *10*, 493-499
Pfizer Global Research and Development, Michigan, United States

An Abbott Laboratories Case Study: Palladium and Iron Removal using Silia*MetS* Thiol

In 2010, Abbott Laboratories published a paper on removal of palladium and iron impurities using Silia*MetS* Thiol (*50 % w/w*). Thus, palladium and iron levels were 6 ppm and 66 ppm respectively. Although this final iron concentration was sufficient for the herein study, a much lower residual iron concentration can ben achieved by optimizing the purification experimental conditions.

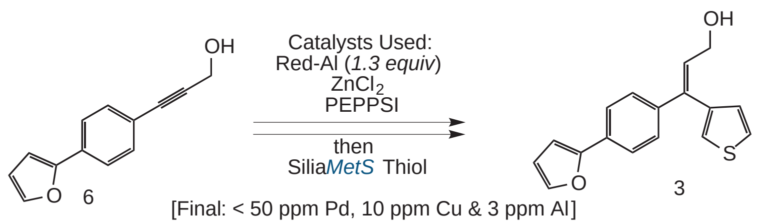
Refer to Abbott's publication for more details.



M. M. Ravn *et al.*, P., *Org. Proc. Res. Dev.*, **2010**, *14*, 417-424
Global Pharmaceutical R&D, Process Research & Development and Discovery, Abbott Laboratories, Chicago, Illinois, United States

A Johnson & Johnson Case Study: Sonogashira Reaction & Metal Scavenging of Various Metals

In 2009, Johnson & Johnson, in collaboration with Solvias, published a paper in which a mild Sonogashira reaction was developed 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.



Note: copper comes from a previous synthesis step.

Refer to J&J's publication for more details.

I. N. Houpis *et al.*, *Org. Proc. Res. Dev.*, **2009**, *13*, 598-606
Johnson & Johnson PRD, API Development, Belgium, and Solvias A.G., Synthesis and Catalysis, Switzerland

Scavenging Solutions

Silia*Bond* Organic Scavengers Application Examples & Case Studies

Nucleophilic Scavenging of Boronic Acids with Silia*Bond* Diol, Carbonate and Silia*MetS* DEAM

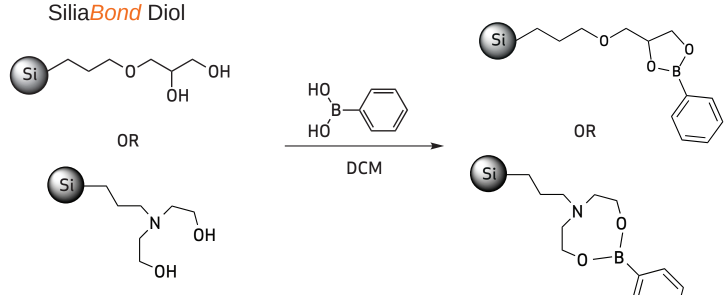
Boronic acids and their derivatives are one of the most widespread intermediates and reagents in organic and medicinal synthesis. On-the-market drugs have even been adding boron atoms to enhance compatibility, selectivity and potency to their target molecules.

Up to very recently, boronic acids had always been reported as lacking apparent toxicity, mutagenic activity or in vivo instability issues. New studies have raised objections about this safe toxicological profile, both based on experimental and clinical data.

This is major in the chemical and pharmaceutical industry, as more and more studies denounce the genotoxicity of boronic acids. Today, in view of new data concerning boronic acids, there is pressure building on the ICH steering committee to assess boron compounds as potential genotoxic impurities (*PGIs*) per ICH M7.

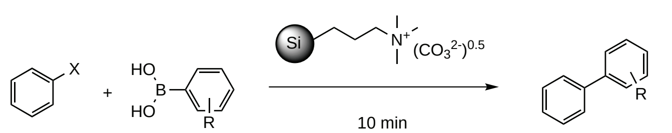
Please see our White Paper for more details on our website.

Silia*Bond* Diol

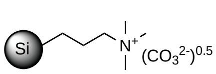
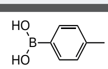
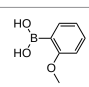
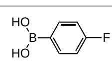
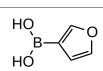


Silia*Bond* DEAM

Scavenging Boronic Acids Results			
Scavengers	**Equivalent**	**Time**	**Efficiency (%)**
Silia*MetS* DEAM	4	1 h	**> 99**
Silia*Bond* Diol	4	1 h	**> 99**



50 to 99 % Yield

Scavenging Boronic Acids Results			
Scavengers	**Boronic Acid**	**Time**	**Efficiency (%)**
 Silia*Bond* Carbonate		10 min	**> 99**
			**> 99**
			**> 99**
			**> 99**

All % scavenged determined by GC-MS

Depending on ones' needs, all three scavengers gave excellent scavenging results and showed to be an efficient, fast and cheap method for the removal of boronic acids.

Silia*MetS* DEAM and Silia*Bond* Diol are both excellent scavengers for Catch & Release: *i.e.,* when the molecule of interest is temporarily bound either ionically or covalently to a functionnalized silica and subsequently released, once all undesirable impurities were washed out.

Scavenging via Silia*Bond* Scavengers vs Functionalized Polymers

Electrophilic Scavenging of Benzylamines with Silia*Bond* Isocyanate

A comparative study between SiliCycle's silica-based Isocyanate and polystyrene-based Isocyanate was performed, using the scavenging of benzylamine as the control reaction. For each scavenger, the experimental conditions were strictly identical.

Scavenging Benzylamine Results (*in %*)

Scavenger	DCE	THF	DCM	ACN
Silia*Bond* Isocyanate	**> 99**	**98**	**98**	**95**
PS-Isocyanate (*supplier A*)	**> 99**	**98**	**98**	79
PS-Isocyanate (*supplier B*)	**> 99**	**98**	**98**	88

Conditions: 3 equiv relative to benzylamine, 1 h at room temperature in solvent
% scavenged determined by GC-MS

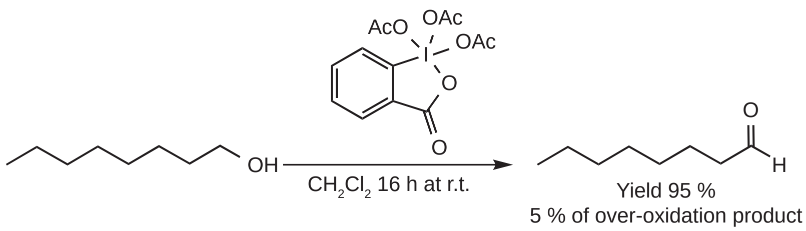
All three scavengers showed to be excellent, albeit Silia*Bond* Isocyanate was the most versatile and unaffected by the polarity of solvents.

Scavenging in two different formats: bulk vs SPE

Ionic Scavenging of 2-Iodobenzoic Acid with Silia*Bond* TMA Acetate and Carbonate

Dess-Martin Periodinane (*DMP*) is a mild and chemoselective oxidant. It is readily accessible, environmentally benign and has a good shelf-life. Furthermore, the ease of handling, simple reaction work-up, product purification and good yields obtained with DMP make it a valuable reagent in organic synthesis.

2-Iodobenzoic acid is the degradation product from DMP formed during the work-up. Most of it can be removed with a basic work-up, but sometimes, it can be difficult to get rid of all this side product.



General Procedure

A solution of 1-octanol (*1.00 mmol; 1.0 equiv*) in CH_2Cl_2 (*6 mL*) at room temperature, was added to DMP (*1.10 mmol; 1.1 equiv*). The reaction mixture was stirred for 16 h, then diluted with 35 mL of MTBE and poured in 20 mL of an aqueous solution of $Na_2S_2O_3$ (*25 %*). The mixture was stirred for 10 min. Another portion of 35 mL of MTBE was added for the liquid-liquid extraction.

The MTBE phase was then washed with water and a saturated aqueous solution of NaCl (*10 mL*) and dried on $MgSO_4$.

Scavenging was done using Silia*Bond* TMA Acetate or Carbonate, both in bulk (*1 g*) and SPE cartridge (*6 mL / 1 g*) for comparison purposes. Each sample was washed or eluted with a fresh portion of MTBE (*8 mL*) and then the 2-iodobenzoic acid concentration was monitored by GC-MS against an internal standard. The over-oxidation product (*carboxylic acid*) was succesfully scavenged using all products and formats.

Scavenging of 2-Iodobenzoic Acid Results (*in %*)

Scavenger	Bulk	SPE
Silia*Bond* TMA Acetate	100	100
Silia*Bond* Carbonate	100	100

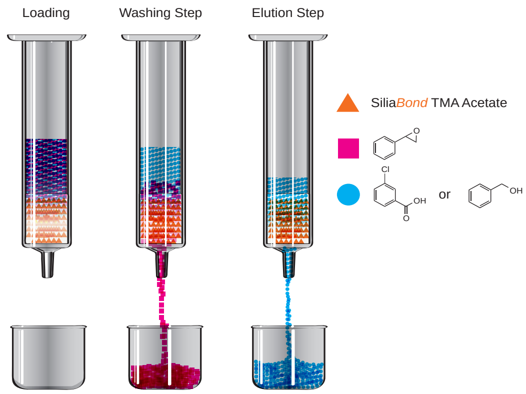
Catch and Release of the API

Carboxylic Acids Purification with SiliaBond TMA Acetate

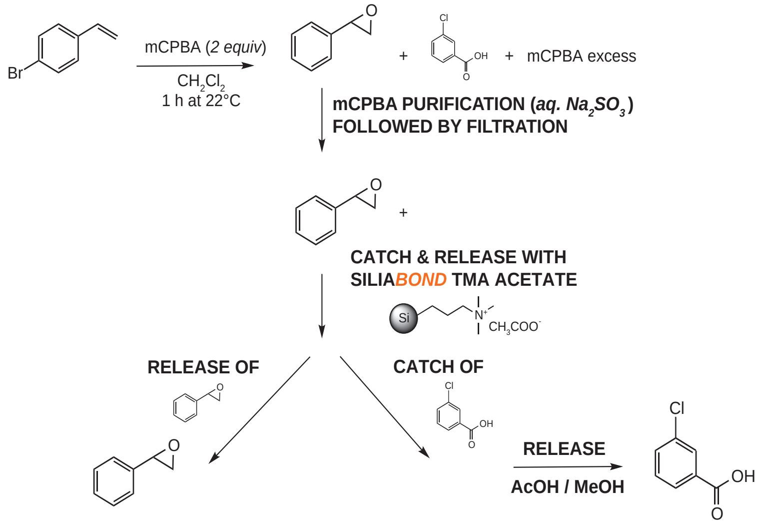
SiliaBond TMA Acetate is an ion exchange media useful to extract organic anions from organic or inorganic matrices. It is less selective than SiliaBond TMA Chloride. The acetate anion being more labile than the chloride, it therefore retains more easily acidic compounds with pK_a in the range of 4 - 5, such as carboxylic acids.
12 mL cartridges were filled with 2 or 4 g of SiliaBond TMA Acetate (*loading of 1 mmol/g, for an equivalent of about 4 mmol of active function*). They were tested with quantities of 1 and 2 mmol of each selected acid.

General Procedure for CATCH & RELEASE Purification

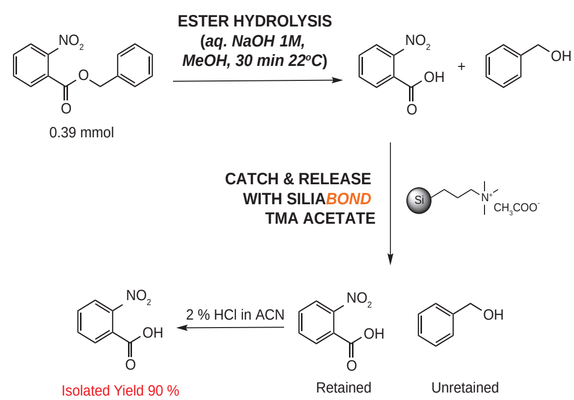
1) 12 mL cartridges (*2 or 4 g of SiliaBond TMA Acetate*) were conditionned with 6 mL of MeOH.
2) Compound was dissolved in 1 - 2 mL of MeOH and loaded onto the cartridge.
3) Column was washed with 15 mL of MeOH.
4) Compound was released with a solution of AcOH / MeOH : 2/98.
5) Solvents were evaporated and final compound weighted.



3-CHLOROBENZOIC ACID PURIFICATION VIA CATCH & RELEASE



ESTER HYDROLYSIS PURIFICATION VIA CATCH & RELEASE

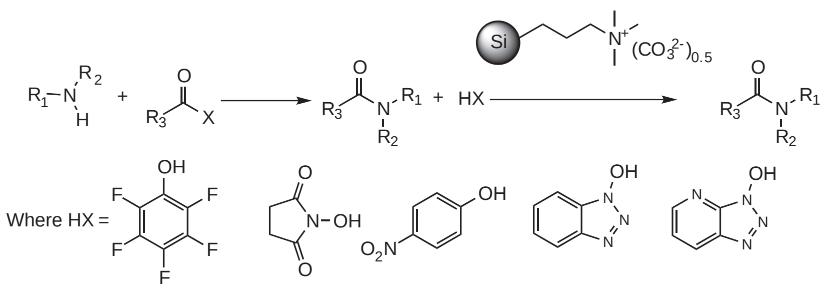


Conclusion

Epoxidation reactions with 3-chloroperbenzoic acid (*mCPBA*) often yield after treatment of the reaction a certain undesirable amount of 3-chlorobenzoic acid, which can sometimes be difficult to separate from the desired product. In the present example, 4-bromostyrene was treated with mCPBA, and the reaction medium is then treated with an aqueous solution of sodium sulfite. The latter allows to destroy excess reagent and eliminates much of the 3-chlorobenzoic acid correspondent. After extraction with dichloromethane and evaporation, the product was loaded on a 12 mL TMA Acetate SPE cartridge of 2 or 4 g. A simple elution with methanol made it possible to isolate 88 % of the desired epoxide product. Similarly, the same strategy was applied for the purification of 2-nitrobenzoic acid after hydrolysis of benzyl-2-nitrobenzoate, to yield the former molecule in a 90 % final yield.
In conclusion, SiliaBond TMA Acetate is very useful for the purification of carboxylic acids. Conversely, it may free the reaction media from compounds having a pK_a lower than 5.

Ionic Scavenging of Phenols and Acids with SiliaBond Carbonate

The efficiency of Silia*Bond* Carbonate as a scavenger of various coupling reagents (*HX*) - including pentafluorophenol, N-hydroxysuccinimide (*HOSu or NHS*), 4-nitrophenol, 1-hydroxybenzotriazole (*HOBt*) and 1-hydroxy-7-azabenzotriazole (*HOAt*) - was studied, as well as a comparison with two suppliers of polymer-supported carbonate.



HX	SiliaBond Carbonate		Polymer 1		Polymer 2	
	5 min	60 min	5 min	60 min	5 min	60 min
Pentafluorophenol[1]	**98**	**98**	92	**95**	85	94
N-Hydroxysuccinimide	93	**> 95**	41	64	40	42
4-Nitrophenol	94	**96**	89	**95**	77	88
1-Hydroxybenzotriazole[2]	88	**96**	68	92	26	**96**
1-Hydroxy-7-azabenzotriazole[2]	**97**	**97**	72	**96**	30	92

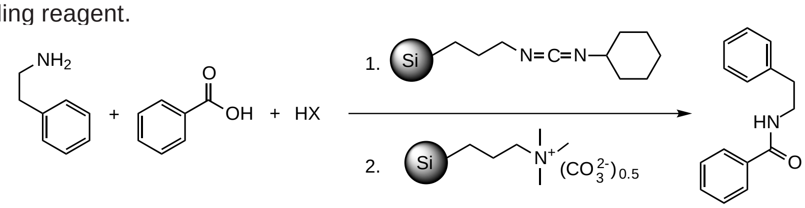
Phenol Scavenging Results (*in %*)

Initial concentration: 5,000 ppm - 3 equiv of Silia*Bond* Carbonate. Analyzed by UV. [1] Analyzed by GC-MS, [2] in THF

Conclusion

For each of the various experimental conditions / coupling reagents that were tested, Silia*Bond* Carbonate yielded better to much better scavenging results than its polymer-bound Carbonate equivalents.

Silia*Bond* Carbonate was also very useful in the scavenging of benzoic acid, in the following amide coupling, using Silia*Bond* DCC as a coupling reagent.



HX	Yield	Purity
No Catalyst	35	**95**
N-Hydroxysuccinimide[1]	67	**98**
1-Hydroxybenzotriazole[2]	**99**	**98**
1-Hydroxy-7-azabenzotriazole[2]	**100**	**99**

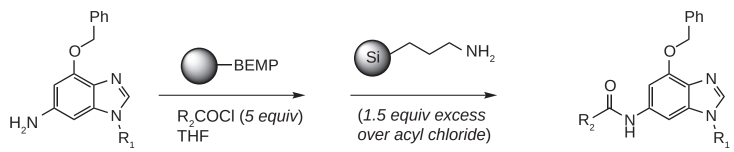
Benzoic Acid Scavenging Results (*in %*)

Note: 1.0 equiv of amine, 1.5 equiv acid, 1.7 equiv catalyst (*HX*), 2.0 equiv SiliaBond Carbodiimide, 7.0 equiv Silia*Bond* Carbonate. Yield refers to the mass of isolated product.
Purity was determined by GC-FID. [1] in DCM, [2] in THF

For experimental details using a silica-bound heterogeneous DCC coupling reagent, please see p. 96

A Roche Case Study: Nucleophilic Scavenging of Acyl Chlorides with Silia*Bond* Amine

The guanine synthesis started with the simple and direct acylation of O-benzyl-2-aminopurine with polymeric BEMP. This convenient acylation approach using polymeric base was attempted in order to avoid the laborious Mitsunobu reaction introducing N9 substituents and tedious aqueous work-up steps. Silia*Bond* Amine was used to sequester the excess acyl chloride instead of using polystyrene-based trisamine resins.



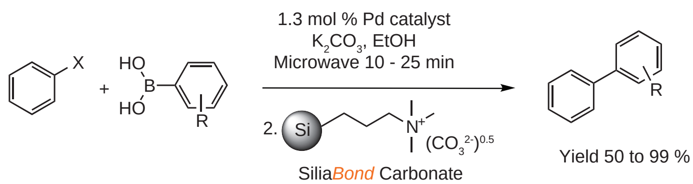
General Procedure

Silia*Bond* Amine (*1.5 equiv)* was added to the reaction mixture and stirred for 1 h at room temperature.
The Silia*Bond* Amine scavenger with bound acyl chloride was then filtered off and rinsed with solvent (*e.g.: MeOH*) to yield an acyl chloride-free solution.

K. Kim *et al.*, *Tett. Lett.*, **2000**, *41*, 3573-3576
Roche Research Center, Hoffmann La-Roche, Inc., Nutley, NJ, USA

An Abbott Case Study: Ionic Scavenging of Boronic Acids with Silia*Bond* Carbonate

An efficient Suzuki coupling protocol was developed and excess boronic acids were rapidly removed using solid-phase extraction and Silia*Bond* Carbonate to yield clean product.

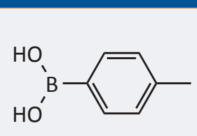
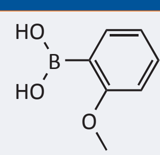
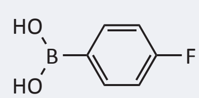
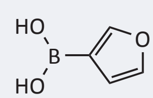


General Procedure

A Smith Process vial was charged with a stir bar, 4-bromobenzonitrile, p-tolylboronic acid and 2 mL of ethanol. A solution of 1 M K_2CO_3 was added followed by the Pd catalyst. The reaction vessel was sealed and heated to 110°C for 600 seconds under microwave irradiation. After cooling, the reaction mixture was transferred to a pre-packed column of Silia*Bond* Carbonate which had been conditioned with MeOH / CH_2Cl_2 (*1:1*), and the eluent was collected via gravity filtration. The column was then washed with MeOH / CH_2Cl_2 (*1:1*) (*3 × 3 mL*).

The eluents were combined, concentrated and purified by flash chromatography to yield a purified compound.

Scavenging Boronic Acids Results (*in %*)

# of Equivalents				
10	**> 97**	**> 97**	**> 97**	**> 97**

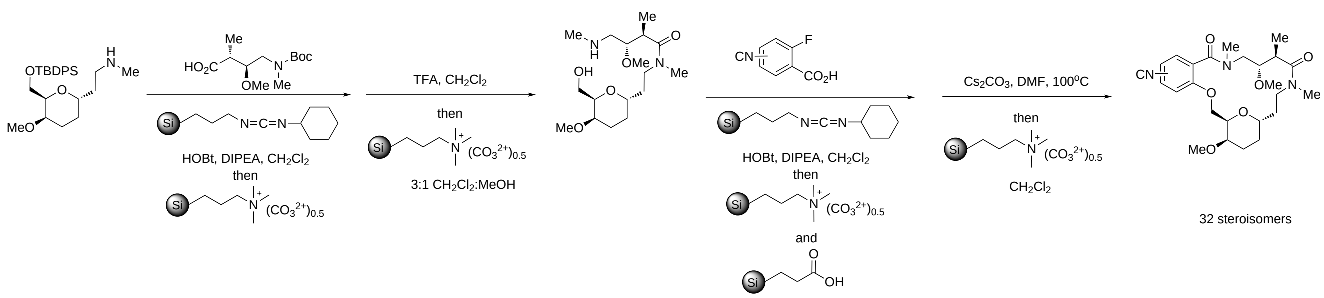
Y. Wang, D. R. Sauer *et al.*, *Org. Lett.*, **2004**, *6*, 2793-2796
High-Throughput Organic Synthesis Group, Global Pharmaceutical R&D, Abbott Laboratories, Illinois, United States

A Broad Institute Case Study: Ionic Scavenging of Acids with Silia*Bond* Carbonate & Electrophilic Scavenging of Amines with Silia*Bond* Carboxylic Acid

In the context of the synthesis of a library of highly complex macrocycles with a pyran core, Silia*Bond* Carbonate (*Si-CO*$_3$) and Silia*Bond* Carboxylic Acid (*Si-WCX*) were used in the purification process.

In the reaction below, Silia*Bond* Carbonate was used to remove excess of the acidic acylating reagent, and used again in the next step to remove excess benzoic acid. Then, Silia*Bond* Carboxylic Acid was added to remove any excess N,N-Diisopropylethylamine or potential o-acylation by-products.

All reactions were carried out using SiliCycle MiniBlock and MiniBlock XT for parallel synthesis.
Purities of various macrocycles were between 70 - 92 %, with an average purity of 87 %.



General Procedures

Acylation: The crude amino alcohols, cyano-fluorobenzoic acid 4-o or 4-p (*0.14 mmol; 1.0 equiv*), Silia*Bond* Carbodiimide (*Si-DCC*) (*0.19 mmol; 1.4 equiv*) and DIEA (*0.090 mmol; 0.7 equiv*) were combined in 2 % dimethylformamide (*DMF / DCM 3.0 mL*), and stirred at room temperature overnight. In cases where acylation is slow, additional Si-DCC (*0.19 mmol; 1.4 equiv*) and a solution of HOBt (*0.03 mmol; 0.2 equiv*) in DMF / DCM (*1.0 mL*) and DIEA base (*0.03 mmol; 0.2 equiv*) were added. After acylation was deemed complete, reactions were scavenged with Si-CO$_3$ (*0.18 mmol; 1.4 equiv*) and Si-WCX (*0.18 mmol; 1.4 equiv*) for 30 min and then filtered and evaporated for 4 h.

S$_N$Ar Macrocyclization: All crude products from above were dissolved in DMF (*4.0 mL*) and heated at 110°C with Cs$_2$CO$_3$ (*approximately* (*0.61 mmol; 4.5 equiv*) for 4 h. Reaction mixtures were filtered through Celite, washed with DCM, and solvents evaporated. Crude products were dissolved in DCM and treated with Si-CO$_3$ (*0.18 mmol; 1.4 equiv*) and Si-WCX (*0.18 mmol; 1.4 equiv*) for 30 min, and then filtered through Celite and concentrated.

Please see p. 112 to learn more about the acylation reaction using Silia*Bond* Carbodiimide.

E. Comer *et al.*, *Proceedings of the National Academy of Sciences of the United States of America*, **2011**, *108*, 6751-6756
Chemical Biology Platform, Broad Institute, Cambridge, MA 02142

Control & Removal of Potential Genotoxic Impurities (*PGI*)

Potential Genotoxic Impurities (*PGI*) have gained considerable attention due to their carcinogenic character to induce genetic mutations and / or chromosomal rearrangements. These compounds cause DNA damage by various mechanisms such as alkylation or other interactions and lead to mutation of the genetic code.

In situations where formation of PGIs cannot be avoided, an ideal solution would be to perform complete removal of PGIs after the synthesis is completed. For example, recrystallization, preparative chromatography or other downstream processing approaches might be considered. Many disadvantages of using such approaches include: potential yield loss, high solvent consumption, additional time and resources required for process development.

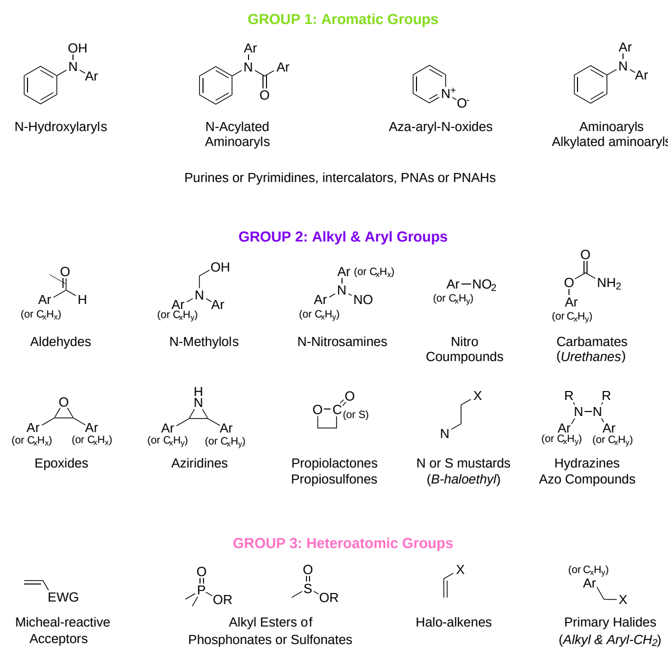
If you are concerned about such impurity regulations, here are regularly updated websites and work of reference you may rely on:

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
http://www.ich.org

The European Medicines Agency
http://www.ema.europa.eu/

References and On-Going Updates from Regulatory Authorities and Industry Practices Related to Genotoxic Impurities
http://www.labcompliance.com/info/links/impurities/genotoxins

Alerting Structures Examples (*ICH*)



Whatever the nature of the impurity you might encounter, you can rely on our family of genotoxic impurity scavengers in order to eliminate tedious post-reaction purifications.

Also available:

- **Silia*MetS* DOTA**
- **Silia*MetS* Tosic acid**
- **Silia*MetS* DEAM**
- **Silia*MetS* Propylsulfonic acid**

METAL SCAVENGER for (Metals to be scavenged)	Silia*MetS* Thiol (Si-Thiol) PN: R51030B	Silia*MetS* DMT (Si-DMT) PN: R79030B	Silia*MetS* TAAcOH (Si-TAAcOH) PN: R69030B	Silia*MetS* Triamine (Si-TRI) PN: R48030B
Loading mmol/g	≥ 1.20	≥ 0.50	≥ 0.41	≥ 1.11
Ag	■			●
Al				
Ca				
Cd		●		●
Ce				
Co		●	■	●
Cr			●	■
Cs			●	
Cu	●	●		●
Fe		●	●	●
Gd				
Hg	■			●
Ir	●	■		
La				
Li				
Mg				
Mn				
Ni		■	■	●
Os	■	■	■	●
Pb	●			●
Pd (II)	■	■	●	■
Pd (0)	■	■	●	■
Pt		■		■
Rh (I)	●	■	●	●
Rh (II)	●	■	●	●
Rh (III)	●	■		●
Ru (II)		■		●
Sc		●	■	●
Sn	●		●	
Ti				
W				●
Zn		●		●

ORGANIC SCAVENGER for (Electrophiles & Nucleophiles to be scavenged)	Silia*MetS* Triamine (Si-TRI) PN: R48030B	Silia*Bond* Piperazine (Si-PPZ) PN: R60030B	Silia*Bond* Tosyl Chloride (Si-TsCl) PN: R44030B
Loading mmol/g	≥ 1.11	≥ 0.83	≥ 0.88
Acid	◉	◉	
Acid chloride	◆		
Acidic phenol	◉	◉	
Alcohol			▼
Aldehyde	◆		
Alkoxide			▼
Amine			▼
Anhydride	◆		
Aniline			▼
Boronic acid			
Carboxylic acid			
Chloroformate	◆		
Hydrazine			▼
Isocyanate	◆		
Ketone			
Organometallic			▼
Sulfonyl chloride	◆		
Thiol / Thiolate			

POTENTIAL GENOTOXIC IMPURITIES :

BEST SCAVENGER: ■
GOOD SCAVENGER: ●
ELECTROPHILE SCAVENGER (*COVALENT BONDING*): ◆
NUCLEOPHILE SCAVENGER (*COVALENT BONDING*): ▼
IONIC BONDING: ◉

Scavenging Solutions

A Merck Case Study: Removal of Electrophilic Potential Impurities Using Silica-Based Nucleophilic Scavengers

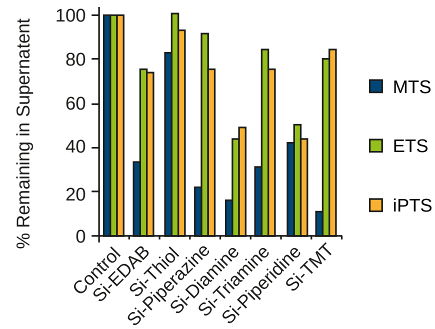
Merck & Co. has reported a rapid approach to remove electrophilic PGIs from APIs. Solutions of methyl, ethyl and isopropyl *p*-toluenesulfonate were treated with different nucleophilic functionalized-silicas for 30 min.

The graph below shows screening results for removal of *p*-TSA methyl (*MTS*), ethyl (*ETS*) and isopropyl (i*PTS*) esters by the different resins. One milliliter of 1 µg/mL *p*TSA ester solution in MeOH was added to 100 mg of each of the functionalized silicas. The solutions were sonicated for 30 min, filtered through a 0.45 µm filter and assayed by LC/MS.

Several scavengers showed extensive removal of methyl *p*-toluenesulfonate, with multiple thiol- or amine-containing Silia*Bond* affording greater than 80 % impurity removal under these conditions.

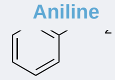
These same resins were less effective in removal of the ethyl and isopropyl esters, presumably owing to the increased steric bulk of the ethyl and isopropyl esters versus the methyl ester.

R. Helmy, M. A. Al-Sayah *et al.*, *Org. Proc. Res. Dev.*, **2010**, *14*, 1021-1026
Merck & Co. Inc., New Jersey, United States

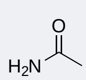
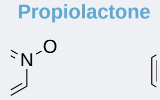
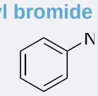
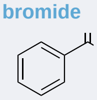
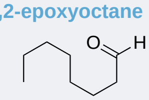


In the same vein, eleven compounds containing structurally alerting functional groups were studied in SiliCycle labs, and scavenged by at least one of our grafted silica: **Best scavenger:** ■ **| Good scavenger:** ●

Scavenging Affinity for Various Potentially Genotoxic Impurities

Alerting Functional Groups	Acetamide	Pyridine N-oxide	Aniline 	Phenyl-hydroxylamine	Benzaldehyde	Octaldehyde
Silia*MetS* DMT					●	●
Silia*MetS* Thiourea						
Silia*MetS* Triamine					■	■
Silia*MetS* TAAcOH		●				
Silia*MetS* TAAcONa						
Silia*Bond* Tosic Acid	■	■	■	■		
Silia*Bond* Tosyl Hydrazine					■	■
Silia*Bond* Tosyl Chloride	●	■	●	●		

Scavenging Affinity for Various Potentially Genotoxic Impurities

Alerting Functional Groups	Methyl methane sulfonate 	Propiolactone 	Benzyl bromide 	Allyl bromide 	1,2-epoxyoctane 
Silia*MetS* DMT	■	■	■	■	
Silia*MetS* Thiourea		●	●	●	
Silia*MetS* Triamine	●	■			
Silia*MetS* TAAcOH					
Silia*MetS* TAAcONa	●	■			
Silia*Bond* Tosic Acid					■
Silia*Bond* Tosyl Hydrazine		■			
Silia*Bond* Tosyl Chloride					■

Silia*MetS* & Silia*Bond* Ordering Information

Many of our customers are pleasantly surprised when they discover how flexible the use of scavengers can be. No matter what your favorite purification technique might be or which one you are most familiar with, scavengers come in various formats for all preferences.

Bulk, SPE cartridges, flash cartridges and even guard cartridges to protect your expensive HPLC columns, all are formats that are frequently used in order to take full advantage of SiliCycle scavengers' strength.

Purity will never be an issue again!

Ordering Information for Batch Reactor Mode (*Bulk*)

All Scavengers are available in the following sizes: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc. Up to multi-ton scale!

All Particle Size and Pore Size are respectively 40 - 63 µm and 60 Å. Other matrices are available upon request.

Silia*MetS* Metal Scavengers

Scavenger Name	Scavenger Product Number
Silia*MetS* AMPA	R85130B
Silia*Bond* Amine (*WAX*)	R52030B
Silia*MetS* Cysteine	R80530B
Silia*MetS* DEAM	R54430B
Silia*MetS* DOTA	R91030B
Silia*MetS* DMT	R79030B
Silia*MetS* Diamine	R49030B
Silia*MetS* Imidazole	R79230B
Silia*MetS* TAAcOH *nec*	R69030B
Silia*MetS* TAAcONa *nec*	R69230B
Silia*MetS* Thiol	R51030B
Silia*MetS* Thiourea	R69530B
Silia*Bond* Tosic Acid (*SCX*)	R60530B
Silia*MetS* Triamine	R48030B

Silia*Bond* Organic Scavengers

Scavenger Name	Scavenger Product Number
Silia*Bond* Amine (*WAX*)	R52030B
Silia*Bond* Carbonate	R66030B
Silia*Bond* Carboxylic Acid (*WCX*)	R70030B
Silia*MetS* DEAM	R54430B
Silia*Bond* DMAP	R75630B
Silia*MetS* Diamine	R49030B
Silia*Bond* Diol	R35030B
Silia*Bond* Guanidine	R68230B
Silia*Bond* Isocyanate	R50030B
Silia*Bond* Maleimide	R71030B
Silia*Bond* Piperazine	R60030B
Silia*Bond* Propylsulfonic Acid (*SCX-2*)	R51230B
Silia*Bond* TMA Acetate *nec*	R66430B
Silia*Bond* Tosic Acid (*SCX*)	R60530B
Silia*Bond* Tosyl Chloride	R44030B
Silia*MetS* Triamine	R48030B

Ordering Information: Available Kits

Because all matrices are unique, and that small differences can influence scavenging efficiency, we recommend first trying one of our Scavenger Kit for screening purposes, especially if you are new to this technology. Steric hindrance of the catalyst, electronic effects, solubility in solvents, all are factors that can influence the removal of your impurity.
These kits are available in 5 g, 10 g, 25 g, 50 g and 100 g formats (*custom formats are also available, contact us for more details*).

How to order

Simply note the **Product Number** which starts with "**K**", add a dash mark and your choice of format, e.g.: **K30730B-10G** to obtain **10G** of each one of the scavengers listed in the kit.

All following kits have been designed for definite needs:

Silia*MetS* Metal Scavenger Kits

Kit Name	Kit PN	Composition
Silia*MetS* Novel Scavenger Kit	**K34530B**	AMPA, DEAM, DOTA, DMT, Guanidine & Thiol
Silia*MetS* Tin Metal Scavenger Kit	**K34730B**	Carbonate, Cysteine, DEAM, DMT, TAAcOH, TAAcONa, Thiourea & Thiol

Silia*MetS* Metal Scavenger Kits (*Con't*)

Kit Name	Kit PN	Composition
Silia*MetS* Universal Metal Scavenger Kit	**K30730B**	Cysteine, DMT, Imidazole, TAAcOH, TAAcONa Thiol, Thiourea & Triamine
Silia*MetS* Palladium Metal Scavenger Kit	**K34630B**	DMT, Diamine, Thiol, Thiourea Imidazole & Triamine

Silia*Bond* Scavenger Kits

Kit Name	Kit PN	Composition
Silia*Bond* Electrophile Introductory Scavenger Kit	**K34230B**	Amine, DMAP, Diamine, Tosyl Hydrazine, Piperazine & Triamine

Silia*Bond* Scavenger Kits (*Con't*)

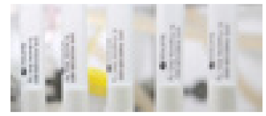
Kit Name	Kit PN	Composition
Silia*Bond* Electrophile Complete Scavenger Kit	**K35230B**	Amine, DEAM, Diol, DMAP, TMA Acetate & Triamine
Silia*Bond* Nucleophile Complete Scavenger Kit	**K32630B**	Carbonate, Isocyanate, Maleimide & Tosyl Chloride

Ordering Information for Fixed-Bed Mode Formats (*SPE or Flash Cartridges*)

Silia*Prep*™ SPE Cartridges and Silia*Sep*™ Flash Cartridges

To build your SPE Cartridge Product Number, simply start with the code SPE, followed by the Product Number of the scavenger you wish your cartridge to be packed with, followed by the code of the desired format.

Example: **Silia*Prep* Thiourea**, **6 mL**, **500 mg** = **SPE-R69530B-06P**



Formats available:

Silia*Prep* SPE Scavenger Cartridges					
Formats available	**3 mL / 200 mg**	**3 mL / 500 mg**	**6 mL / 500 mg**	**6 mL / 1 g**	**6 mL / 2 g**
Associated code	03G	03P	06P	06S	06U
Units / Box	50	50	50	50	50

Silia*Sep*™ Flash Cartridges

To build your Flash Cartridge Product Number, simply start with the code FLH, followed by the Product Number of the scavenger you wish your cartridge to be packed with, followed by the code of the desired format.

Example: **Silia*Sep* Open-Top TAAcONa**, **70 mL**, **10 g** = **FLH-R69230B-70Y**

Silia*Sep* TAAcONa, **4 g** = **FLH-R69230B-ISO04**

Formats available:

Silia*Sep* OT Scavenger Cartridges					
Formats available	**12 mL / 200 g**	**25 mL / 5 g**	**70 mL / 10 g**	**70 mL / 15 g**	**70 mL / 20 g**
Associated code	12U	20X	70Y	70i	70Z
Units / Box	20	20	16	16	16
Formats available	**150 mL / 25 g**	**150 mL / 50 g**	**150 mL / 70 g**	**276 mL / 100 g**	
Associated code	95K	95M	95N	276F	
Units / Box	10	10	10	12	

Silia*Sep* Scavenger Flash Cartridges					
Formats available	**4 g**	**12 g**	**25 g**	**40 g**	**80 g**
Associated code	ISO04	ISO12	ISO25	ISO40	ISO80
Units / Box	2	1	1	1	1
Formats available	**120 g**	**220 g**	**330 g**	**800 g**	**1,600 g**
Associated code	IS120	IS220	IS330	IS750	I1500
Units / Box	1	1	1	1	1

Silia*Sep* Scavenger Flash Cartridges for Industrial Scale				
Formats available	**2.5 kg**	**5 kg**	**20 kg**	**41 kg**
Associated code	150iM	150iL	400iM	400iL
Units / Box	1	1	1	1

Ordering Information for HPLC Guard Cartridges

Silia*Chrom* Guard Cartridges

Silia*Chrom* HPLC Guard Columns are designed to effectively protect both analytical and preparative HPLC columns. The usage of this shorter column is highly recommended to prolong column lifetime and does not alter the results.
Silia*Chrom* Guard Columns are cost effective and easy to use as a pre-filter to remove contaminants prior to injection. In liquid chromatography, contaminants introduced into the column can cause:

- Higher backpressure
- Resolution loss
- Baseline noise or drift
- Peak shape changes
- Irreversible damages (*column + system*)

Silia*Chrom* Guard Columns Dimensions

Silia*Chrom* Guard Columns are available in lengths of 10 - 20 mm and three internal diameters (*ID: 4.0, 10 and 21.2 mm*). You can check the most suitable dimension combinations on page 158 in our Analytical Catalog, or our website.

The Guard Column internal diameter should be the same as the HPLC column or one size smaller. Never use a guard column with a larger ID than that of the HPLC column (*risk of efficiency loss*).

Silia*Chrom* Guard Columns Packings & Dimensions

Silia*Chrom* Metal & Organic Scavenger Guard Columns

Guard Cartridges Name	Palladium’s Favorite Metal Guard Cartridge	Universal Metal Guard Cartridge
Scavenger Packing #	K346	K307

To build your Part Number, simply start with the code HPLG, followed by the PN of the scavenger packing you wish your cartridge to be filled with, followed by the code of the desired format.

Example: **Silia*Chrom* Plus Guard Cartridge** for **Pd removal**, **5 µm**, **4.6 x 20 mm** = **HPLG-K34605E-A-N020**

Available formats:

Silia*Chrom* Scavenger Guard Column Formats

Particle Size of Sorbent (*µm*)	Formats Available (*internal diameter x length in mm*) 4.0 x 10	4.0 x 20	10 x 10	21.2 x 10
5	05E-A-N010	05E-A-N020	05E-A-Q010	05E-A-T010
10	07E-A-N010	07E-A-N020	07E-A-Q010	07E-A-T010

Silia*Chrom* Guard Cartridges Package Information:

- 4.0 mm ID Guard Cartridges are sold in pack of 4 cartridges
- 10 mm ID Guard Cartridges are sold in pack of 2 cartridges
- 21.2 mm ID Guard Cartridges are sold in pack of 1 cartridge

Silia*Chrom* Guard Holder information:

- **HPH-N010** (*for 4.0 x 10 mm Guard Cartridges*)
- **HPH-N020** (*for 4.0 x 20 mm Guard Cartridges*)
- **HPH-Q010** (*for 10 x 10 mm Guard Cartridges*)
- **HPH-T010** (*for 21.2 x 10 mm Guard Cartridges*)

*Other dimensions and particle sizes could be available on a custom basis. Contact us.

Scavenging Solutions