

Metal Scavenger Guide



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What are Metal Scavengers?

Biotage supported resin and silica based metal scavengers are effective reagents for the removal of trace metals (such as PGM's) from catalyzed reactions to final API's. This technology can be applied to a variety of different industries, from pharmaceutical to fine chemical; from agrochemical to water and waste treatment.



Figure 1: Metal Scavenging Tool Kit

Tool Kit of Metal Scavengers:

- Now incorporating the industry leading universal scavenger for metal scavenging / removal work, MP-TMT
- Higher metal affinity – low $K_d(\text{Pd})$ relative to API $K_d(\text{Pd})$ – excellent metal scavenging
- Fast kinetics / filtration at room temperature – enhanced by heating
- Diverse solid supports – silica and polystyrene backbones
- Work Flow Compatible – generic, use in diverse conditions
- Minimal loss of API – less / no non-specific binding
- Higher purity of final product – no leachables
- Short development time – faster method optimization

Solid supported metal scavengers have been shown to be highly selective, and also offer cost-effective scavenging, enabling chemists to reach metal purity goals⁴. Precious metals such as Pd, Pt, Ru and Rh in organometallic catalysts are becoming more widespread in industrial synthesis due to atom economy and green credentials^{1,2}. These PGM group catalyzed reactions are commonly used in the manufacture of active pharmaceutical ingredients (API's) and fine chemicals. Achieving purity levels for metal contamination is becoming increasingly challenging, with 5 ppm (ingested), and 1 ppm (parenteral) API now the benchmarked standard³. This poses particular difficulties in downstream purification of Pd based chemistries.

Traditional methods to remove metals include chromatography, activated carbon, extraction, distillation and recrystallization but, these can offer poor selectivity and lead to high API loss. Biotage has assembled an optimized tool kit (K-MS-2) to facilitate the process of metal screening and method development.

Biotage are leaders in metal scavenging in a variety of different application areas.

Shelf-Life and Stability:

- Mechanically robust, and may be stirred vigorously without breakdown
- Bioanalytical grade silica
- Can also be added in batch processes and stirred
- Optimum flow characteristics as fixed beds
- May be stored in closed containers at RT, or longer term in a cool dry (4°C) environment.

References:

1. King, A. O.; Yasuda, N. *Topics in Organometallic Chemistry*, **2004**, 6, 205-245.
2. Carey, J.S.; Laffan, D.; Thompson, C.; Williams, M.T. *Org. Biomol. Chem.* **2006**, 4, 2337-2347.
3. European Agency for the Evaluation of Medicinal Products, Guidelines on the Specification Limits for Residues of Metal Catalysts or metal reagents, 2008 accessed December **2009**: <http://www.emea.europa.eu/pdfs/human/swp/444600en.pdf>
4. Welch, C.J.; Albaneze-Walker, J.; Leonard, W.R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D.J.; Spencer, S.; Bu, X.; Wang, T.; *Org.Proc.Res.Dev.* **2005**, 9, 198-205

Selection Guide

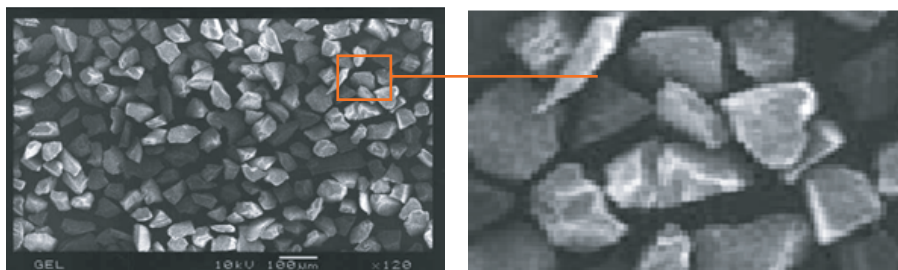


Figure 2: Scanning Electron Micrograph image of silica scavengers (x 120 magnification)

Selection Guide

Product	Particle Size µm	Ligand-M Strength	Compatible API's	Batch Performance	Fixed Bed (Cartridge) Performance	Main Metals scavenging	Typical Catalysts	Typical Reactions	Other Metals Scavenged	Solvent Compatibility	Typical Load vs API (flow)	Typical Load vs API (batch)
MP-TMT	150-350	■	ABN	■	■	Pd	Pd(OAc) ₂ , Pd(PPh ₃) ₄ , Pd(PPh ₃)Cl ₂ , Pd(dppf)Cl ₂	Suzuki, Heck, Sonogashira, Ulman etc.	Rh, Ru, Pt, Ni, Rh	All*	n/a	2-20 wt%
Si-TMT	45-60	■	ABN	■	■	Pd	Pd(OAc) ₂ , Pd(PPh ₃) ₄ , Pd(PPh ₃)Cl ₂ , Pd(dppf)Cl ₂	Suzuki, Heck, Sonogashira, Ulman etc.	Rh, Ru, Pt, Ni, Rh	All*	5-10eq	2-20 wt%
Si-Thiol	45-60	■	ABN	■	■	Pd	Pd(OAc) ₂ , Pd(PPh ₃) ₄ , Pd(PPh ₃)Cl ₂ , Pd(dppf)Cl ₂	Suzuki, Heck, Sonogashira, Ulman etc.	Rh, Ru, Pt, Ni, Rh	All*	5-10eq	2-20 wt%
SCX-2	45-60	■	AN	■	■	Fe	M(I)	Various	M(I)	All*	5-10eq	2-20 wt%
Si-Trisamine	45-60	■	BN	■	■	Pd	Pd(OAc) ₂ , Pd(PPh ₃) ₄ , Pd(PPh ₃)Cl ₂ , Pd(dppf)Cl ₂ , M(II)	Suzuki, Heck, Sonogashira, Ulman etc.	Ni, Sn, Fe, Cu, Zn, M(II)	All*	5-10eq	2-20 wt%

■ Excellent / Preferred

■ Very Good

■ Good

ABN for Acids, bases, neutral products, 2 > pH > 10, extremes possible for short times

AN for Acids, neutral products, 2 > pH > 10, extremes possible for short times

BN for Bases, neutral products, 2 > pH > 10, extremes possible for short times

M = Transition metal

*All common laboratory and process solvents

Advantages of Biotage Metal Scavengers

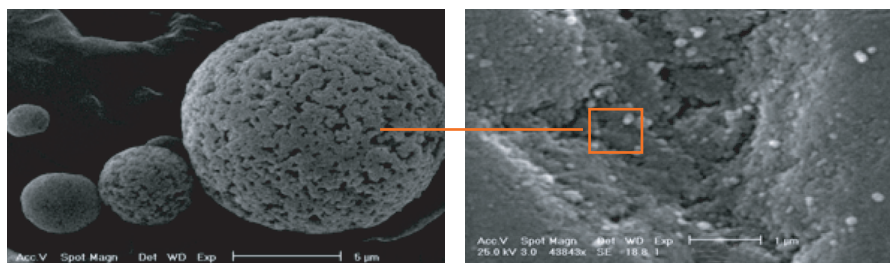


Figure 3: SEM image of MP-resin; permanently open pores allow greatest solvent compatibility

Features and Benefits

No Leaching	Used in final / late stage API synthesis, each product supplied with full QC ISO certification, detailing extractables, LOD, elemental analysis, FTIR, physical inspection, particle size, MSDS, TSE statement supplied as standard. Further information in support of regulatory compliance available on request.
High Selectivity	Excellent extraction of metal.
Excellent Range of Metal Affinities	Tuneable by metal or oxidation state, variety of scavengers as standard.
Many Oxidation States Covered	Can be applied to mother liquors or extracted product of reaction.
Solvent Compatibility	Scavengers work in both organic or aqueous or mixtures of solvents.
Fast Kinetics	Room temperature kinetics, can also be heated.
Easily Scalable	From mg screening experiments to multi-Kg applications.
Generic Method for Batch	High efficiency generic add, stir, filter protocols.
Generic Method for Flow	High efficiency fixed-bed format protocols.
Cost Efficient	Reduces solvent, reduces labor, high metal recovery, reduces waste solvent disposal.
Controlled Loading	Each batch lot controlled, very consistent lot-lot reproducibility.
Thermally and Mechanically Stable	Works well with overhead stirring or mechanical shaking, withstands temperatures up to approx 150-200 °C (i.e. microwave chemistry heating conditions).
Biotage has a flexible cartridge packing facility to accommodate many scale-up paths and options, from grams to Multi-Kg and in a variety of formats for processing.	

Regulatory Support Information

Biotage Metal Scavengers

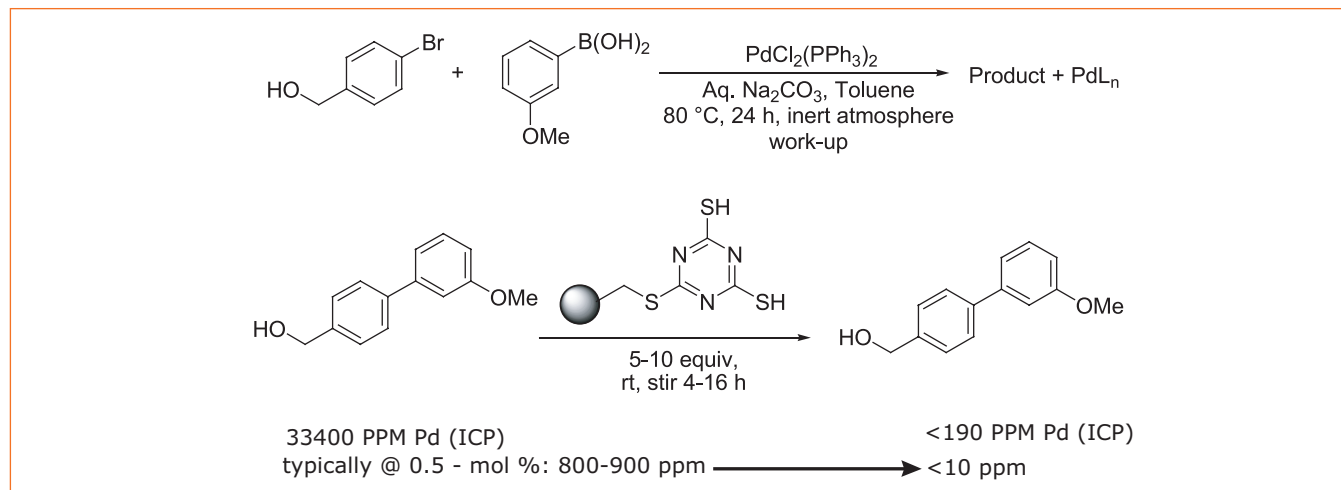
Biotage metal scavengers are made in an ISO9001:2008 compliant manufacturing facility and have served GMP pharmaceutical, drug discovery and fine chemical industries for many years. Each material is batch and lot controlled, with benefits of full traceability.

The metal scavengers are industry proven and supported by a comprehensive regulatory qualification support package incorporating:

- **Certificate of Analysis**
 - Extractables
 - Chemical loading
 - Lot information
 - Batch identity
- **MSDS**
- **BSE/TSE statement**
- **Full Instructions and Suggestions for Use**



Case 1: Removal of Pd from Suzuki Reaction using MP-TMT (xs. catalyst)



Conclusion:

Adding 5 equiv of MP-TMT (wrt Pd catalyst) to the extracted biaryl product of the Suzuki reaction and stirring at RT reduced Pd contamination 100-1000 fold. It is typical to start with initial Pd contamination approx 800 ppm, resulting in final scavenged Pd at <10 and typically <5 ppm in final product.

Case 2: Comparison of different TMT resins⁶

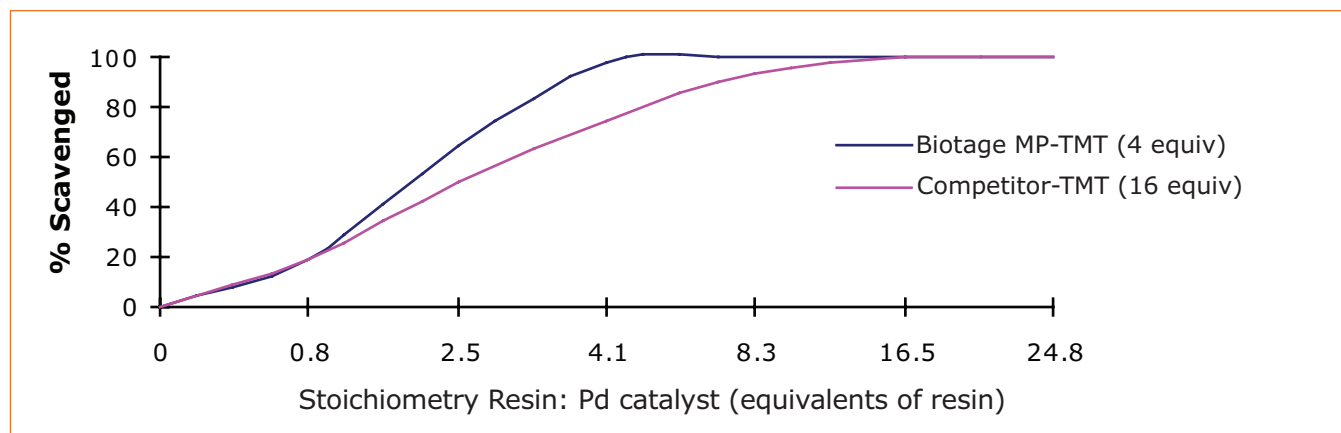


Figure 4: Biotage MP-TMT or Bound-TMT resin was exhaustively stirred with Pd(Cl)₂(PPh₃)₂ in THF/DMF (50:50) (2 mL / total 8 μmole / 852ppm Pd) for 16 hours at RT to investigate total capacity. Residual Pd was determined following scavenging.

Conclusion:

Not all Resin-TMTs are the same. Under these conditions, for 100% scavenging, it was necessary to add 16 equiv of a competitor-TMT, compared to only 4 equiv of Biotage MP-TMT. The difference was due to the precision engineered polymer back bone which gives more scavenging per unit mass of resin in the case of the Biotage scavengers. This results in lower actual costs.

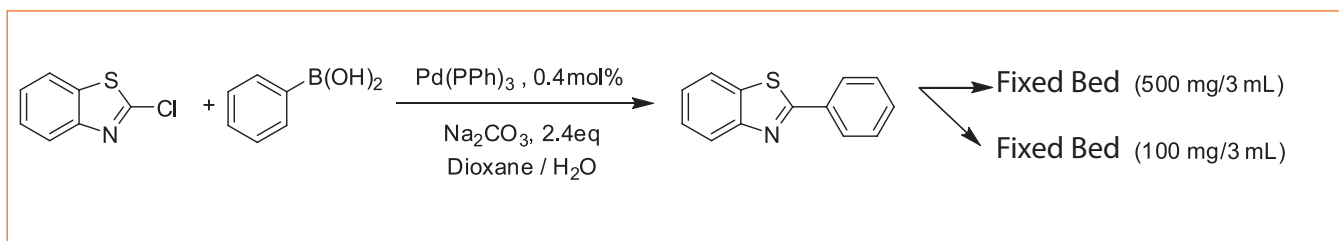
References:

6. Davies G.; Jordan S. and Rana, S. OPRD FT Lauderdale, April 2009

Case Studies

Case 3: Comparison of supported TMT Ligands⁵

In metal scavenging cartridges %Pd reduction was monitored by ICP, following one-pass gravity flow through cartridges filled with either Si-TMT or Si-Thiol.



Scavenger		500 mg/3 mL	100 mg/3 mL
Si-Thiol	ICP Pd reduction	86%	45%
Si-TMT	ICP Pd reduction	>99%	95%

Conclusion:

In very challenging scavenging situations, it is important to use the scavengers that have high Pd affinity. The TMT ligands Biotage use are amongst the strongest available; allowing more efficient scavenging with less scavenger material.

Case 4: Removal of Pd from a Pd(dppf)Cl₂ solution at RT by fixed bed methods. Si-TMT proved very effective under these challenging conditions.

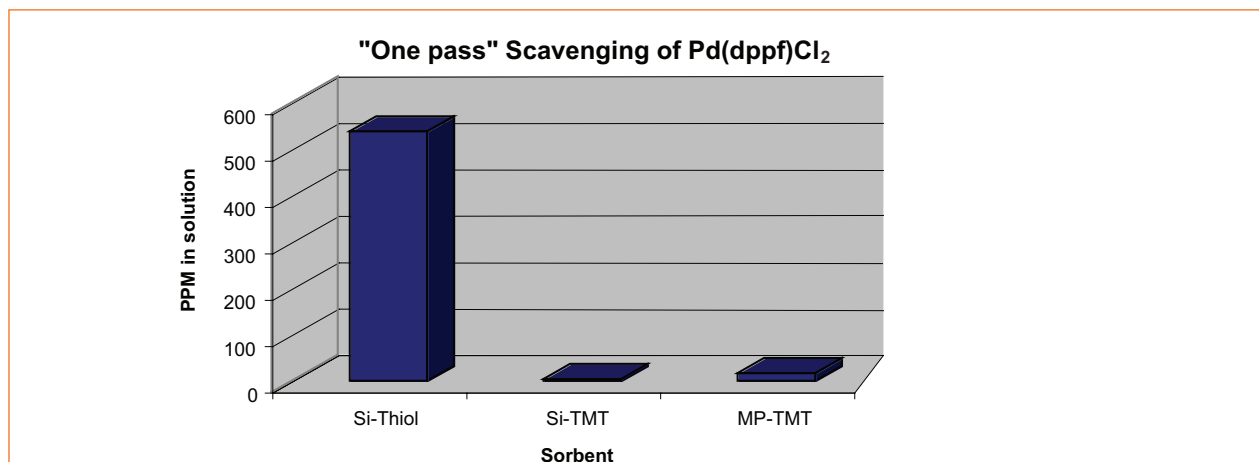


Figure 5: Initial Concentration 1000ppm Pd, Fixed bed: 500 mg / 3 mL std fritted polyprop cartridge, Gravity flow, one pass. Si-TMT in fixed bed format was most effective in removal of the contaminated Pd solution.

Conclusion:

Whilst Si-Thiol is a very good all-rounder, in very challenging situations (for example if there is sulfur in the product), alternatives may be more efficient. Si-TMT in fixed bed format was more effective for metal scavenging than Si-Thiol, under identical conditions. Due to the smaller particle size; the Si-TMT was more effective than MP-TMT; as the bed was better packed. Metal scavengers can be applied directly to reaction mother liquors or to later stage, post extraction and purification. Many of end-users apply the scavengers to final stage API synthesis as they are most effective in those environments.

References:

5. S.Rana, Unpublished Results, Biotage 2008. Method as per: Heo, Y.; Song, Y.S.; Kim, B.T.; Heo, J. Tetrahedron Lett. 47 (2006), 3091-3094

Generic Metal Scavenging Methods

Screening Protocol - Batch (Best for Resins)

1. Add solid scavenger to the product dissolved in a suitable solvent. In initial scoping to select the best scavenger, add 0.5 – 1 equivalents of scavenger directly to the solution of API or synthetic intermediate from which metal residues are to be removed.
2. No pre-wetting of the scavenger is required for batch stirring.
3. Agitate the mixture for at least an hour at room temperature for initial investigations.
4. Scavenging progress can be followed by normal analytical techniques. In many cases a strong indication of the progress of metal removal can be gained by the loss of color from the solution. Often the scavenging appears to be complete within 5-10 minutes at room temperature and this can be checked by measuring the metal content.
5. Coloration of the white, off-white or cream colored scavenger is an indication of metal removal from the solution.
6. At the end, the metal scavenger is removed via filtration, typically using a sintered funnel, glass wool or SPE cartridge. The scavenger is washed with additional solvent and combined solution concentrated.
7. At this stage, the best scavenger(s) procedure can be scaled directly. Further optimization of scavenger quantity, temperature, scavenging time and solvent type can be undertaken if required (see next page).
8. Cartridge or slurry applications are possible.

Typical results Pd (800 ppm) —> <10ppm in one application (best for Si-scavengers)

Screening Protocol - Flow (Resins and Silicas)

The metal scavenging kit (KMS-2) kit contains Si-TMT in a 500 mg / 6 mL SPE cartridge. Due to the highly efficient nature of the Pd binding onto the scavenger, this fixed-bed format, using Si-TMT is directly scalable to multi-Kg scale. As a guide, based on typical values for the 9 factors in figure 6 (P.T.O.), a 500mg cartridge of Si-TMT in a 6mL cartridge will completely remove all traces of Pd from a 1 mol% catalytic screening / test reaction at 1 mmol (product) scale.

1. Equilibrate cartridge by passing 3-5 bed volumes of API / product solvent through. This will remove any air gaps and enhance the scavenging process. This step is not critical if the cartridge is to be used under capacity.
2. Add dissolved product to cartridge and allow to flow through at RT under gravity. The cartridge may be 'pushed' using slight air or nitrogen pressure or it may be 'pulled' gently, using light vacuum (this method is especially amenable to processing on Biotage FlashVac).
3. Pd (even in 'clear colorless' solutions, on scavenging will cause Si-TMT to change color. It is normal to see a dark brown /black band of Pd at the top of the silica bed. Breakthrough of Pd was not observed, even following multiple (50+) bed volume washes using solvent under extreme testing.
4. Once product has passed through, wash cartridge with 5 bed volumes of solvent.
5. Products are not retained on the Si-TMT support as the silica is overall neutral, simple washing with bed volumes of solvent is enough to elute all product. Depending on the structure, some compounds may require more washing for complete elution.

Typical results Pd (800 ppm) —> <10 ppm in one pass flow approach

Optimizing Generic Scavenging Methods

Optimizing Generic Scavenging Methods

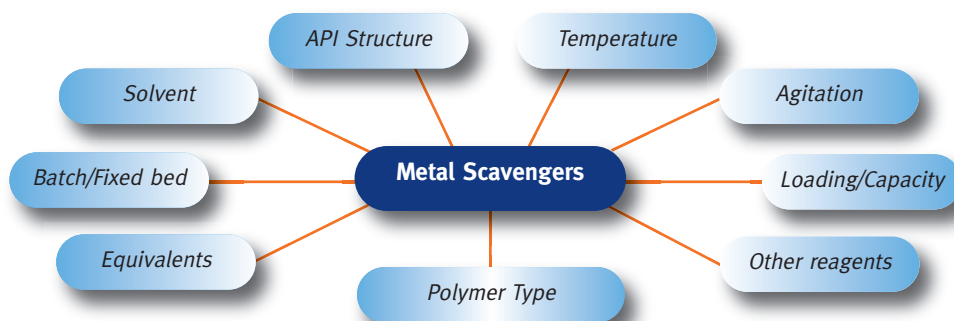


Figure 6: Metal Scavenging

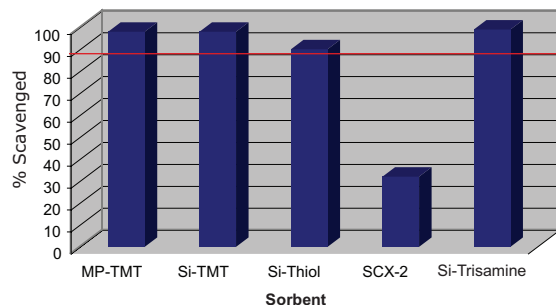
Equivalents of scavenger

If ICP data is available, typically 2-4 equivalents of scavenger wrt metal can be used as a starting point in the calculation, or 50 wt% scavenger to metal in the API is usually a good place to start if ICP is not available. Once the preferred scavenger is identified then the scavenging process can be further optimized by reducing the number of equivalents. Depending on product and solvent conditions, it is possible to use 10-20 wt% scavenger wrt API to remove metals to <5 ppm.

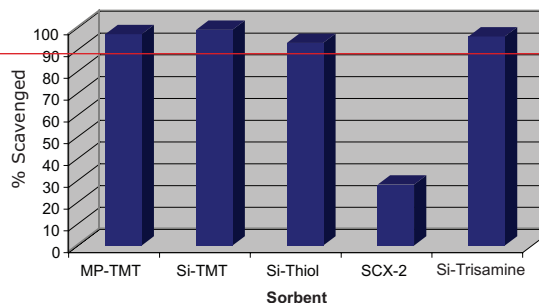
Temperature

Many scavenging process steps can be operated at RT in reasonable timescales (typically 15 min to 2 hr). Faster rates of metal removal can be achieved by heating or via fixed bed protocols. Although similar performance was seen at RT compared to elevated temperatures under identical conditions Biotage media can withstand elevated temperatures without degradation and can be added directly to warm reaction mixtures and process streams.

Batch Scavenging (2hr stir) 1000ppm Dichlorobis TPP Pd II @>10⁰ C



Batch Scavenging (2hr stir) 1000ppm Dichlorobis TPP Pd II @>40⁰ C



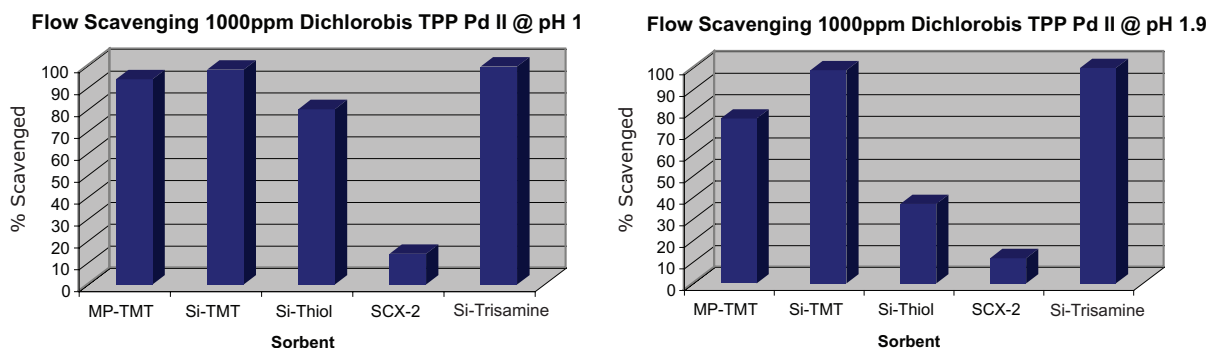
pH of the Aqueous Reaction Mixtures

Biotage scavengers can be used across a wide pH range (pH 2-10), though should be given to the optimum pH range for abstraction of target metal or organic impurity. High pH (above pH 10) should generally be avoided with silica supported scavengers; resin based scavengers should be tested if it is necessary to work at this level of pH.

Conclusion:

"Neutral" ligands (such as Si-Thiol, MP-TMP) have very wide pH scope. Charged ligands can be switched on and off depending on pH.

Optimizing Generic Scavenging Methods



Agitation rate

For batch processes, higher agitation rates can enhance scavenging performance by improving mass transport. Typically, gentle to moderate agitation rate using magnetic, overhead or shaking methods is sufficient though.

Other Reagents present in the Reaction Mixture

Reactants that may be left in the reaction mixture may interact with the scavengers. Clearly there should be no interaction between the functional groups on the scavenger and the other reagents, otherwise this may necessitate the use of additional equivalents of the scavenger.

Solvent

Macroporous resin (MP) and silica supported (Si) scavengers can be used in a wide range of aqueous and organic solvents, including THF, DMF, ethyl acetate, toluene, MeOH, ethers, chlorinated solvents and water. Co-solvent / solvent substitution should be considered if kinetics are slow. Biotage has excellent support and advice in this respect.

Batch / Flow

Si scavengers are usually more efficient in fixed beds or in flow due to their smaller particle size and enhanced packing, resins are typically employed in batch stirring processes, where additional mechanical rigidity and robustness is desired

Structure of the API

If the product or API of interest has a strong affinity for Pd, it will be necessary to use a more powerful metal scavenger to perform the optimization. In these cases, depending on the format (batch or flow) we would recommend using the MP-TMT or the Si-TMT scavengers.

Loading and Capacity

Loading capacity is not the critical factor for metal scavenging, activity of the resin or silica is the paramount. A lower loaded Si-TMT for example can outperform a more highly loaded Si-Thiol depending on the product being scavenged. Si-TMT used in fixed bed, can outperform the identical quantity of Si-TMT in batch stirring due to the kinetic amplification that fixed-bed formats can offer. The key is to consider the effect of format, ligand and work-flow. Biotage has 30+ years experience in silica and polymer chemistry and can assist in such matters.

Ordering Information

MP-TMT

Paladium Scavenger

Chemical Name: Macroporous polystyrene-2,4,6-trimercaptotriazine

Resin Type: Highly cross-linked macroporous poly(styrene-co-divinylbenzene)

Capacity: > 0.5 mmol/g (elemental nitrogen analysis)

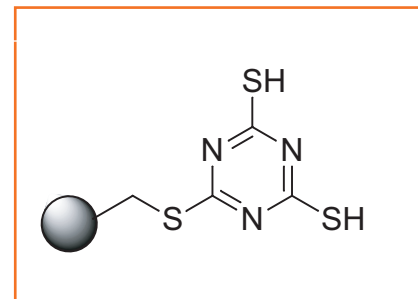
Bead Size: 150-355 microns; 45-100 mesh (>90% within)

Application: Scavenging palladium from aqueous and nonaqueous solutions

Typical Scavenging Conditions: 5 equivalents Argoresin MP-TMT relative to palladium content, 16-24 h, room temperature

Compatible Solvents: THF (4.3 mL/g), dichloromethane (DCM) (3.8 mL/g), toluene (<4.9 mL/g), acetonitrile (ACN) (<4.6 mL/g), methanol (MeOH) (4.3 mL/g), water (3.7 mL/g)

Storage: Cool, dry location



Part Number	Quantity
801506	3 g
801469	10 g
801470	25 g
801471	100 g
801472	1000 g

Si-TMT

Scavenger/Reagent

Material Type: 2,4,6-trimercaptotriazine silica

Solid-Support Type: Silica

Typical Capacity: 0.3 mmol/g

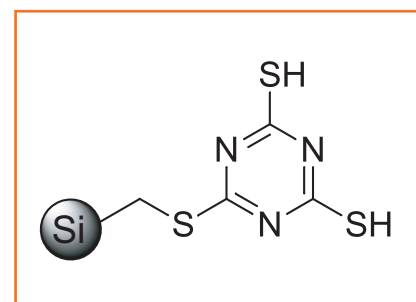
Size: 60 μ m

Appearance: Free flowing off-white powder

Application: Metal scavenging

Typical Conditions: 3 equiv ISOLUTE Si-TMT, 30 min, room temperature

Compatible Solvents: Water, Acetonitrile (MeCN), methanol, Dimethylsulfoxide (DMSO), Dichloromethane (DCM), tetrahydrofuran (THF), N,N-Dimethylformamide (DMF), Dioxane



Part Number	Quantity
9538-0010	10 g
9538-0025	25 g
9538-0100	100 g
9538-1000	1000 g

Ordering Information

Si-Thiol

Metal Scavenger/Reagent

Chemical Name: Silica 1-propanethiol; 3-Mercaptopropyl silica gel (Si-Thiol; Si-SH)

Solid-Support Type: Silica

Typical Capacity: 1.3 mmol/g

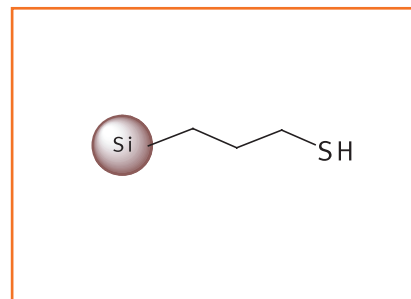
Size: 63 μm

Appearance: Free flowing off-white powder

Application: Metal scavenger (e.g. Pd, Pt, Cu, Hg, Ag and Pb); electrophile scavenger (e.g. alkyl-, benzyl- and allyl- halides, acid chlorides, isocyanates)

Typical Conditions: Add 2-6 equiv to crude reaction mixture, stir for 1-12h, and then filter.

Storage: Cool (4 $^{\circ}\text{C}$), dry location



Part Number	Quantity
9180-0010	10 g
9180-0025	25 g
9180-0100	100 g
9180-0500	500 g
9180-1000	1000 g

Si-Trisamine

Scavenger/Reagent

Material Type: Propyl tris-(2-aminoethyl)amine silica

Solid-Support Type: Silica

Typical Capacity: 1.2 – 2.1 mmol/g based on benzoyl chloride uptake

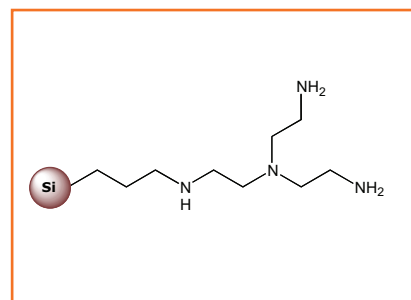
Size: 65 μm (average)

Extraction Residue: <0.1%

Application: Metal scavenging, scavenging acid chlorides, sulfonyl chlorides, isocyanates, chloroformates, anhydrides and other electrophiles

Compatible Solvents: water, acetonitrile, methanol, DMSO, DCM, THF, DMF, Dioxane

Storage: Cool (4 $^{\circ}\text{C}$), dry location



Part Number	Quantity
9495-0010	10 g
9495-0025	25 g
9495-0100	100 g
9495-0500	500 g
9495-1000	1000 g

Ordering Information

Si-Propylsulfonic Acid (SCX-2)

Scavenger/Reagent

Chemical Name: Silica Propylsulfonic Acid (Si-propylsulfonic acid; SCX-2)

Solid-Support Type: Silica

Typical Capacity: 0.7 mmol/g

Size: 52 μm

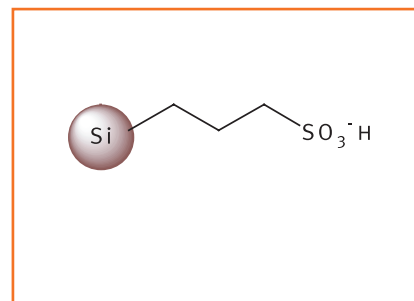
Appearance: Free flowing off-white powder

Application: Scavenger of amine, Catch-and-Release, Acid catalyst

Typical Conditions: Stir crude reaction mixture with 2-4 equivalents for 1 h and filter.

Compatible Solvents: Methanol (MeOH), Dichloromethane (DCM), Acetonitrile (MeCN), Acetone, Ethyl Acetate (EtOAc), N,N-Dimethylformamide (DMF), Dimethylsulfoxide (DMSO)

Storage: Cool (4 $^{\circ}\text{C}$), dry location



Part Number	Quantity
9536-0010	10 g
9536-0025	25 g
9536-0100	100 g
9536-1000	1000 g

Metal Scavenging Tool Kit

MP-TMT 3 g

SCX-2 3 g

Si-TMT 3 g

Si-TMT 500 mg/6 mL cartridges Pk/5

Si-Thiol 10 g

Si-Trisamine 10 g



Part Number	Quantity
K-MS-2	1

Appendix - Biotage Resin Family Selection Guide

Biotage offer the following resin bound reagents for use in a variety of different applications.

Product	Metal Scavenging	Peptide / Coupling Chemistry	Reductive Amination	Oxidation	C-C Bond Formation	Work-up Scavenging
MP-TMT	■					
Si-TMT	■					
Si-Thiol	■					
Si-Trisamine	■					■
SCX-2 / 3	■		■			■
PS-Carbodiimide		■		■		
PS-TBD		■			■	
PS-HOBt		■				■
PS-DIEA		■				■
PS-DMAP		■				■
ACTU		■				
MP-Triacetoxyborohydride			■			
MP-Cyanoborohydride			■			
MP-Borohydride			■			
PS-TsNHNH2			■			■
PS-Isocyanate			■			■
MP-Isocyanate			■			■
Si-Carbonate					■	■
PS-PPh3-Pd					■	
PS-PPh3					■	■
PS-Benzaldehyde			■			■
PS-TEMPO			■	■		
MP-TsOH	■		■			■
PS-Trisamine	■		■			■
MP-Trisamine	■		■			■
Si-Triamine	■		■		■	■

■ Excellent / Preferred
 ■ Very Good

Biotage specializes in a range of resins designed for a large variety of applications for more information visit www.biotage.com



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