Functionalised Silicas: Addressing the Industrial and Environmental Challenges of API Synthesis

Novel high performance functionalised silicas have been designed that a) allow the selective removal of a wide range of metals from active pharmaceutical ingredients with enhanced affinity, and b) catalyse a variety of organic reactions, including metal-promoted oxidations and acid-catalysed transformations, effectively replacing stoichiometric amounts of environmentally-unfriendly metal oxidants and strong mineral acids respectively.

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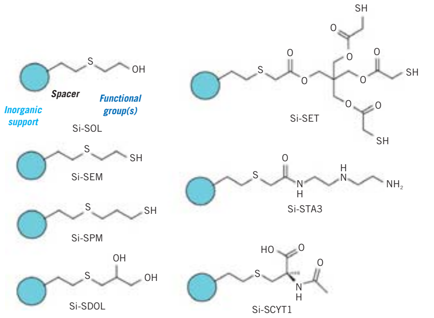
The potential of solid-supported technologies to address key industrial and environmental problems, as well as providing technology solutions for new opportunities, has become increasingly apparent in recent years. Examples include: product purification and separation where impurities emanating from unused reagents, catalysts and side products have to be removed down to very low levels due to their toxicity; chiral separations and the separation of regioisomers; and heterogeneous catalysis where reductions in the use of toxic reagents and homogeneous catalysts are critically needed in the drive towards sustainable technologies. Additional uses include biosensors, biomedical coatings and slow-release applications.

PhosphonicS (1), a spin-out company from Queen Mary, University of London, has discovered and developed a novel solid-phase platform technology that is applicable to many different industries including the pharmaceutical, biotechnology, fine chemical, agrochemical, water, lectronics and nuclear sectors.

Figure 1: A selection of PhosphonicS precious metal scavengers



API RESIDUAL METAL CONTENT

Recent surveys within the pharmaceutical industry have suggested that a very high percentage of small molecule therapeutics in development will have undergone at least one metal-catalysed reaction during synthesis. In particular, palladium-catalysed carbon-carbon and carbon-hetero-atom coupling reactions are now widely utilised, offering the synthetic chemist an increased ability to effectively manipulate complex molecules containing a wide variety of functionality.

However in most cases, the metal – often present in multiple oxidation states – remains strongly bound to the final active pharmaceutical ingredient (API). The metal can frequently have been carried through a number of synthetic steps, with traditional methods for its removal – such as extraction, crystallisation and distillation – having proven ineffective at various synthetic stages, often even after multiple cycles. Adsorption onto activated charcoal can also be used for metal removal from APIs, though this usually results in significant loss of the valuable API (2). The need to reduce the residual metal content in APIs has grown as regulatory restrictions on the level of metals allowed in pharmaceutical products have become increasing stringent (3). Similar standards of compliance are now being requested by environmental regulators.

A further key goal for the pharmaceutical and fine chemical industries is to make product manufacture environmentally acceptable by the use of sustainable or green technologies (4). The replacement of hazardous, corrosive or toxic reagents, often used in stoichiometric amounts, with cleaner solid-phase catalysts, represents a major opportunity to achieve this vital aim, specifically addressing the problem of elimination of toxic aqueous and inorganic waste from chemical processes.

FUNCTIONALISED SILICAS – A SOLUTION

Solid-supported reagents and catalysts facilitate the purification of chemical reactions – a benefit initially widely exploited for the preparation of chemical libraries (5), and more recently adopted by high-throughput medicinal chemistry and process development groups. Here, the rising cost of drug candidate production has increased the need for effective technologies which enable faster problem solving, reduce impurities to acceptable regulatory levels, increase production speed and have an overall positive impact on drug development time.

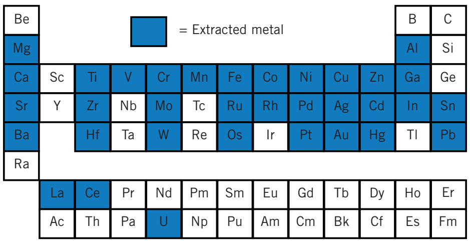
Solid supports have traditionally been based on cross-linked polystyrene and similar derivatives; however, the available range of functionality attached to these materials is somewhat narrow due to restrictive chemical methods for their preparation. Their use is also limited due to the requirement for resin swelling in order to utilise their inherent functionality – a necessity that precludes the use of many common solvents and diminishes the usefulness of polystyrene supports for large-scale applications.

Functionalised silicas do not require swelling, have a broad solvent compatibility and possess excellent properties in terms of thermal, mechanical and chemical stability. Their broad solvent compatibility has added importance for process development groups, as it allows existing process streams to be treated with the supported material, rather than necessitating a timely and costly solvent switch. The capability to customise the properties of the silica – including particle size and shape, active site loading, accessible surface area and pore size – allows the silica to be specifically modified for purpose.

Functionalised silicas have been used as catalysts for a variety of organic reactions of industrial importance including aldol condensations (6a), epoxidations (6b), carbonyl and hydroxyl group protections (6c) and palladium-catalysed carbon-carbon bond formations (6d). Functionalised silica reagents – including supported bases and supported condensation reagents for amide formation, and functionalised silica scavengers, such as supported acids and amines – are described in the literature (5) and a selection are available commercially.

At PhosphonicS, we have developed a broad portfolio of functionalised solid materials through the use of a novel process to prepare new trialkoxysilyl compounds. The process is robust and scaleable, allowing quantities from kilograms to metric tons to be produced. The flexibility of the process allows the inclusion of a diverse range of novel functional groups within the materials, and variation of the spacer between the inorganic support and the functional group(s). The process also allows the materials to be designed and tailored appropriately for function; for example, Figure 1 depicts some early design variants from a precious metal scavenging programme which achieved excellent affinity for the metal from several of the designed scavengers.

Figure 2: Range of metals (shown in blue) scavenged using PhosphonicS materials



🟦 = Extracted metal

Be											B	C
🟦 Mg											🟦 Al	Si
🟦 Ca	Sc	🟦 Ti	🟦 V	🟦 Cr	🟦 Mn	🟦 Fe	🟦 Co	🟦 Ni	🟦 Cu	🟦 Zn	🟦 Ga	Ge
🟦 Sr	Y	🟦 Zr	Nb	🟦 Mo	Tc	🟦 Ru	🟦 Rh	🟦 Pd	🟦 Ag	🟦 Cd	🟦 In	🟦 Sn
🟦 Ba		🟦 Hf	Ta	🟦 W	Re	🟦 Os	Ir	🟦 Pt	🟦 Au	🟦 Hg	Tl	🟦 Pb
Ra												
	🟦 La	🟦 Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er
	Ac	Th	Pa	🟦 U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm

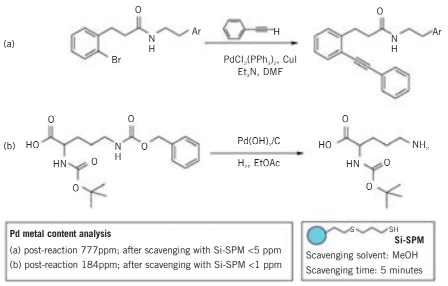
With this ever-increasing armoury of novel functionalised silicas (and other inorganic supports such as alumina, oxides and silicones not described in this article), we have been able to address problems that now represent significant and ongoing challenges for the pharmaceutical industry, such as metal scavenging and recycling, and the use of cleaner alternatives to strong acids for selected organic reactions.

METAL SCAVENGING

The removal of residual metals from APIs is a complex challenge, impacted by the polarity and chemical characteristics of the API, and the oxidation state(s) and complexation of the metal. The broad structural diversity and nature of APIs necessitates the use of a multi-faceted approach to the problem. Based on a number of successful projects, we have developed a unique understanding of the processes and mechanisms involved and, to address the problem, we have designed a toolbox of metal scavengers which cover a wide range of precious, transition and heavy metals, as illustrated by Figure 2.

PhosphonicS materials encompass multiple functional groups to achieve faster kinetics (in fact, most of the scavenging experiments can be performed at room temperature, where very low levels of residual metal can be reached in seconds) and higher affinity, allowing the multiple binding groups and high binding affinity of APIs to the metal to be overcome. The scavengers are individually designed for particular metals and specific applications. For example, palladium removal can be very specific with respect to the physical characteristics of the compound (API) being purified and the form of palladium to be removed.

Figure 3: Palladium scavenging from (a) Sonogashira reaction, and (b) amino acid deprotection



Pd metal content analysis

(a) post-reaction 777ppm; after scavenging with Si-SPM <5 ppm

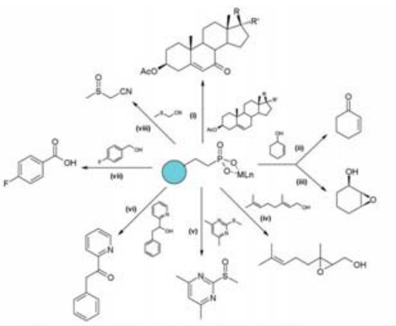
(b) post-reaction 184ppm; after scavenging with Si-SPM <1 ppm

Scavenging solvent: MeOH

Scavenging time: 5 minutes

One of the many benefits of the silica inorganic backbone is that scavenging can be performed in

Figure 4: Selective oxidation reactions using PhosphonicS heterogeneous oxidation catalysts



Reaction conditions (For SiPOCo, MLn = Co (II); SiPOVO, MLn = VO; SiPOCe, MLn = Ce(IV)

(i) Typically 6.8 mol% Si-POCo, tBuOOH (6 eq), MeCN, 50°C, 24 hours (80-97%)
(ii) 5.8 mol% Si-POCo, BuOOH (6 eq), MeCN, 80°C, 12 hours (87%)
(iii) 5.7 mol% Si-POVO, BuOOH (6 eq), MeCN, 80°C, 6 hours (79%)
(iv) 5.7 mol% Si-POVO, BuOOH (6 eq), MeCN, 80°C, 2.5 hours (80%)
(v) ~2 mol% SiPOCe, $NaBrO_3$ (1.5 eq), MeCN/$H_2$0 (6:1), 50°C, 1.75 hours (100% conversion; no sulfone observed)
(vi) ~3 mol% SiPOCe, $NaBrO_3$ (2 eq), MeCN/H20 (8:1), reflux, 48 hours (92%)
(vii) ~3 mol% SiPOCe, $NaBrO_3$ (2 eq), MeCN/H20 (8:1), reflux, 24 hours (93%)
(viii) ~2 mol% SiPOCe, $NaBrO_3$ (1.5 eq), MeCN/H20 (6:1), 50°C, 3 hours (100% conversion; no sulfone observed)
or ~3 mol% SiPOVO, 30% aq H_20_2 (2 eq), MeCN, r.t., 1 hour (99% conversion; trace sulfone observed)

a broad range of solvents, as dictated by the nature of the API, from which weight loss is generally minimal, especially in comparison with the more traditional methods described earlier (2). Metal content is routinely reduced from 300-1,000ppm post-reaction down to <5 ppm after the scavenging process. Figure 3 (page 87) shows palladium scavenging from a Sonogashira reaction that generates a product containing functionality with considerable potential for palladium chelation, and a CBz-deprotection of a protected amino acid.

Further results featuring alternative palladium coupling reactions and other precious metal-catalysed reactions will be published in due course, as will the scavenging of other metals of particular interest to the pharmaceutical and fine chemical industries, including ruthenium, rhodium, osmium and tin. Importantly, a simple wash protocol typically allows high recovery of the metal from the silica scavenger; for example, 85-90% of palladium is routinely collected for potential recycling.

Our experience with metal scavenging from APIs now encompasses compounds with a broad range of common functional groups including amines, amides, carboxylic acids, amino acids, alcohols, nitriles and esters. For some of the more frequently encountered problematic metals – such as copper, chromium and ruthenium – and for precious metals, we have assembled kits that include a selected range of the scavengers successfully employed for removal of a particular metal (7).

HETEROGENEOUS CATALYSTS

Cross coupling reactions

An alternative approach to the reduction of metal content in APIs involves the use of heterogeneous metal catalysts, where the metal remains bound to the functionalised material. PhosphonicS has a range of heterogeneous palladium catalysts currently in development. Results with Suzuki and Heck reactions are high-yielding and the catalysts have been recycled five times without any apparent loss of activity, any palladium leaching or any apparent palladium black formation. Applications of these catalysts for additional industry-wide, metal-catalysed cross couplings will be reported in due course.

Metal-mediated oxidations

The use of manganese- and chromium-based oxidising agents presents significant problems in terms of potential hazards and toxic aqueous inorganic waste, as well as often presenting separation difficulties in the isolation of the product. Despite these drawbacks, oxidants continue to be used industrially, typically in stoichiometric amounts, for allylic and benzylic oxidations, alcohol oxidations and epoxidations, due in part to the lack of effective alternatives.

PhosphonicS heterogeneous oxidation catalysts (8) – where the metal catalyst is supported on silica – are easily handled, readily filtered off and re-used. The catalysts when used with a suitable re-oxidant allow selective and effective oxidations of a broad range of substrates, as illustrated by Figure 4, and eliminate the environmental problems outlined above. Catalyst residues detected from use of the heterogeneous palladium and oxidation catalysts described are minimal (<1ppm).

Differences in reactivity between the oxidation systems allow reaction parameters of importance for a particular substrate to be readily adjusted; for example in Figure 4, oxidation of the sulphide (viii) can be achieved at room temperature rather than at 50°C by use of the vanadyl alkyl phosphonate catalyst – in this case with environmentally friendly aqueous hydrogen peroxide used as the re-oxidant, rather than the corresponding cerium catalyst. No metal leaching is observed and, in the absence of the supported metal catalyst, no substrate oxidation is observed. Other heterogeneous catalysts – including Mn(II), Ti(IV), Ni(II) and Cu(II) – are currently in development.

Heterogeneous acid catalysts

Within the pharmaceutical industry, homogeneous acid catalysts – such as Lewis acids or mineral acids – represent an additional source of large levels of inorganic waste, which cannot be easily recovered or recycled. Heterogeneous acid catalysts offer advantages in terms of both waste reduction and ease of handling. At PhosphonicS, we have developed a mild alkylphosphonic acid silica and the stronger phenyl sulphonic acid ethyl sulphide silica as re-usable acid catalysts; these can be utilised for a wide variety of organic transformations including esterification (as shown in Figure 5), hydrolysis, dehydration, carbonyl and alcohol protection, and deprotection. The catalysts have also been applied to Fischer Indole and Friedel-Crafts reactions where, in the latter case, the usually employed aluminium trichloride has been effectively replaced by either an alkylphosphonic acid silica or a supported zinc phosphonate (also shown in Figure 5).

Alkylphosphonic acid silica and phenylsulphonic acid ethyl sulphide silica have also found application for solid phase extraction (SPE) clean-up of crude reaction mixtures. Strong cation exchange (SCX) allows a 'catch and release' process to occur, where basic products are removed from the reaction mixture and subsequently released with enhanced purity, free from any acidic or neutral materials. The silica-supported acid is easily regenerated for future use.

FUTURE OUTLOOK

PhosphonicS has designed and assembled a broad portfolio of novel functionalised inorganic materials, which demonstrate excellent performance when challenged by real problems from the pharmaceutical industry. These novel functionalised silicas show enhanced affinity for metal impurity scavenging from a diverse range of APIs and have broad applicability for organic scavenging. The use of these functionalised silicas as heterogeneous catalysts reduces the environmental burden of metal-catalysed and strong acid-promoted organic reactions.

Further applications of these functionalised materials currently in development include their use as chiral stationary phases for separation purposes, as slow-release agents and as asymmetric catalytic supports. Further benefits in performance by incorporation with new technologies, such as microwaves and flow chemistry, will be presented in due course.

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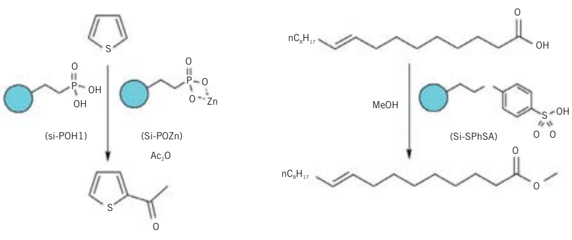

Figure 5: PhosphonicS heterogeneous acid catalysts in use for (a) Friedel-Crafts acylation, and (b) fatty acid esterification

References

1. PhosphonicS Ltd, www.phosphonics.com
2. Garrett CE, Prasad K (2004). The Art of Meeting Palladium Specifications in Active Pharmaceutical Ingredients Produced by Pd-Catalyzed Reactions. *Adv Synth Catal*, 346, 889. Refers to the synthesis of a biaryl API in which, after Suzuki reaction to provide the precursor of the API, ~0.5 to 0.6 g./g of carbon used was adsorbed to the carbon after filtration.
3. US Food and Drug Administration (www.fda.gov), European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).
4. Green Reaction Media in Organic Synthesis. K Mikami (Ed), Blackwell Publishing, (2005).
5. Ley SV, Baxendale IR, Bream RN, *et al.* (2000). Multi-step organic synthesis using solid-supported reagents and scavengers: a new paradigm in chemical library generation. *J Chem Soc*, Perkin Trans, 1, 23, 3815.

6a) Shimizu K, Hayashi E, Inokuchi T, *et al.* (2002). Self-aldol condensation of unmodified aldehydes catalysed by secondary-amine immobilised in FSM-16 silica. *Tet Lett*, 43, 9073; 6b) Choudary BM, Ramani T, Maheswaran H, et al. (2006). Catalytic Asymmetric Epoxidation of Unfunctionalised Olefins using Silica, LDH and Resin-Supported Sulfonato-Mn(salen) Complex. *Adv Synth Catal*, 348, 493; 6c) Shimizu K, Hayashi E, Hatamachi T, *et al.* (2004). SO_3H-functionalized silica for acetalization of carbonyl compounds with methanol and tetrahydropyranylation of alcohols. *Tet Lett*, 45, 5135; 6d) Tyrrell E, Al-Saardi A, Millet J (2005). A Novel Silica-Supported Palladium Catalyst for a Copper-Free Sonogashira Coupling Reaction. Synlett, 3, 487; Okubo K, Shirai M, and Yokoyama C (2002). Heck reactions in a non-aqueous ionic liquid using silica supported palladium complex catalysts. *Tet Lett*, 43, 7115.

7. Metal removal products are available from PhosphonicS or Strem Chemicals Inc. (www.strem.com).
8. *Oxidation substrates*: Al-Haq N, Sullivan AC, Wilson JRH (2003). 'Oxidation of *alcohols* using cerium (IV) alkyl phosphonate modified silica. *Tet Lett*, 44, 769; Jurado-Gonzalez M, Sullivan AC, Wilson JRH (2003). Allylic and benzylic oxidation using cobalt (II) alkyl phosphonate modified silica. *Tet Lett*, 44, 4283; Jurado-Gonzalez M, Sullivan AC, and Wilson JRH (2004). Selective oxidations of *allylic alcohols* using vanadyl and cobalt (II) alkyl phosphonate modified silicas. *Tet Lett*, 45, 4465; Al-Hashimi M, Roy G, SullivanAC, and Wilson JRH (2005). Selective oxidations of *sulphides* to sulfoxides using immobilised cerium alkyl phosphonate. *Tet Lett*, 46, 4365; Al-Hashimi M, Fisset E, Sullivan AC, and Wilson JRH (2006). Selective oxidation of *sulphides* to sulfoxides using a silica immobilised vanadyl alkyl phosphonate catalyst. *Tet Lett*, 47, 8017.