Recycling Precious Metals Using Functionalised Silica Scavengers and Catalysts

RSC Symposium
The Sustainability Challenge
19th June 2008

David Astles
CEO, PhosphonicS
PhosphonicS™ overview

Key industry issue: “the lost metal”

The challenge for metal catalysis

Solutions based on PhosphonicS™ materials
- Pharmaceutical Purification
- Precious Metal recovery
- Heterogeneous Catalysis
Established 2003 to commercialise novel platform technology

Expertise in ligand immobilisation onto inorganic supports and design of functionalised solid materials

Located at Milton Science Park, Oxford, UK

Portfolio of outstanding metal removal products, organic purification products and heterogeneous catalysts

Screening, design and outsourcing services

Assured supply from test kits to large bulk scale
PhosphonicS™ Technology & Materials

Novel PhosphonicS™ process to readily attach high performance ligands to surface of inorganic support
Opens up a world of novel materials

Inorganic Support

Functional group

Silica, Alumina, Silicones & Oxides

Phosphonic acid
Sulfonic acid
Phosphates
Amides
Carboxylic acids
Esters
Aldehydes
Ketones
Alcohols
Amines
Thiols
Sulfides
Sulfones
Amino acids
Phosphines
Heterocyclic amines
Nitriles
Isocyanates
Sugars
Enzymes
Polyamine
Poly alcohols
Amino Alcohols
Chiral compounds

designed to solve high value problems
Applications of Functionalised Solid Materials

Purification
- Solid Phase Extraction
- Chromatography
- Small molecule
- Biological
- Endotoxin removal

Bio-Applications
- Nuclear
- Water

PhosphonicS Platform Technology

Metal Removal & Recovery
- Pharma
- Chemicals

Catalysis
- Polymer
- Chemical
- Enzyme

Coatings

Energy
- current target applications
- future target applications
Key industry issue - “the lost metal”

- Catalysts widely used in pharmaceutical and fine chemical processes, petrochemical and refining industry
- Broad range of precious and base metal catalysts used: homogeneous, heterogeneous, chiral, supported homogeneous
- Provide efficient and clean routes to high value products
- Objectives are maximum conversion and high selectivity …

…but where does the metal go?
The product

Current Acceptable Metal Limits in Active Pharmaceutical Ingredients (APIs)

<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>

SOURCE: European Agency for the Evaluation of Medicinal Products

- Metal must be removed from API product and intermediates
- Toxicity concerns - permitted levels will continue to decline
- Residual metal - problems in work-up & later reaction steps
Independent market survey: scale of metal removal problem from APIs

- 50% of “small molecule” drugs in development use metal catalysed reactions
- Survey suggests up to 40% of these developments has a metal removal problem “not readily resolved”
- Existing techniques are not able to effectively deal with growing problems
The waste stream

Example: Catalyst Cost Contribution: 5% Rh on C; 6% metal loss

- Significant effect on economics of metal loss
- At a time of rising metal prices and increased demand
- Environmental and economic need to recover valuable asset

Data Source: Johnson Matthey
The effluent stream

- Metals **somehow** find a way to effluent plant.
- Once present, a major challenge to remove metals from complex, high volume streams.
- Regulatory requirements to be met.
- Significant costs in waste treatment on/off-site.
- Includes PGMs, Cr, Cu, Fe, Ni, Hg, As ….

- Environmental pressure - does the industry have control of its production processes?
- Increasing cost of regulatory compliance.
- Industry wishes to demonstrate enhanced CSR profile.
The challenge for metal catalysis

In summary:
- The (uncontrolled) loss of valuable/toxic metals
- The problems of removal and capture from product, waste and effluent streams
- The environmental, economic and societal consequences

The response:
- A need for improved catalysts and processes
- Better methods to capture and recover the metal
- Continued technology innovation required
PhosphonicS contribution

Product purification

Waste & Effluent

Metal Immobilisation

↓

Novel metal scavengers

Liquid Metal Recovery

Heterogeneous Catalysts
PhosphonicS™ Metal Scavengers

Meeting the need to reduce residual metal levels in pharmaceuticals and fine chemicals

Step-change performance for Pd removal from APIs
Removing Metals from APIs: The Issues

- Need for a rapid, reliable, one-stop metal removal technology for all APIs
- Minimizing loss of API within environment of process intensification
- Regulatory assurance around all materials used in late synthetic steps
- Finding a solution which will scale economically from lab, through process, to plant
## Adsorbents for Metal Removal from APIs

<table>
<thead>
<tr>
<th>Adsorbent</th>
<th>Performance</th>
<th>API Recovery</th>
<th>Purity</th>
<th>Practical Issues</th>
<th>Material Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charcoal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vessel contamination</td>
<td>.. But large quantities consumed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple treatments</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High Temps</td>
<td></td>
</tr>
<tr>
<td>MP-TMT</td>
<td>✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time dependence</td>
<td></td>
</tr>
<tr>
<td>PhosphonicS™ Metal Scavengers - Silicas</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rapid kinetics</td>
<td>Scalable economics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Temps required</td>
<td></td>
</tr>
<tr>
<td>Standard Silicas</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grafted Fibres</td>
<td>✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS-Resins</td>
<td>✓</td>
<td>✓ ✓</td>
<td>✓</td>
<td></td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.. Depends on grade/supplier</td>
</tr>
</tbody>
</table>

- Highly variable
- Loss 10 - 20%
- Loss typically ~1%
- ROI <0.05wt%
- Swelling
- Solvent compatible?
The Challenge - Winning the Tug of War

Multiple Binding Sites for Pd(II) and Pd(0)

API intermediate

= Pd (II) or Pd(0)

Multifunctional Metal Scavengers designed to compete and remove the metal from the API binding site
PhosphonicS™ scavengers: fast removal of precious metal from solution

- Metals removed to below 1 ppm in less than 30 seconds!
- One scavenger removing both Pd(II) and Pd(0)

Palladium chloride bis triphenyl phosphine in solution

Graph showing Pd Scavenging:
- 30 seconds
- Pd ppm vs. Seconds

Pd (II) complex
Pd (0) complex
Full range of PhosphonicS™ Metal Scavengers designed to remove range of metals from highly functionalised substrates

- Leading Palladium removal products
- Used at full process scale
- Available ex stock
PhosphonicS™ Functionalised Silicas

- **Performance**: extremely high metal affinity across diverse range of APIs, with very high API recovery
- **High purity**: strictly no added impurities
- **Track record**: use on pilot and production scale by large pharmaceutical and fine chemical clients
- **Speed**: the route to a quick, first time solution
- **Simple, scalable, cost-effective** processes
Pharmaceutical Syntheses involving challenging Pd Removals

Sonogashira Reaction

- Model substrate based on a calcium entry blocker
- Known to possess strong ability for chelation of palladium
- Late stage Sonogashira reaction caused insurmountable Pd removal problems, necessitating reorganisation of the synthesis

<table>
<thead>
<tr>
<th>Scavenging</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd Content/ppm</td>
<td>700</td>
<td>5</td>
</tr>
</tbody>
</table>
Valsartan is a potent, orally active angiotensin II antagonist. Potential route into analogues employs a Suzuki coupling.

\[
\begin{align*}
\text{HCl} & \quad \text{H}_2\text{N}\text{CH}_{3}\text{COO}^- \\
\text{NaBH}_4 & \quad \text{B(OH)}_2 \\
\text{NaN} & \quad \text{NH}_2 \\
\text{B(OH)}_2 & \quad \text{N} \\
\text{Cl} & \quad \text{O} \\
\text{CN} & \quad \text{I} \\
\text{B(OH)}_2 & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{CN} & \quad \text{NaBH}_4 \\
\text{DIPEA} & \quad \text{Pd(PPh}_3)_4\text{, Na}_2\text{CO}_3 \\
\text{DME, EtOH, H}_2\text{O, reflux} & \quad \text{Scavenger, MeOH, r.t.}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Scavenger</th>
<th>Pd Content/ppm Before</th>
<th>Pd Content/ppm After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scavenger 1</td>
<td>2100</td>
<td>1.6</td>
</tr>
<tr>
<td>Scavenger 2</td>
<td>2100</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Scavenger 3</td>
<td>2100</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
PhosphonicS™ materials are normally applied:

- in powder (filtration) or syringe formats for small scale applications
- in powder, pre-packed cartridges (Metal SPE) or in packed vessels for process scale applications

Cartridges developed to fit existing standard filter housings (pilot to manufacturing scale)
PhosphonicSTM Liquid Metal Recovery

*Extracting high value precious metals from waste streams*
Liquid Metal Recovery - Background

- Precious metals (PM): wide range of applications in catalysts, electrochemicals, fuel cells, electronics …
- PM recovery is essential for process economics
- Recovery of PM from solid wastes is well established
- Recovery of PMs from liquid wastes and process streams presents a technical challenge
- Conventional methods of recovery can be ineffective
  - Dilute solutions
  - Highly acidic environment
  - Organic / aggressive solvents
Catalysts: Precious Metal Recovery Cycle

1. Precious Metal acquisition
2. Metal Account
3. Catalyst Production
4. Precious Metal Recovery
5. Customer Application
   - Application losses ~ 1 - 100%
6. Refining losses

Flowchart:
- Precious Metal acquisition → Metal Account
- Metal Account → Catalyst Production
- Catalyst Production → Precious Metal Recovery
- Precious Metal Recovery → Customer Application
  - Customer Application losses ~ 1 - 100%
- Customer Application → Refining losses
- Refining losses → Metal Account
  (Closing the cycle)

PhosphonicS
Drivers - economic and environmental

- Economic need to remove these metals from high volume site effluent/waste streams
- Often an environmental or regulatory requirement
- Transport of liquid streams for metal recovery can be restricted or impossible
- Solutions containing low levels of PMs may not be cost effective to transport and treat
- Client confidentiality
What is PhosphonicS™ Liquid Metal Recovery?

- Specially designed portfolio of cost-competitive metal scavengers
- Broad spectrum activity across range of precious metals
- Maximum metal capacity
- Designed for high volume flow environments
- Sized for easy packing and handling
- Easily processed by standard metal refining processes
How are they applied?

- Powder, cartridge formats or bag filters for **smaller, batch** applications
- Multi cartridge, bag filter or fixed bed for **larger, process scale** applications
Operational Advantages

• High Affinity for all common precious metals in different oxidation states.
• Fast acting - highly active at ambient temperatures; scavenging accelerated at elevated temperature
• Effective in **dilute** and **concentrated** solutions
• High selectivity for the target metal
• Broad solvent and pH compatibility, in organic and aqueous systems
• Excellent stability - thermal, physical, chemical, mechanical
• Wide operating parameters
• Used in variety of **engineered formats** (column, cartridge etc)
• Simple **Metal Recycling** – efficient solid or liquid recovery
Metal Loading & Economics

- Loading capacity: 20-100 g PM adsorbed per kg silica
- Economics depend on objectives, metal, concentration, treat rate, metal recovery process
- Total metal recovery achieved usually exceeds conventional methods - “lost” metal captured
Benefits

• Recover **Lost Metal Value** for **Minimal Capital Investment**

• Minimise or Eliminate **Waste Disposal Costs**

• Meet **Discharge Targets** for heavy metals

• Enhance **Corporate Social and Environmental Responsibility Policy**
Current industrial applications include:

- ruthenium removal from electrochemical processing solutions
- rhodium removal from low concentration catalyst recycle streams
- selective gold removal from base metal streams
- platinum removal from reactive chemical process streams
- palladium recovery from chemical catalyst stream
Rhodium recovery: Case Study

Recovery of rhodium from an Oxo catalyst process stream

- Multi tonne scale
- Simple low-cost column design
- > 96% metal capture and > 3 w/ w% loading achieved over just 1-2 cycles
- Fast capex payback

130 ppm Rh

<5 ppm Rh
Platinum recovery: Case Study

Recovery of platinum from reactive halide stream

- Multi mt - production scale
- High viscosity stream
- Reduction from ~ 50ppm to < 5ppm
- > 90% metal capture
- Highly selective mode of action
- Unique solution
- Potential savings > $5m
Heterogeneous Catalysis

- Using an Immobilised Metal to avoid metal leaching
- Using a solid phase to make catalysis easier and greener

Pd-Catalysed Cross-couplings, Metal-catalysed oxidations and Acid-catalysed reactions
Heterogeneous Phosphines & Metal Catalysts

- Range of specialised phosphine ligands immobilised onto silica
- Conversion to variety of heterogeneous Pd and Pt catalysts achieved
- Offer clean cross-coupling reactions and catalyst recycling
- Particle size, pore diameter and metal loading as required for application
Heterogeneous Pd Catalysts

- Palladium loading: 0.01 to 0.4 mmol/g
- Particle Size: 60-200 microns
- Pore Diameter: 60Å (SCRpd, SEM2Pd, SPM3Pd); 110Å (PAPd1r, PAPd2r)
- Variants: PdCl$_2$, PdCl$_2$(CH$_3$CN), PdCl$_2$(C$_6$H$_5$CN)
- Used for variety of common cross-coupling reactions in **batch** and **flow**

Suzuki & Heck Reactions

- Range of substrates, yields >93%
- 5 Recycles without any apparent loss of activity
- No apparent Pd black formation
- No apparent leaching – based on hot filtration test
- Surface analysis (EDAX) indicates Pd surface unchanged after reaction

**Suzuki Reactions : Phosphaadamantane Catalysts**

\[
\text{Ar—Br} + R\text{—B(OH)}_2 \xrightarrow{\text{Catalyst (0.1 mol%)}} \text{Ar—R}
\]

- **Representative reaction products - catalyst, conversion (recycles)**

- **PAPd1r**; 91% (3 recycles 92-95%)*
- **PAPd2r**; 99%
- **PAPd2r**; 95% (4 recycles 95-99%)
- **PAPd1r**; 99%*
- **PAPd1r**; 85%*
- **PAPd2r**; 95%*
- **PAPd1r**; 68%
- **PAPd2r**; 99%*

*Performed in microwave

- **MeO**
- **Cl**
- **NH**

- **3-Br selective over 2-Cl**
- **Aryl I selective over Br**
- **From vinyl pinacolboronate**

---

*K₂CO₃ or Na₂CO₃
xylene or DME/EtOH
reflux*
Heterogeneous Metal Oxidation Catalysts

- Allylic/Benzylic Oxidation
- Epoxidation
- Alcohol Oxidation
- Sulfoxidation

- High yields
- Recyclable catalysts
- No detectable metal leaching
- Clean reactions
- Easy to handle reagents

Oxidation processes widely used in Discovery Chemistry
- Typical homogeneous reagents are difficult to handle, produce toxic waste and give contaminated products, difficult purifications & as a result generally low yields
- Uses environmentally-friendly re-oxidants

...immobilised metal gives a ‘clean’ and ‘green’ reaction
Heterogeneous Metal Oxidation Catalysts

<table>
<thead>
<tr>
<th>Oxidation Catalyst</th>
<th>Code</th>
<th>Substrate</th>
<th>Product</th>
<th>Re-oxidant</th>
<th>Leading References</th>
</tr>
</thead>
<tbody>
<tr>
<td>POCo</td>
<td>Allylic/Benzylic CH₂</td>
<td>Ketones</td>
<td>tBuOOH</td>
<td>TL, 2003, 44, 4283</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allylic Alcohols</td>
<td>Enones</td>
<td></td>
<td>TL, 2004, 45, 4465</td>
<td></td>
</tr>
<tr>
<td>POVO</td>
<td>Allylic Alcohols</td>
<td>Epoxides</td>
<td>tBuOOH or NaBrO₃ or H₂O₂</td>
<td>TL, 2004, 45, 4465</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sulfides</td>
<td>Sulfoxides</td>
<td></td>
<td>TL, 2006, 47, 8017</td>
<td></td>
</tr>
<tr>
<td>POMn</td>
<td>Allylic/Benzylic CH₂</td>
<td>Ketones</td>
<td>tBuOOH</td>
<td>Unpublished</td>
<td></td>
</tr>
<tr>
<td>POCe</td>
<td>1° Alcohols</td>
<td>Acids</td>
<td>NaBrO₃ or tBuOOH</td>
<td>TL, 2003, 44, 769</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2° Alcohols</td>
<td>Ketones</td>
<td></td>
<td>TL, 2005, 46, 4365</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sulfides</td>
<td>Sulfoxides</td>
<td></td>
<td>Unpublished</td>
<td></td>
</tr>
<tr>
<td>POCr</td>
<td>Sulfides</td>
<td>Sulfoxides</td>
<td>NaBrO₃ or tBuOOH</td>
<td>Unpublished</td>
<td></td>
</tr>
</tbody>
</table>

**Oxidation Catalysts Review:** *Chemistry Today, 2007*, 25 (4), 22 & refs therein

Simple, scalable, cost effective processes
Heterogeneous Acid Catalysts

- Substitutes for strong acids, avoiding toxic, inorganic waste
- Easy-to-use acid catalysts for esterification, trans-esterification, hydrolysis, rearrangements, dehydration, protection & deprotection, cyclisations, etherifications, acylation & alkylation
- High thermal stability
- Readily recycled

**Acid Catalysts Review:** *Manufacturing Chemist, 2007, July/August Ed., 27*
Heterogeneous Acid Catalysts

Effective catalysis of a full range of organic transformations...

\[ X = \text{PO(OH)}_2 \]

\[ X = \text{S-C}_6\text{H}_4-p\text{SO}_3\text{H} \]

\[ \text{BuSi(Me)}_2\text{OMe} \]

Quantitative yield

OPRD, 2007, 11, 406
Fatty Acid Esterifications

\[ R \text{OH} \xrightarrow{(5 \text{ mol\%})} \text{R'OH} \]

<table>
<thead>
<tr>
<th>R'</th>
<th>( R = \text{C}<em>8\text{H}</em>{17}\text{CH}=\text{CH}^- ) Yield/%</th>
<th>( R = \text{C}_4\text{H}_9^- ) Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>Et</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>( ^n\text{Pr} )</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>( ^i\text{Pr} )</td>
<td>49</td>
<td>na</td>
</tr>
<tr>
<td>( ^n\text{C}<em>8\text{H}</em>{17} )</td>
<td>89</td>
<td>na</td>
</tr>
<tr>
<td>Bn</td>
<td>67</td>
<td>na</td>
</tr>
</tbody>
</table>

*na = reaction not performed*

- Enhanced yields *cf’d* to homogeneous acids & other heterogeneous catalysts
- Cleaner reactions

*Acid Catalysts Review: Manufacturing Chemist, 2007, July/August Ed., 27*
Heterogeneous Acid Catalysts

- Developed as an alternative to AlCl₃ for Friedel-Crafts reactions

![Thiophene conjugate addition](image)

- Also applied to Fischer indole synthesis

![Indole synthesis](image)

- Cleaner reactions, higher yields, fewer impurities

Summary

- Significant metal losses from catalytic processes
- Major economic and environmental impact
- Creates a challenge to resolve problems of metal removal and capture from product, waste and effluent streams
- Technology innovation required to deliver improved catalysts and better recovery methods

**PhosphonicS contribution:**
- Developed enhanced scavengers for product purification and precious metal recovery
- Immobilised heterogeneous metal catalysts

Thank you for your attention

www.phosphonics.com