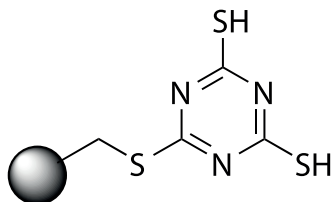
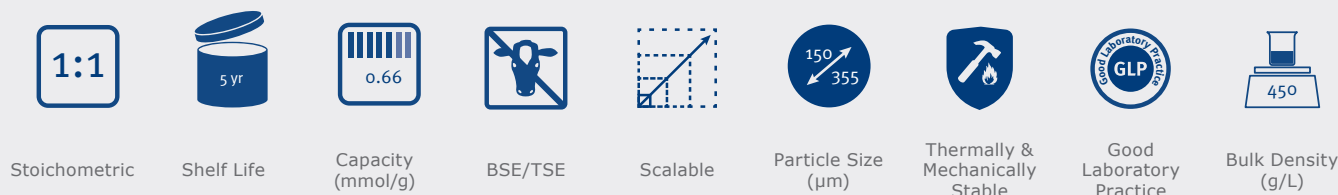


Biotage® MP-TMT

Palladium Scavenger



Key Facts



Specifications

Chemical Name:	Macroporous polystyrene-2,4,6-trimercaptotriazine
Resin Type:	Highly cross-linked macroporous poly(styrene-co-divinylbenzene)
Application:	Scavenging palladium from aqueous and non-aqueous solutions
Typical Scavenging Conditions:	3–5 equivalents Biotage MP-TMT relative to palladium content, up to 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

and generality of this approach. Originally to address the solubility issue, a polymer-bound version of TMT was prepared by covalently attaching TMT to an insoluble gel-type polystyrene support.⁴ This resin was demonstrated to effectively reduce palladium (II) acetate concentration in THF solution by a factor of 1,000⁵ and has been found to be highly effective in reducing the concentration of palladium in both aqueous and non-aqueous solutions.

The Biotage MP base co-polymer is a purpose designed, robust, low-swelling material, which makes it ideal for restricted volume environments. Its unique pore structure provides greater access to the reactive sites resulting in faster reactions and higher product recoveries. The abrasion-resistant matrix has better mechanical handling characteristics and reduced transfer losses. After treatment with Biotage MP-TMT, soluble product is isolated by filtration of the resin followed by solvent removal.

Biotage MP-TMT resin has a TMT loading 0.66 mmol/g. Typical conditions for palladium scavenging require 3–5 equivalent of resin relative to the palladium for up to 24 hrs. at RT. These conditions will typically reduce Pd by a factor of 100–1000. (**Table 1**). Scavenging has been demonstrated in THF, dichloroethane (DCE), toluene, and acetonitrile (MeCN and aqueous solvents).

Palladium-catalyzed reactions very popular in organic synthesis.³ Some of the most widely practiced examples include Suzuki-Miyaura cross coupling reactions, Heck reactions, Buchwald aminations, Wacker-type oxidation, hydrogenation, allylation, reductive deallylation and indole formation.

Despite the widespread use of these palladium-mediated reactions, removal of residual palladium during workup and product isolation remains a major problem. Reducing the palladium content to the low parts per million (ppm) levels, as is required for active pharmaceutical ingredients, is particularly challenging.² Biotage® MP-TMT is a macroporous polystyrene-bound trimercaptotriazine, a resin-bound equivalent of 2,4,6-trimercaptotriazine (TMT). The resin is designed to scavenge residual palladium from products derived from palladium catalyzed reactions.¹

Molecular 2,4,6-trimercaptotriazine has been used effectively to bind and precipitate palladium and other heavy metals from solution.³ Unfortunately, the solubility of TMT–palladium complexes in polar organic solvents limits the effectiveness

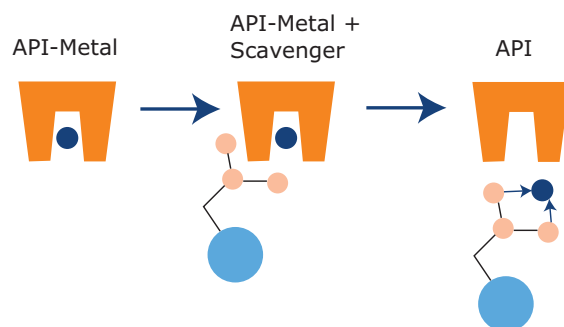
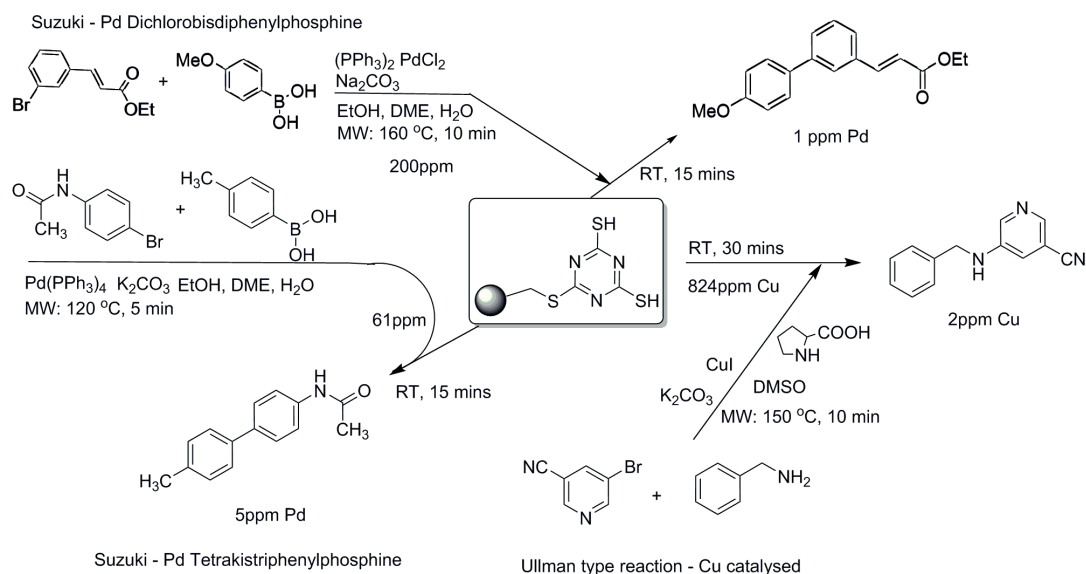


Figure 1. Metal Scavenging

MP-TMT (equivalents)	Pd Scavenged (%)
1.1	79
2	96
5	98
10	96

Table 1. Scavenging of $\text{PdCl}_2(\text{PPh}_3)_2$ from THF solution with various equivalents of MP-TMT. Initial Pd concentration = 0.0045. Molar.



Scheme 1. Representative Uses of Biotage® MP-TMT in the removal of transition metals

Not all resin-TMTs are the same. Be wary of weaker alternatives or copies.

Biotage MP-TMT is the original commercial scale resin supported TMT that has been used in the industry for well over 10 years. It remains one of the most effective generic scavengers for Pd on the market. The more effective a scavenger is, the less is required in process, resulting in lower development and process costs. In this example, we compared a popular competitive TMT under like for like conditions of scavenging.

MP-TMT was 2–3 times more efficient at removing Pd than a competitive material, at the point of scavenging completion. This suggests the overall real comparative cost of the competitive material if used in a process would have been deceptively higher than Biotage. Thus, cost-per-mole of palladium removed per Kg of resin; assuming similar per-Kg supplier prices meant the Biotage product was far more economical and cost effective for the screen and ultimate process development, and in this case was a reason MP-TMT was chosen as the scavenger.

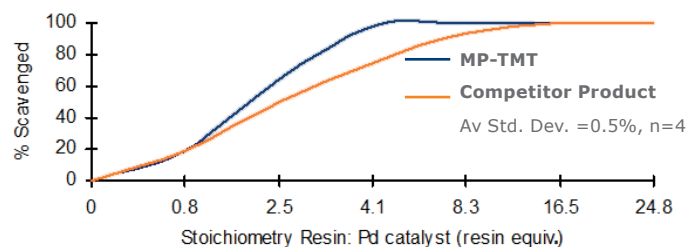
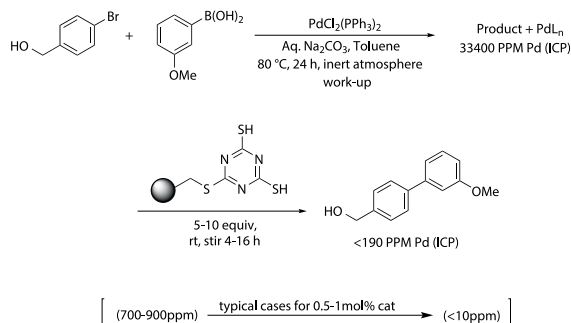


Figure 1. MP-TMT or competitive TMT resin was stirred $\text{Pd}(\text{Cl})_2(\text{PPh}_3)_2$ in THF/DMF (50:50) (2mL / total 8 μmole / 852ppm Pd) for 16 hours at RT, and residual Pd determined. Under these conditions, for 100% scavenging, it was necessary to add ca16equiv of competitive TMT, compared to only ca4.1equiv of MP-TMT

Representative Procedures

Scavenging of Palladium from Suzuki Coupling Reaction Catalyzed by $\text{PdCl}_2(\text{PPh}_3)_2$

A mixture of 1-bromo-4-hydroxymethylbenzene (1.26 g, 6.7 mmol), 3-methoxyphenyl boronic acid (1.11 g, 7.3 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.5 g, 0.71 mmol) in toluene (110 mL), and aqueous Na_2CO_3 (6.7 mL, 0.5 M) was stirred at 80 °C for 24 h under an inert atmosphere. The mixture was cooled to room temperature and washed with brine (2 x 50 mL). The organic solution was dried over MgSO_4 , and filtered through a small plug of celite yielding a yellow-orange solution. A portion of this solution was concentrated and found to contain 3.34% palladium by weight as determined by ICP analysis.⁶ Excess boronic acid may be scavenged using MP-Carbonate. A portion of the above filtrate (15 mL) was transferred to an empty cartridge body with a 20- μm frit, a stopcock, and a cap.⁷ It was treated with MP-TMT (0.6 g, 0.48 mmol, 5 equivalents relative to starting Pd) and agitated at room temperature for 18 h on an orbital mixer. The solution was filtered away from the resin and the resin was washed with toluene (2 x 10 mL). The combined filtrates were evaporated to give a light yellow oil. The residual palladium level in the product was determined to be < 190 ppm.



Scheme 2. Palladium scavenging after Suzuki reaction using MP-TMT

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- Palladium(II) acetate concentration was reduced from 47 ppm to 45 ppb upon a single treatment.
- Quantitative inductively coupled plasma (ICP) analysis was conducted by Galbraith Laboratories, Knoxville, TN.
- Parts needed include: ISOLUTE® empty reservoirs (Part Number 120-113-C), universal stopcocks (Part Number 121-0009), and column caps (Part Number 1201-0123-C).

Ordering Information

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

For larger quantities please contact your local Biotage representative.

MP-TMT is included in the comprehensive metal scavenging screening tool kit, an essential tool to quickly and effectively find the right metal scavenger for the application in hand. With protocols, guidance and recommendations, this all in one kit showcases all of the key metal scavengers.

Part Number: K-MS-2.

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