Metal Scavengers for the Process Industry

Steve Jordan Snr Director R&D Biotage
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.
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.
Metal Catalysis & Pharmaceutical metal limits

- Current acceptable limits:

<table>
<thead>
<tr>
<th>Metal</th>
<th>Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Pt, Pd, Ir, Rh, Ru, Os</td>
<td>5</td>
</tr>
<tr>
<td>Mo, V, Ni, Cr</td>
<td>10</td>
</tr>
<tr>
<td>Cu, Mn</td>
<td>15</td>
</tr>
<tr>
<td>Zn, Fe</td>
<td>20</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Method</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Charcoal Adsorption</td>
<td>• Significant loss of API</td>
</tr>
<tr>
<td></td>
<td>• Reaction vessel contamination</td>
</tr>
<tr>
<td></td>
<td>• Failure to remove metals to desired level</td>
</tr>
<tr>
<td>Crystallization</td>
<td>• API structure dependent</td>
</tr>
<tr>
<td>Extraction</td>
<td>• Reproducibility</td>
</tr>
<tr>
<td>Distillation</td>
<td></td>
</tr>
</tbody>
</table>

**Metal Scavengers ideal properties**

- Selective
- Non-contaminating
- Efficient removal of metals to acceptable levels
- Reproducible
Scavenging Metals from APIs

Benefits of Bound Metal Scavengers

• Higher metal affinity – low $K_d$(Pd) relative to API $K_d$(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
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
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
## Current metal scavenger portfolio

### Catalyst & Solvent

| Catalyst & Solvent | Pd(OAc)$_2$ | Pd(OAc)$_3$ | $\sigma$PH$_2$PdCl$_2$ | Pd(PPh$_3$)$_4$ | RuCl$_3$($H_2$Cl$_2$P$_2$) | Rh(PPh$_3$)$_3$Cl | CuSO$_4$ | C$_{6}$H$_{14}$NO$_2$ |
|--------------------|-------------|-------------|----------------------|----------------|--------------------------|-------------------|---------|----------------|---|
| CH$_3$CN           | DMF:THF (1:1) | DMF:THF (1:1) | DMF:THF:CH$_3$CN (1:2:1) | DMF:THF (1:1) | DMF:THF (1:1) | DMF:THF (1:1) | DMF:THF (1:1) | DMF:THF (1:1) | --- |

### Media

<table>
<thead>
<tr>
<th>Media</th>
<th>% scavenged*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si-Thiol</td>
<td>100</td>
</tr>
<tr>
<td>Si-TsOH (SCX3)</td>
<td>100</td>
</tr>
<tr>
<td>Si-Propylsulfonic acid (SCX2)</td>
<td>100</td>
</tr>
<tr>
<td>Si-Trisamine</td>
<td>100</td>
</tr>
<tr>
<td>Si-Trisamine</td>
<td>100</td>
</tr>
<tr>
<td>MP-TMT</td>
<td>100</td>
</tr>
<tr>
<td>MP-Trisamine</td>
<td>100</td>
</tr>
<tr>
<td>PS-Thiophenol</td>
<td>0*</td>
</tr>
<tr>
<td>PS-Trisamine</td>
<td>0*</td>
</tr>
<tr>
<td>PS-NH$_2$</td>
<td>0*</td>
</tr>
<tr>
<td>PS-TBD</td>
<td>0*</td>
</tr>
<tr>
<td>PS-DEAM</td>
<td>0*</td>
</tr>
<tr>
<td>PS-PPh$_3$</td>
<td>0*</td>
</tr>
</tbody>
</table>

* % Catalyst scavenged from 600 ml of 0.000 ppm catalyst solution by 0.5 g media when stirred for 2 h at room temperature.

* PS-based resins require swelling solvents for activity. No scavenging was observed in CH$_3$CN, due to lack of swelling whereas 100% scavenging was observed in DMF:THF (1:1).
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
Initial Work in optimizing a colourimetric metal screen.
Catalyst Pd(Cl)_{2}(PPh_{3})_{2} in DMF / THF (1:1)

MP-TMT was the best non-basic / uncharged bound ligand in the screens.
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.
Metal Screening Studies: Bound-TMT materials

MP-TMT or Bound-TMT resin was stirred \( \text{Pd(II)} \text{Cl}_2(\text{PPh}_3)_2 \) in THF/DMF (50:50) (2mL / total 8 \( \mu \)mole / 852ppm Pd) for 16 hours at RT, and residual Pd determined following scavenging.

Under these conditions, for 100% scavenging, it was necessary to add ca 16equiv of Bound-TMT, compared to only ca 4.1equiv of MP-TMT.
MP-TMT Removal of Pd from a Pd(PPh₃)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
MP-TMT Removal of Pd from a (Ph₃P)₂PdCl₂ 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
MP-TMT Removal of Copper from a CuI catalyzed Ullman type reaction

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

Ghassemi, S. ACS Fall 2007, Boston, MA
Merck-Rahway screened 30 different scavengers for a palladium-catalyst removal process. Merck picked Biotage MP-TMT as the clear winner for this application.

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.

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.

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
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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- Available in multi-Kg quantities
Si-TMT initial chemical application work

Si-TMT: Synthesis of Benzothiazoles

\[
\text{Cl} \quad \text{B(OH)}_2 \quad \text{Pd(PPh)}_3 \text{, 0.4mol%} \quad \text{Na}_2\text{CO}_3, 2.4\text{eq} \quad \text{Dioxane / H}_2\text{O}
\]

Batch (5eq)
Flow (500mg/3mL)
Flow (100mg/3mL)

<table>
<thead>
<tr>
<th></th>
<th>Batch Studies 5eq media</th>
<th>Flow (cartridge) scavenging 500mg/3mL</th>
<th>100mg/3mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si-Thiol (Biotage)</td>
<td>91%</td>
<td>86%</td>
<td>45%</td>
</tr>
<tr>
<td>Si-Thiol (competitor)</td>
<td>82%</td>
<td>91%</td>
<td>45%</td>
</tr>
<tr>
<td>Si-TMT (Biotage)</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>95%</td>
</tr>
</tbody>
</table>

S. Rana, Unpublished Results, Biotage 2008,
Metal scavengers comparison: PdCl$_2$(dpff)

Activity Trend 4 media with 8mM Dichlorobis Palladium II (dpff)

Kinetic Activity Si-TMT vs MP-TMT, Competitor TMT resin, Si Thiol Scavenging of 1000ppm Dichlorobis(1PP)Pd II
Metal scavengers comparison: Pd(OAc)₂

Activity Trend 4 media with 24mM Palladium Acetate

- Si-Thiol
- Si-TMT
- MP-TMT
- Competitor TMT resin

Kinetic Activity Si-TMT vs MP-TMT, PL-TMT, Si Thiol
Scavenging of 1000 ppm Palladium Acetate

PPM in solution
- Si-Thiol
- Si-TMT
- MP-TMT
- Competitor TMT resin
How should I decide which backbone to use?

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

<table>
<thead>
<tr>
<th>MP-polymers</th>
<th>Si-reagents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not swell</td>
<td>Do not swell</td>
</tr>
<tr>
<td>200-300 um particles</td>
<td>60 um particles</td>
</tr>
<tr>
<td>Wide range of solvents</td>
<td>Wide range of solvent</td>
</tr>
<tr>
<td>Low loading</td>
<td>Low loading</td>
</tr>
<tr>
<td>Ideal for batch mode</td>
<td>Ideal for filtration</td>
</tr>
<tr>
<td>More expensive</td>
<td>Less expensive</td>
</tr>
</tbody>
</table>
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)
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!