Metal Scavengers for the Process Industry

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Overview

- Process Chemists in Pharma and CRO firms are increasing the number of precious group metal (PGM) catalyzed reactions and the scale of synthesis.
- The US and EU FDA require these catalysts be reduced to less than 5ppm. Homogeneous catalysts (soluble metal-organic complexes) are used at 100-1000 PPM. Even heterogeneous catalysts (metal on carbon) leach metals at these levels.
- Classic solutions (crystallization or activated carbon) have poor selectivity, i.e. have low yield of drug / high metal level.
- These applications require a highly selective, cost-effective scavenging process to reach the purity goals
- Biotage's strategy employs a toolbox of metal scavenger solutions

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Why is it growing now?

"Why spend years trying to perfect a chemistry for a compound that may never make it to the market" has become the trend

- The pressure to take products to market faster has led pharma to move their pipeline into clinical trials faster and scale-up of early stage compounds is done with minimal modification to medchem synthetic routes.

- Catalysts have recently gained acceptance in manufacturing due to their 'Green' properties in atom economy and energy consumption vs stoichiometric reactions.

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Metal Catalysis & Pharmaceutical metal limits

- Current acceptable limits:

Metal	Concentration (ppm)	
	Oral	Parenteral
Pt, Pd, Ir, Rh, Ru, Os	5	0.5
Mo, V, Ni, Cr	10	1
Cu, Mn	15	1.5
Zn, Fe	20	2

- Permitted limits of metals in API, fine and specialty chemicals will continue to decline

- New technology required to meet this challenge

Traditional methods of metal removal from APIs

Method	Drawbacks
Activated Charcoal Adsorption	• Significant loss of API • Reaction vessel contamination • Failure to remove metals to desired level • API structure dependent • Reproducibility
Crystallization	
Extraction	
Distillation	

Metal Scavengers ideal properties

- Selective
- Non-contaminating
- Efficient removal of metals to acceptable levels
- Reproducible

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Scavenging Metals from APIs

Benefits of Bound Metal Scavengers

- Higher metal affinity – low Kd(Pd) relative to API Kd(Pd)
- Fast kinetics at room temp – enhanced by heating
- Diverse solid supports – silica and polystyrene backbones
- Generic – use in diverse conditions
- Minimal loss of API – less / no non-specific binding
- Faster purification – kinetic effects allowed
- Higher purity of final product – no leachables
- Short development time – faster method optimization

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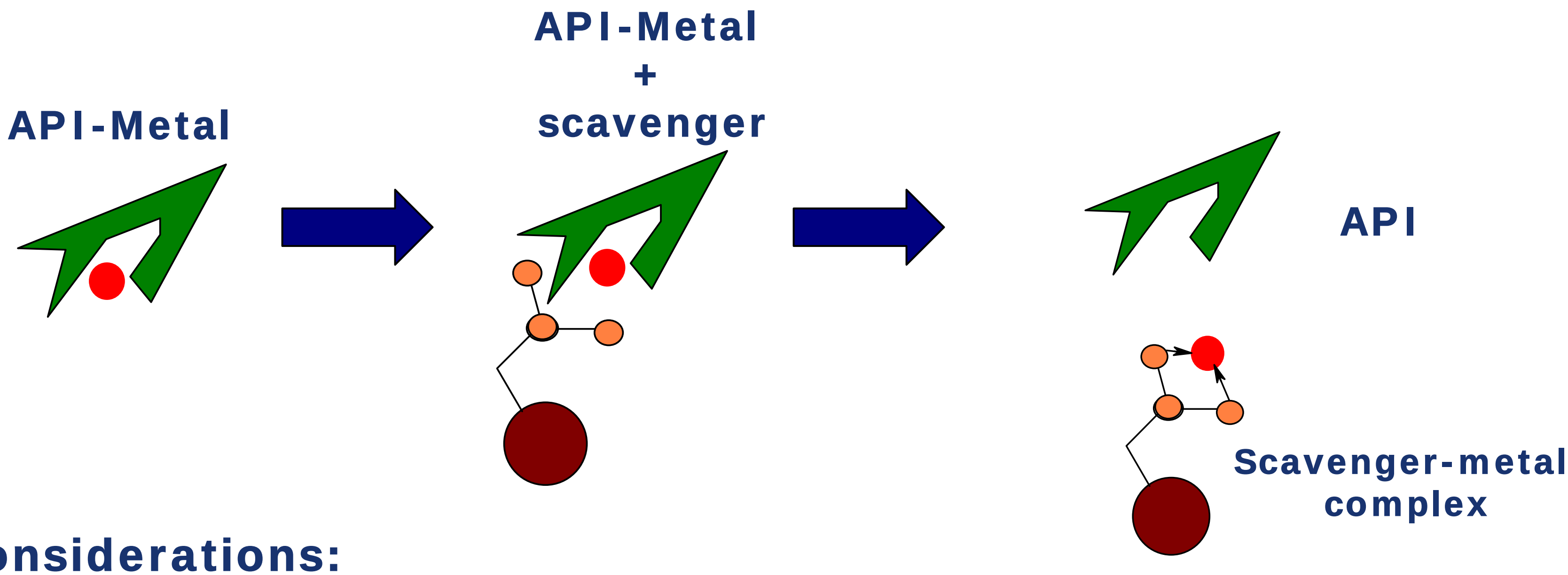
Scavenging metals from APIs



Considerations:

- API structural diversity
- Varied and multiple binding groups
- Diversity of metals and oxidation states
- Solvent polarity and pH of reaction

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Typical usage of scavengers in the process industry

- Step 1: Screening of (~30) scavengers against metal removal problem; mg quantities are required.
- Step 2: Use chosen scavenger in first campaign; ~1 kg is required per reaction.
- Step 3: If first campaign successful, next campaigns will require multikilo quantities of scavengers (15 kg upwards)
- Step 4: If compound goes into production, larger scale will require larger quantities of scavenger

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Current metal scavenger portfolio

Media	$Pd(OAc)_2$	$Pd(OAc)_2$	$(Ph_3P)_2PdCl_2$	$Pd(PPh_3)_4$	$Ru(C_{43}H_{72}Cl_2P_2)$ (Grubbs)	$Rh(PPh_3)_3Cl$	$CuSO_4$	$C_{10}H_{14}NiO_4$
	CH_3CN	DMF:THF (1:1)	DMF:THF (1:1)	DMF:THF:CH_3CN (1:2:1)	DMF:THF (1:1)	DMF:THF (1:1)	DMF	DMF
	% scavenged*							
Si-Thiol	100	100	94	100	43	66	99	54
Si-TsOH (SCX3)	100	100	92	100	49	71	97	85
Si-Propylsulfonic acid (SCX2)	100	95	0	100	50	80	100	81
Si-Triamine	100	100	100	100	96	29	100	92
Si-Trisamine	100	100	100	100	90	28	93	91
MP-TMT	100	100	100	100	82	41	0	74
MP-Trisamine	100	100	100	99	93	27	100	91
PS-Thiophenol	0[a]	100	100	100	90	55	95	76
PS-Trisamine	0[a]	100	100	100	95	18	100	94
$PS-NH_2$	0[a]	100	100	99	82	20	64	93
PS-TBD	0[a]	100	100	100	70	44	85	56
PS-DEAM	0[a]	100	55	0	31	32	100	47
$PS-PPh_3$	0[a]	100	100	98	84	41	97	3

* % Catalyst scavenged from 6mL of 1000ppm catalyst solution by 0.5g media when stirred for 2 h at room temperature

[a] PS-based resins require swelling solvents for activity. No scavenging was observed in CH3CN, due to lack of swelling whereas 100% scavenging was observed in DMF-THF(1:1).

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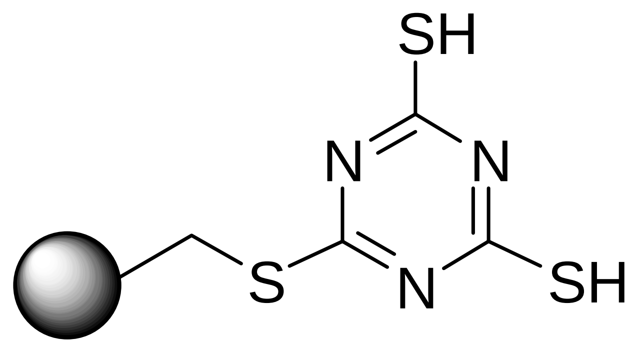
Products available in multikilo scale

- MP-TMT
- Si-Thiol
- Si-TMT
- A metal scavenging tool box with 8 scavengers available at multi-Kg scale is currently in development

MP-TMT – Palladium Scavenger

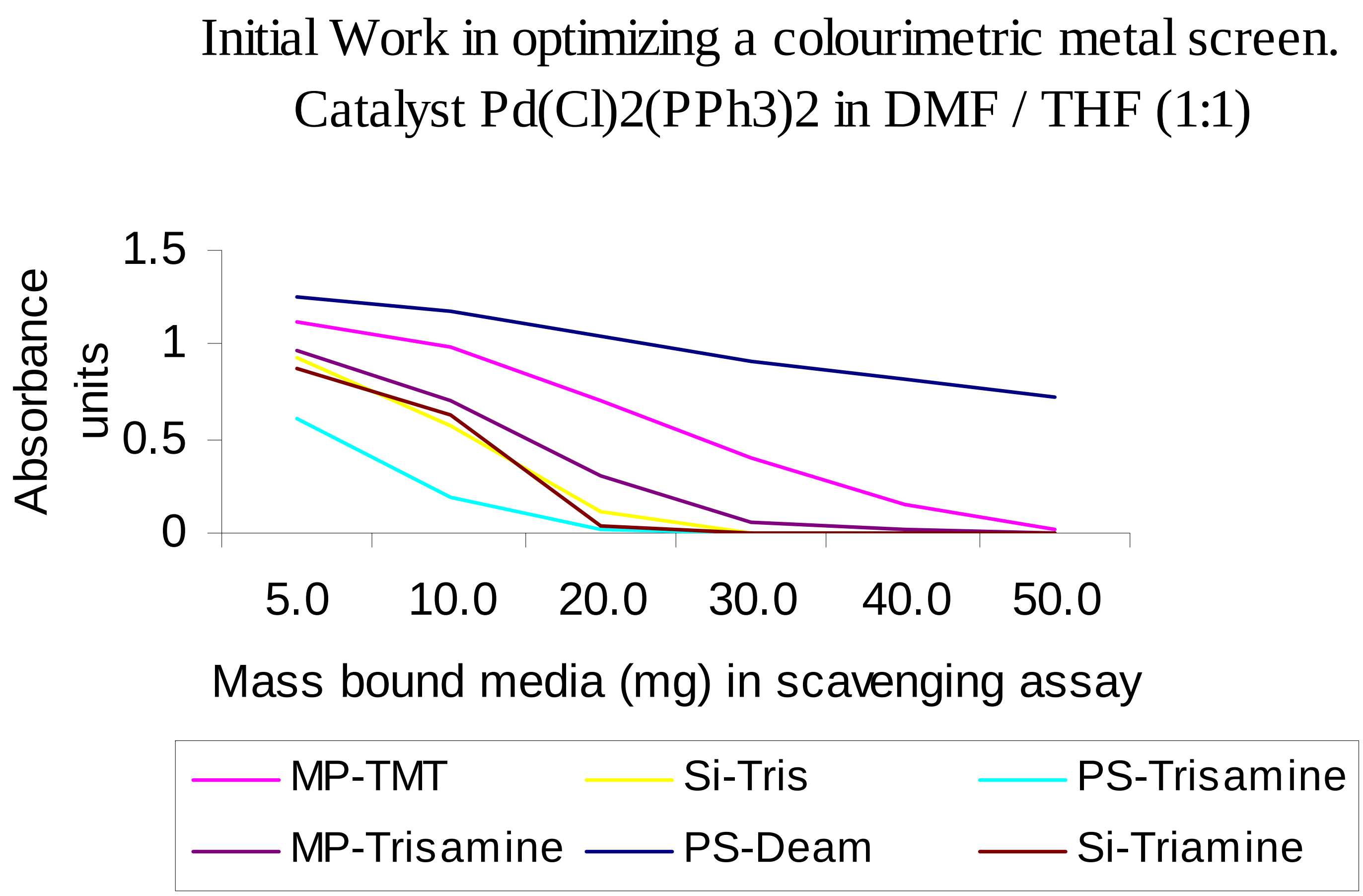
- Bound TMT ligand on macroporous resin
- Scavenges Pd(II) and Pd(0), ligated palladium
- Effective in aqueous and non-aqueous solutions
- Useful for compound polishing
- Reduces residual palladium to low ppm levels
- Has been used for other transition metal removal
- Available in multikilo quantities



Macroporous polystyrene-2,4,6-trimercaptotriazine

Metal Screening Studies: Bound ligands

MP-TMT was the best non-basic / uncharged bound ligand in the screens



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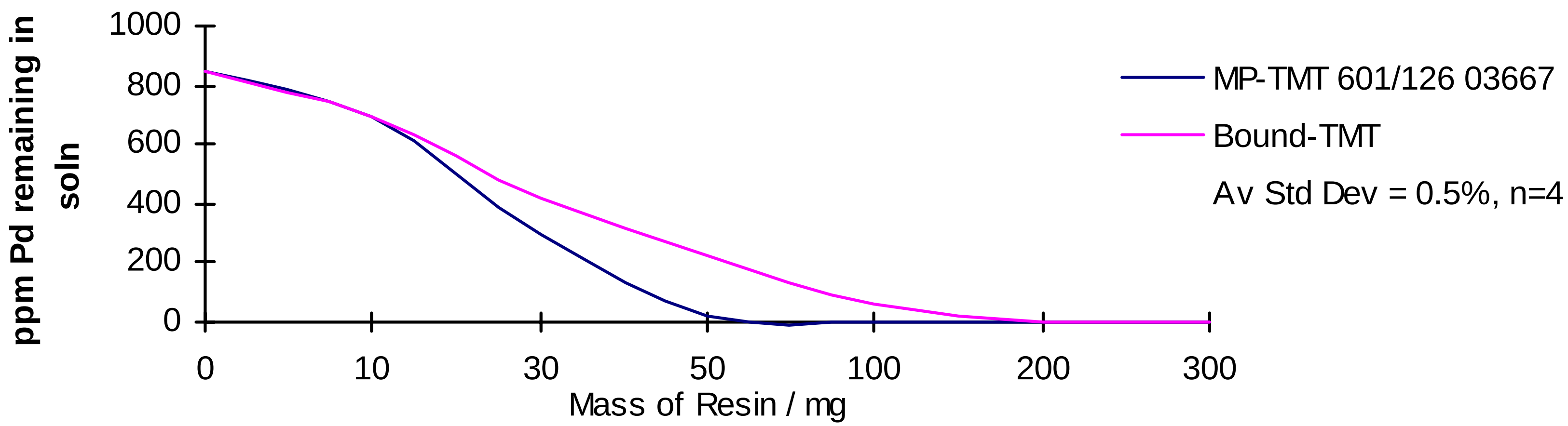
Metal Screening Studies: Bound-TMT materials



MP-TMT or Bound-TMT resin was stirred with Pd(Cl)2(PPh3)2 in THF/DMF (50:50) (2mL / total 8 µmole / 852 ppm Pd) for 16 hours at RT, and residual Pd determined following this scavenging.

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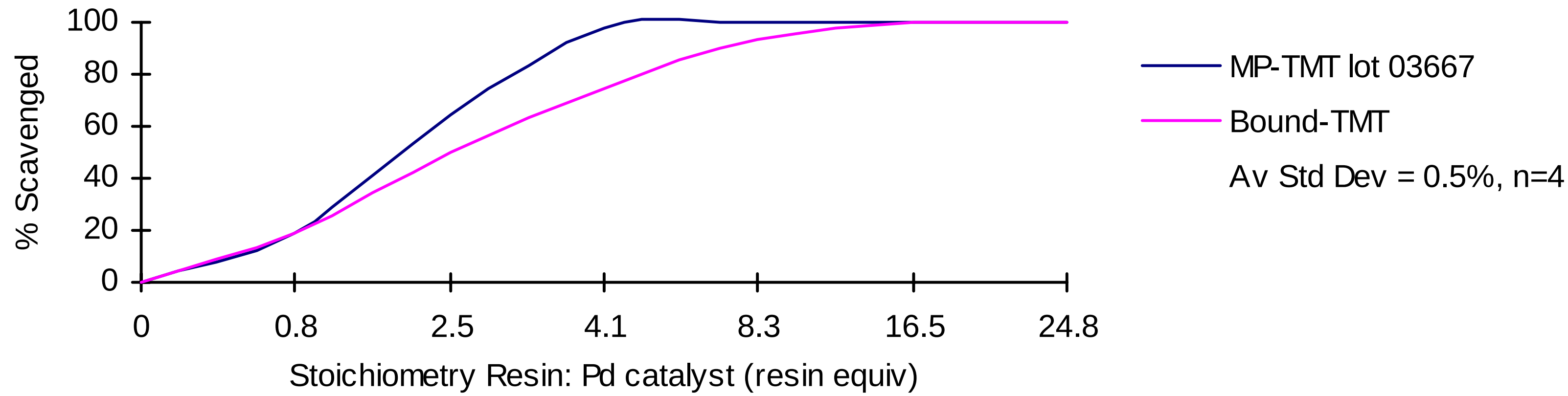
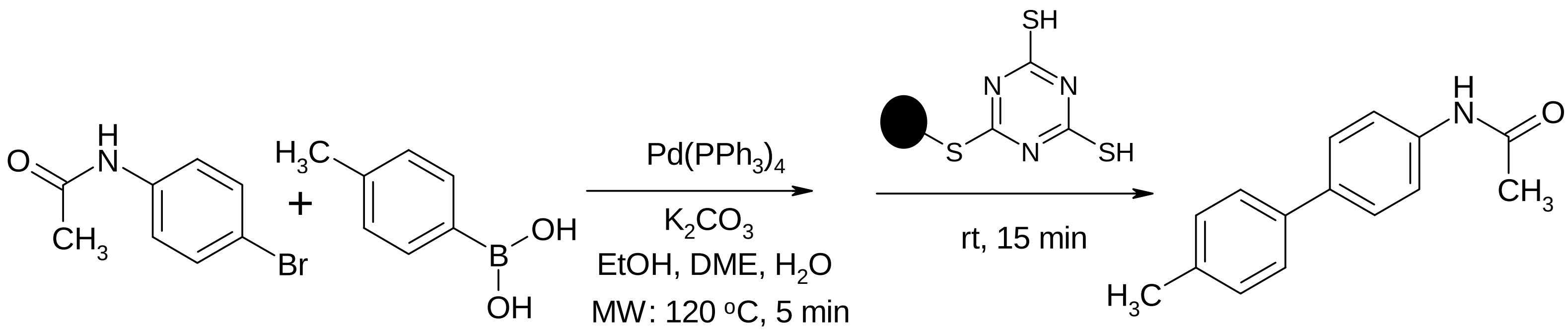
Metal Screening Studies: Bound-TMT materials



MP-TMT or Bound-TMT resin was stirred Pd(Cl)2(PPh3)2 in THF/DMF (50:50) (2mL / total 8 µmole / 852ppm Pd) for 16 hours at RT, and residual Pd determined following scavenging.

Under these conditions, for 100% scavenging, it was necessary to add ca16equiv of Bound-TMT, compared to only ca4.1equiv of MP-TMT.

MP-TMT Removal of Pd from a $Pd(PPh_3)_4$ catalyzed Suzuki reaction



	Before	After
		
Pd conc.	610 ppm	5 ppm

ICP results from reaction mixture before and after treatment with MP-TMT

Ghassemi, S. *ACS Fall 2007, Boston, MA*

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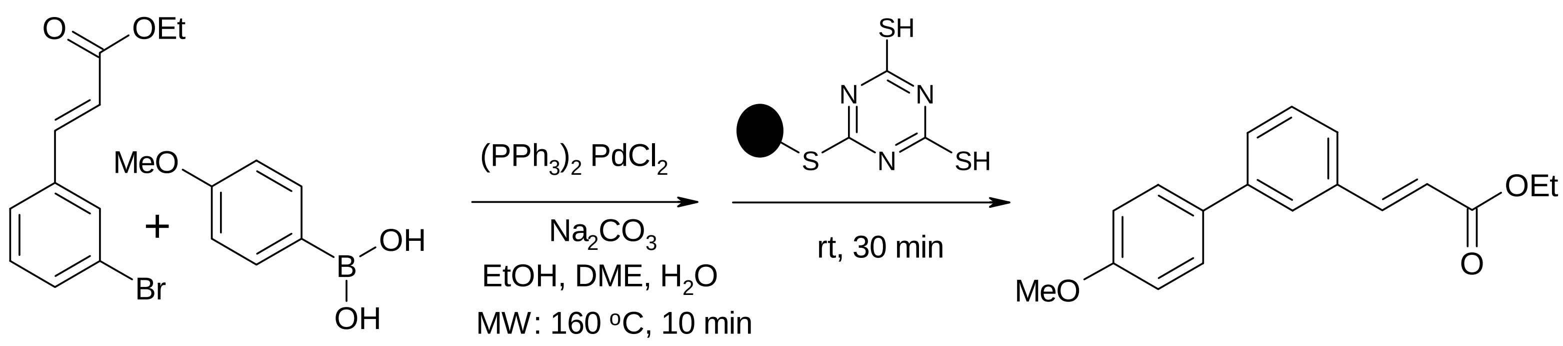
MP-TMT Removal of Pd from a $(Ph_3P)_2PdCl_2$ catalyzed Suzuki reaction



	Before	After
Pd conc.	200 ppm	1 ppm

ICP results from reaction mixture before and after treatment with MP-TMT

Ghassemi, S. *ACS Fall 2007, Boston, MA*

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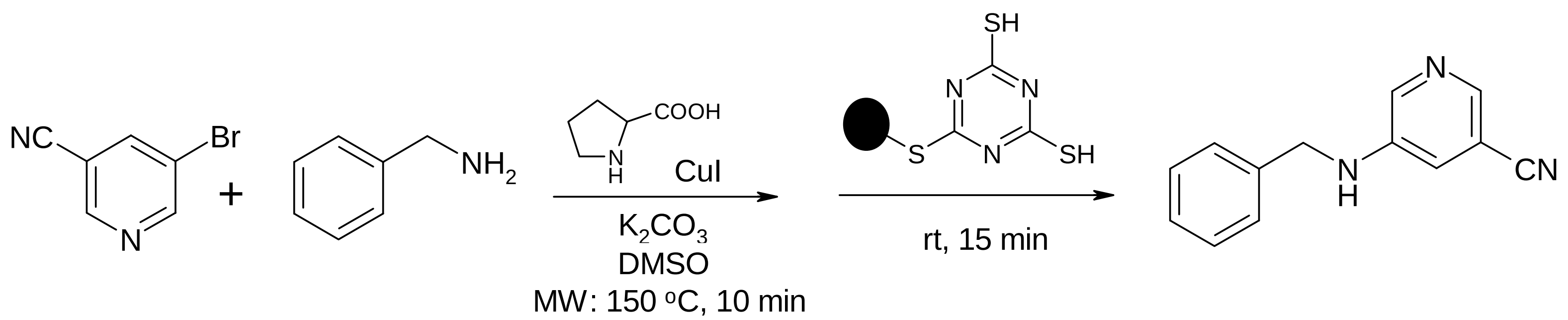
MP-TMT Removal of Copper from a CuI catalyzed Ullman type reaction



	Before	After
Cu conc.	824 ppm	2 ppm

ICP results from reaction mixture before and after treatment with MP-TMT

Ghassemi, S. *ACS Fall 2007, Boston, MA*

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Merck metal scavenger screen results

Merck-Rahway screened 30-different scavengers for a palladium-catalyst removal process.
Merck picked Biotage MP-TMT as the clear winner for this application

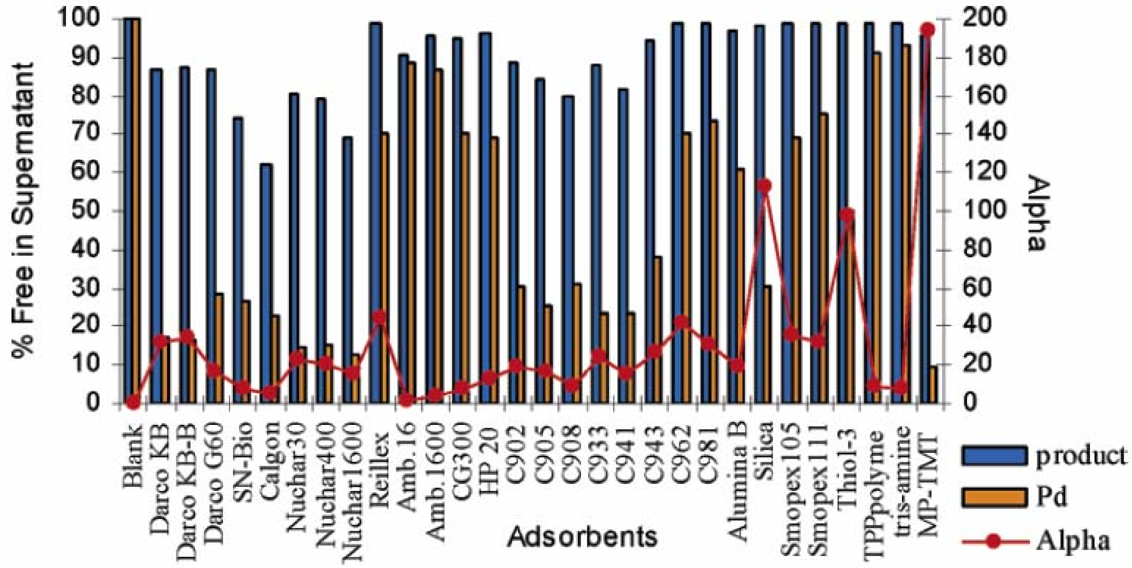

Figure 6. Selective removal of palladium from the process stream coming from workup of Suzuki−Miyaura biaryl coupling reaction. Adsorbent screening conducted at 50 wt % loading.

Alpha is the ratio of metal removed divided by the ratio of product lost.
High Alpha is strongly preferred solution, with low levels of metal and high yield of product

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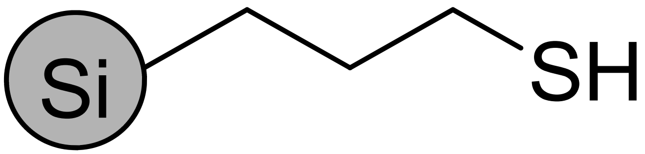
Welch, C.; *OPRD*, **2005**, *9*, 198-205

ISOLUTE® Si-Thiol



- Typical capacity 1.3 mmol/g
- Ultrapure analytical grade silica backbone
- Chemically stable
- Reduces Pd, Ru and Rh residues to the lower ppm levels
- Available in multi-Kg quantities

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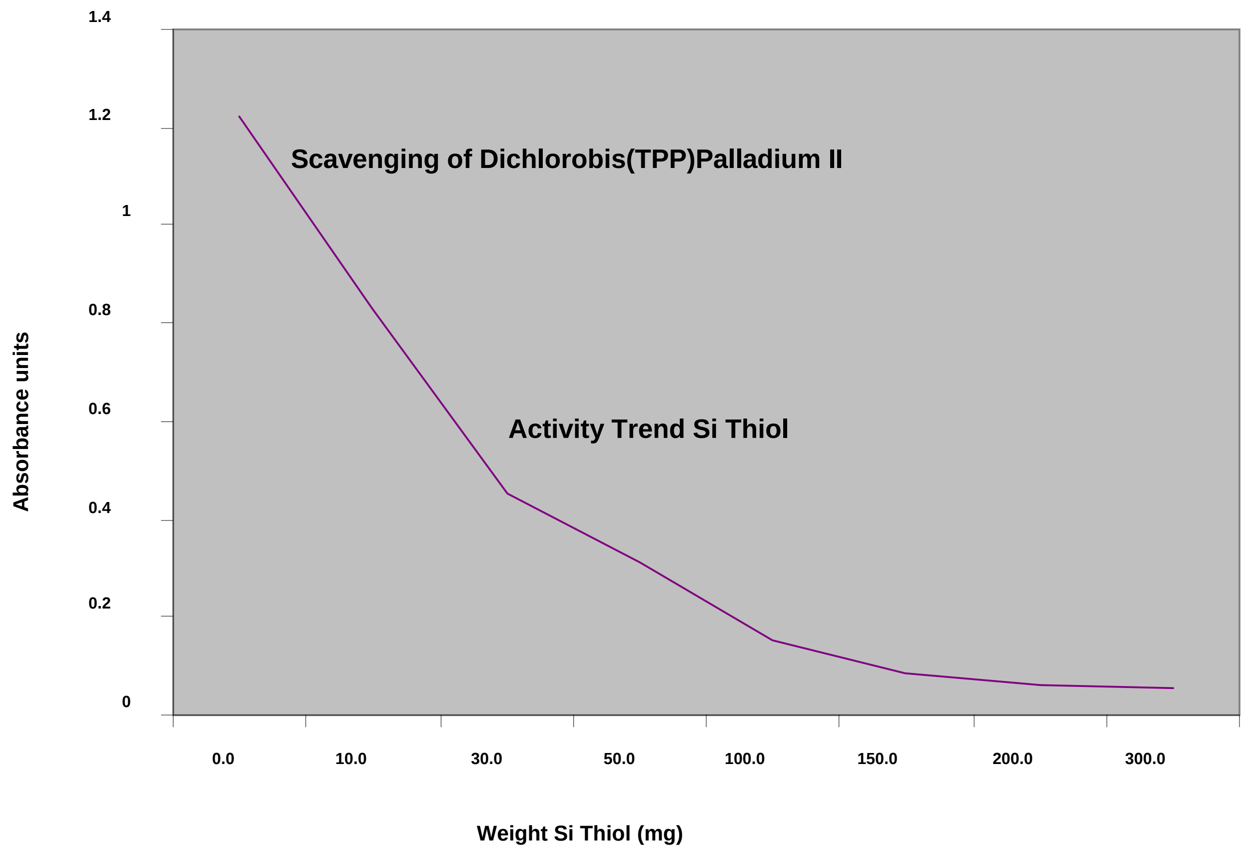
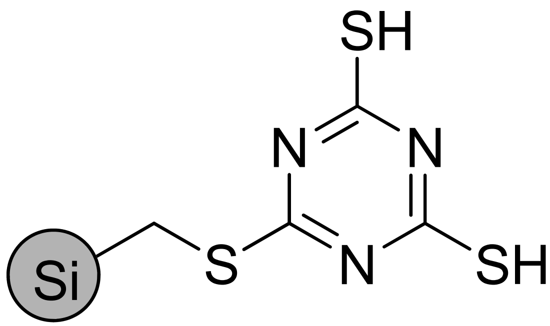
Palladium scavenging using Si-Thiol

Pd scavenging efficiency was investigated using dichlorobis-(tetraphenylphosphine) Palladium (II) as the test analyte. UV activity was measured after 16h of exposure to various concentrations of Si-Thiol



ISOLUTE® Si-TMT



- Typical capacity 0.3 mmol/g
- Ultrapure analytical grade silica backbone
- Chemically stable
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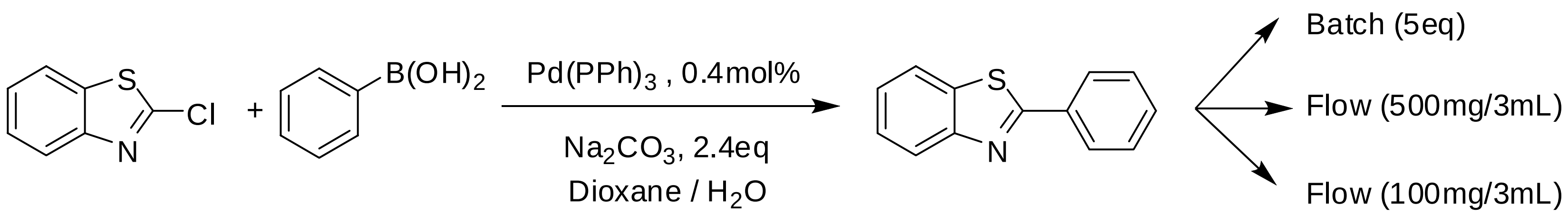
Si-TMT initial chemical application work

Si-TMT : Synthesis of Benzothiazoles



	Batch Studies 5eq media	Flow (cartridge) scavenging 500mg/3mL	100mg/3mL
Si-Thiol (Biotage)	91%	86%	45%
Si-Thiol (competitor)	82%	91%	45%
Si-TMT (Biotage)	>99%	>99%	95%

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

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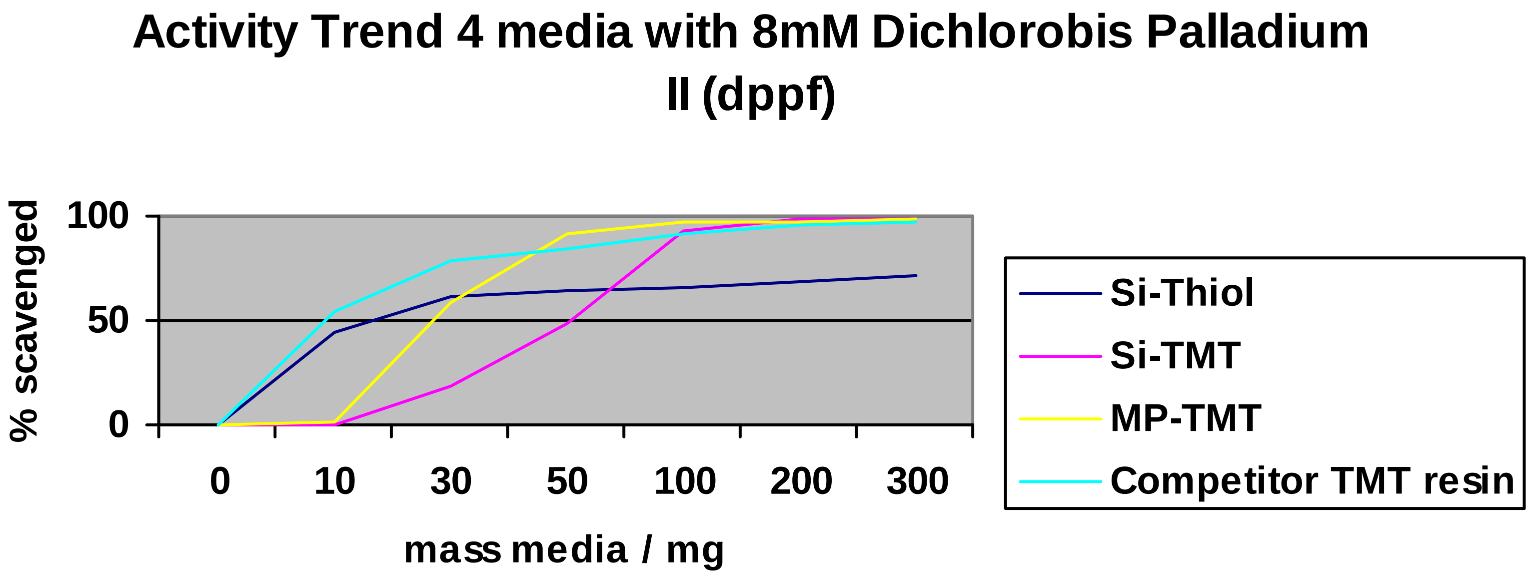
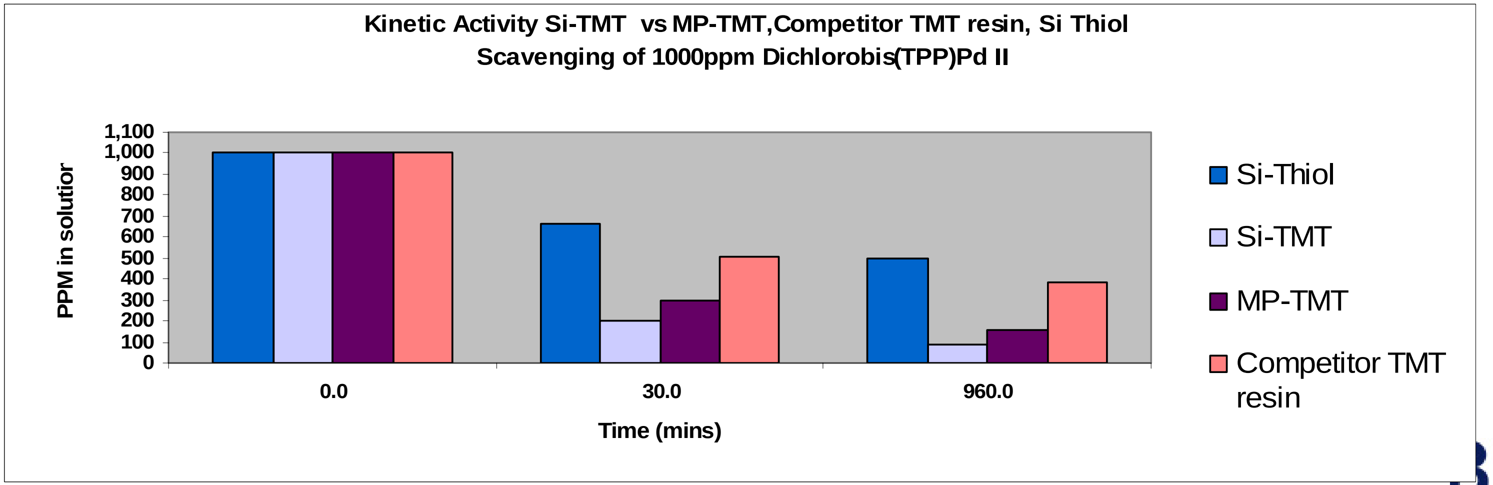
Metal scavengers comparison: $PdCl_2$(dppf)





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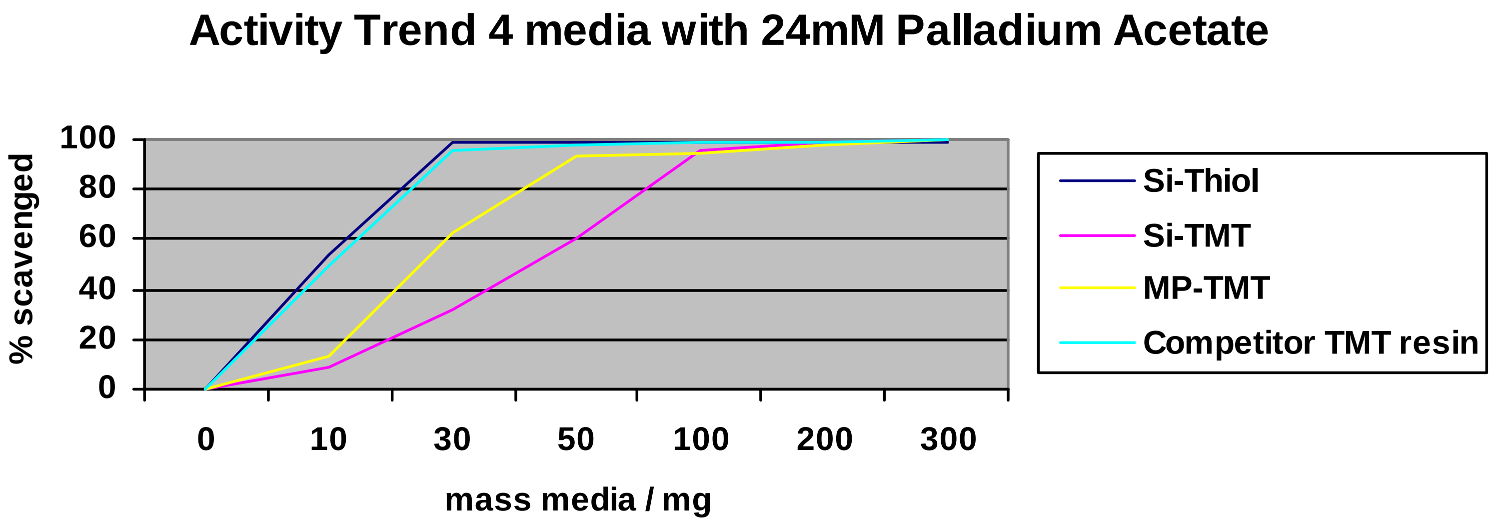
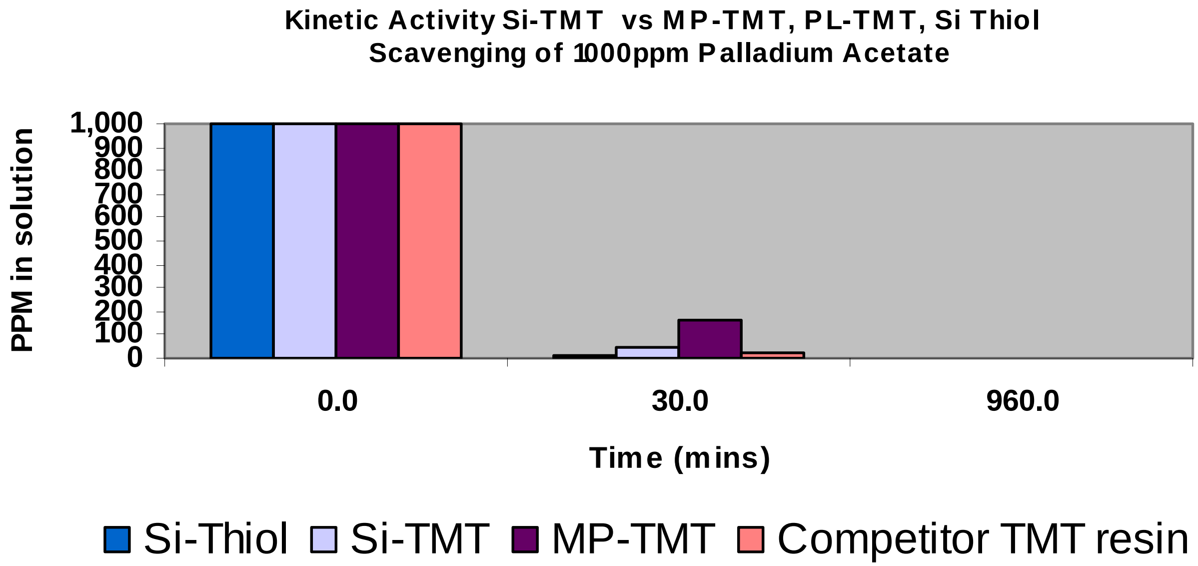
Metal scavengers comparison: Pd(OAc)2





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How should I decide which backbone to use?

The choice of backbone depends on what best fits the workflow.

MP-polymers	Si-reagents
Do not swell	Do not swell
200-300 um particles	60 um particles
Wide range of solvents	Wide range of solvent
Low loading	Low loading
Ideal for batch mode	Ideal for filtration
More expensive	Less expensive

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Summary: Biotage Metal Scavengers

- Biotage metal scavengers remove transition metals to levels approved by FDA guidelines prior to clinical trials
- Both silica and polymer based metal scavengers offered for both filtration and batch processing
- MP-TMT, Si-Thiol and Si-TMT available in multi-Kg qtys
  - At cost effective prices
  - Within a few weeks of order
- TSE certified (no animal / human origins)

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Biotage strategy

- To offer a tool box of metal scavengers to the process, contract and large scale industries

- To be included in customer's screening:
  - Offer supporting documentation (i.e. TSE statement, leachables data)
  - To be capable of delivering multiKg quantities within reasonable timelines
  - Comprehensive technical assistance

Thank You for Your Attention!

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