

SCAVENGING USING **SiliaMetS[®]** AND **SiliaBond[®]** SCAVENGERS

Scavenging studies and results in one place



Scavenging of:

■ Antimony (<i>Sb</i>)	2
■ Cesium (<i>Cs</i>)	2
■ Copper (<i>Cu</i>)	3
■ Iridium (<i>Ir</i>)	4
■ Manganese (<i>Mn</i>)	4
■ Osmium (<i>Os</i>)	5
■ Palladium (<i>Pd</i>)	5
■ Platinum (<i>Pt</i>)	21
■ Ruthenium (<i>Ru</i>)	22
■ Tin (<i>Sn</i>)	25
■ Uranium (<i>U</i>)	27
■ Multiple Metals	28
■ Organic Impurities	36



Application Notes & Case Studies

SiliaMetS Metal Scavengers

Removal of **Sb**

In situ speciation of dissolved inorganic antimony in surface waters & sediment porewaters

Antimony is a priority environmental contaminant, yet very little research on the behavior and fate of Sb in the environment has been reported. The primary source is mining and processing of Sb for industrial applications. To properly understand the processes controlling the movement of Sb through the environment, there is a need for tools to accurately measure the speciation of Sb, not just total concentration.

Both toxicity & mobility of Sb are affected by oxidation state, thus the accurate measurement of Sb speciation is essential for investigating the behavior of this contaminant in aquatic systems.

The authors present herein a diffusive gradients in thin films (*DGT*) technique, which utilizes a binding layer containing SiliaMetS Thiol, for the selective measurement of Sb^{III} in surface waters and sediment porewaters.

The mercapto-silica showed a high affinity for Sb^{III}, with uptake efficiencies > 97 % and elution efficiencies of 86.9 +/- 2.6 %

The SiliaMetS Thiol based *DGT* technique was also applied to measure porewater concentrations of Sb^{III} and As^{III} in a contaminated freshwater sediment at high resolution.

Initial and/or residual metal content was not disclosed.

Bennet, W. W. *et al. Environ. Sci.: Processes Impacts*, **2016**, *18*, 992-998
Griffith University, South East Queensland, Australia

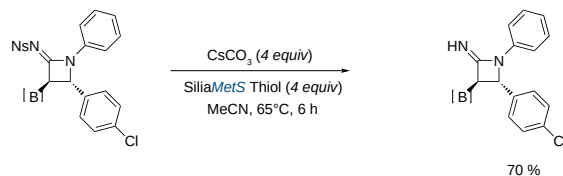
Removal of **Cs**

Amphoteric borylketenimines: versatile intermediates in the synthesis of borylated heterocycles

Reported herein was the 1st synthesis of amphoteric borylketenimines from ethynyl *N*-methyliminodiacetic acid (*MIDA*) boronate and sulfonyl azides via copper catalysis.

This work highlights the unexplored utility of borylketenimines in the synthesis of potentially bioactive molecules.

In situ SiliaMetS Thiol (4 equiv) successfully removed the remaining Cs in deprotection reaction, which resulted in complete conversion and high selectivity.



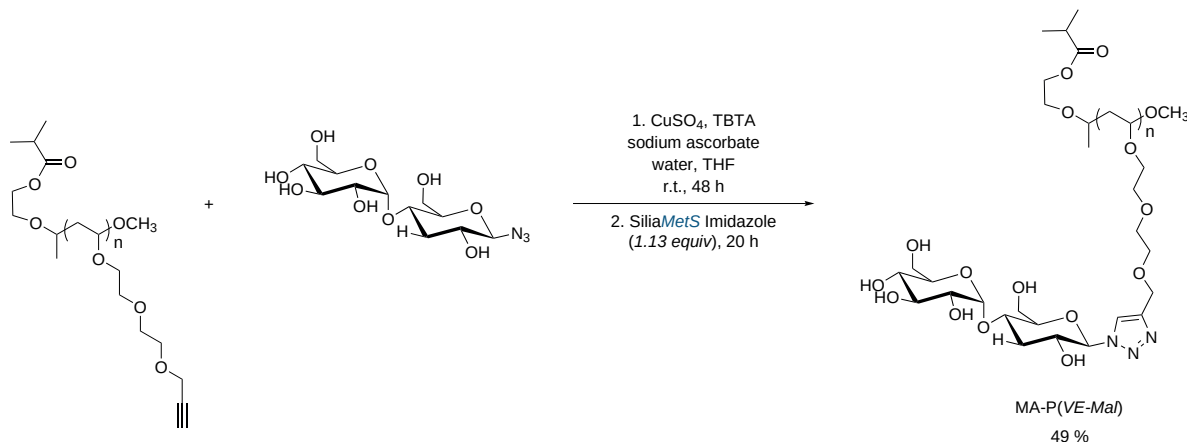
Initial and/or residual metal content was not disclosed.

Yudin, A. K. *et al. Chem. Eur. J.*, **2017**, *23*, 9711-9715
University of Toronto, Ontario, Canada

SiliaMetS Imidazole in the synthesis of polymer films for measurement of optical properties

An asymmetric bifunctional monomer having both an unprotected alkynyl group and a vinyl ether (VE) polymerization of VEEP smoothly proceeded in a controlled manner under a living cationic polymerization condition to give alkyne-substituted polyVE (*poly-VEEP*) without any protection of the pendant alkynyl function.

In the click reaction of precursor macromonomer MA-PVEEP, the resultant polymer MA-P(VE-Ma) was purified from contaminating copper with SiliaMetS Imidazole (0.192 mmol, 1.13 equiv).



Initial and/or residual metal content was not disclosed.

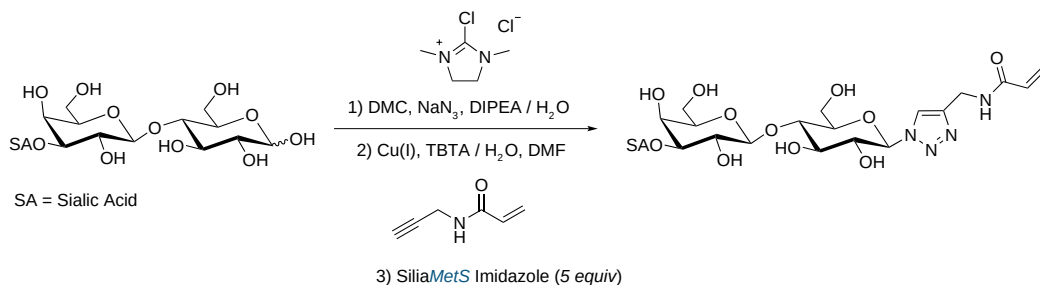
Minoda, M. *et al.* *J. Polym. Sc. Part A. Polym. Chem.*, **2018**, 1
Kyoto Institute of Technology, Sakyo-Ku, Japan

Synthesis of a multivalent glycoligand against avian and human influenza viruses

A glycopolymer bearing α 2,3-linked sialyltrisaccharides was synthesized by living radical polymerization using a glycomonomer prepared by a protecting-group-free process, direct azidation of the free sialyllactose, and subsequent azide-alkyne cycloaddition.

The prepared glycopolymer with pendant 3'-sialyllactose moieties strongly interacted with both avian & human influenza viruses.

SiliaMetS Imidazole (5 equiv for Cu) was successful in removing contaminating Cu, with only 5 equiv, O.N. at r.t.



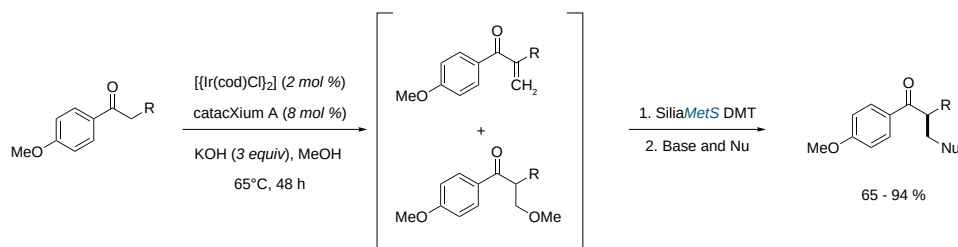
Initial and/or residual metal content was not disclosed.

Tanaka, T. *et al.* *J. Appl. Glycosci.*, **2017**, 64, 43-48

Hydrogen-borrowing and interrupted-hydrogen-borrowing reactions of ketones and methanol catalyzed by iridium

The use of catalytic $[\{\text{Ir}(\text{cod})\text{Cl}\}_2]$ was shown to facilitate hydrogen-borrowing reactions of ketone enolates with methanol at 65°C. An oxygen atmosphere accelerated the process, and when combined to a bulky monodentatephosphine ligand, the catalytic cycle could be interrupted by preventing the enone reduction.

Subsequent addition of pronucleophiles to the reaction mixture allowed a one-pot methylenation/conjugate addition protocol to be developed: the enone and methoxy adduct were not isolated but reacted *in situ* with an external nucleophile and extra base. In most cases they found to be beneficial to treat the crude reaction mixture with the Ir scavenger SiliaMetS DMT while stirring the solution, open to the atmosphere, for 1 hour, before the addition of base and nucleophile. The team suggested that the removal of most of the metal catalyst from solution and prevented complications caused by methanol oxidation during the second phase of the reaction.



Initial and/or residual metal content was not disclosed.

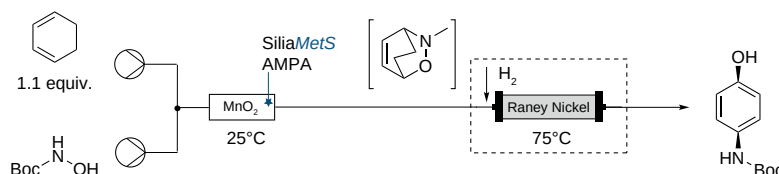
Donohoe, J. *et al. Angew. Chem. Int. Ed.*, **2014**, *126*, 1-5
 Donohoe, J. *et al., Angew. Chem. Int. Ed.*, **2015**, *54*, 1642-1645
 University of Oxford, Oxford, United Kingdom
 Novartis Institute for Biomedical Research, Cambridge, United States

Diastereoselective synthesis of cis-N-Boc-4-aminocyclohexanol with reductive ring opening method using continuous flow

N-protected cis-4-aminocyclohexanol derivatives are valuable intermediates in the syntheses of APIs.

Compared with previously reported batch processes, the present multistep flow process is much more efficient in synthesizing valuable 4-aminocyclohexanol derivatives, and avoids some isolation and purification steps.

In this procedure, a nitroso hetero-Diels-Alder cycloaddition step using MnO_2 as the oxidant was fully integrated to a novel continuous flow process for the hydrogenation and ring opening of cycloadducts to the corresponding cis-4-aminocyclohexanols using H-Cube Pro.



It was shown that Raney Nickel was a significantly more performant catalyst compared to 10 % Pd/C and 5 % Ru/C in this last cleavage, and highly selective ($\geq 99\%$ toward final *cis*-4-aminocyclohexanol). Yet, the Raney Nickel cartridge lost its activity after a few measurements. A possible manganese leaching into the reaction mixture was presumed as the cause for catalyst deactivation. Based on the atom absorption measurements the average extent of manganese was 15 ppm in the reaction mixture. Filling the end of the MnO_2 column with SiliaMetS AMPA as a Mn scavenger allowed the Raney nickel catalyst activity to be kept constant for longer time.

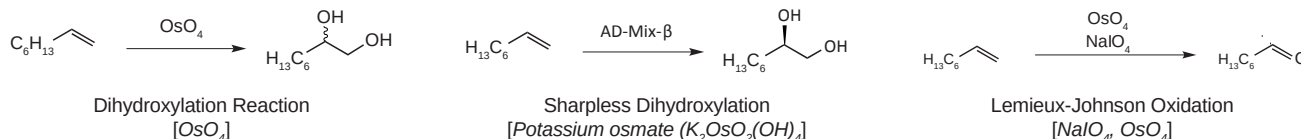
Initial and/or residual metal content was not disclosed.

Szabó, B. *et al. J. Flow Chem.*, **2019**, *9*, 13-17
 University of Technology and Economics, Budapest, Hungary

Osmium scavenging with SiliaMetS

Osmium tetroxide (OsO_4), is a very reliable and powerful reagent for the cis-dihydroxylation of alkenes. However, osmium compounds, in particular OsO_4 , are highly poisonous, even at low exposure levels, and must be handled with appropriate precautions.

Therefore, it is important to efficiently remove residual osmium from products of interest. A scavenging study on three organic reactions involving osmium reactants were performed. The metal scavenging efficiency of SiliaMetS is highlighted in the following table.



Osmium Scavenging using SiliaMetS (in %) at 22°C					
SiliaMetS	Dihydroxylation	Sharpless Dihydroxylation		Lemieux-Johnson Oxidation	
	4 equiv, 4 h	8 equiv, 4 h	8 equiv, 16 h	8 equiv, 4 h	8 equiv, 16 h
SiliaMetS Thiol	87	> 98	> 98	87	92
SiliaMetS Cysteine	89	> 98	> 98	87	91
SiliaMetS DMT	92	97	> 98	87	91
SiliaMetS Imidazole	87	> 98	> 98	89	91
Initial Os Concentration (in EtOAc)	132 ppm	25 ppm		21 ppm	

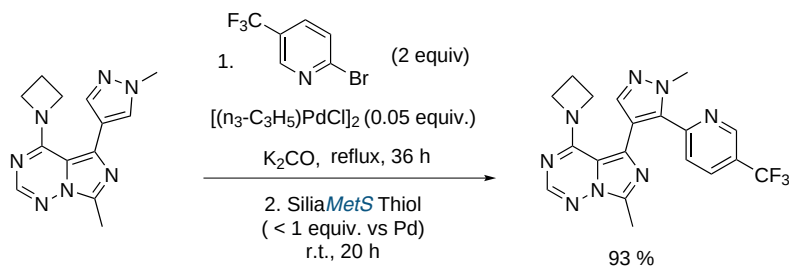
Note: > 98 % of scavenging means < 0.5 ppm of osmium.

All scavengers were equally effective for Sharpless dihydroxylation or Lemieux-Johnson oxidation. As for simple dihydroxylation, SiliaMetS DMT was slightly more efficient.

Identification of a potent, highly selective, and brain penetrant phosphodiesterase 2A inhibitor clinical candidate

Computational modeling was used to direct the synthesis of analogs of previously reported phosphodiesterase 2A (PDE2A) inhibitor with an imidazotriazine core to yield compounds of significantly enhanced potency.

The analog PF-05180999 was subsequently identified as a preclinical candidate targeting cognitive impairment associated with schizophrenia.



SiliaMetS Thiol was used to remove Pd from the palladium-catalyzed C-H arylation on the pyrazole C-5 position with heteroaryl halide to synthesize the PF-05180999. It was found that C-H arylation chemistry was superior to Suzuki coupling for heteroaromatic derivatives, likely due to instability of the required heteroaryl boronates.

Initial and/or residual metal content was not disclosed.

Helal, C. et al. *J. Med. Chem.*, **2018**, *61*, 1001-1018
 Research API, Pfizer Global Research & Development, Connecticut, United States

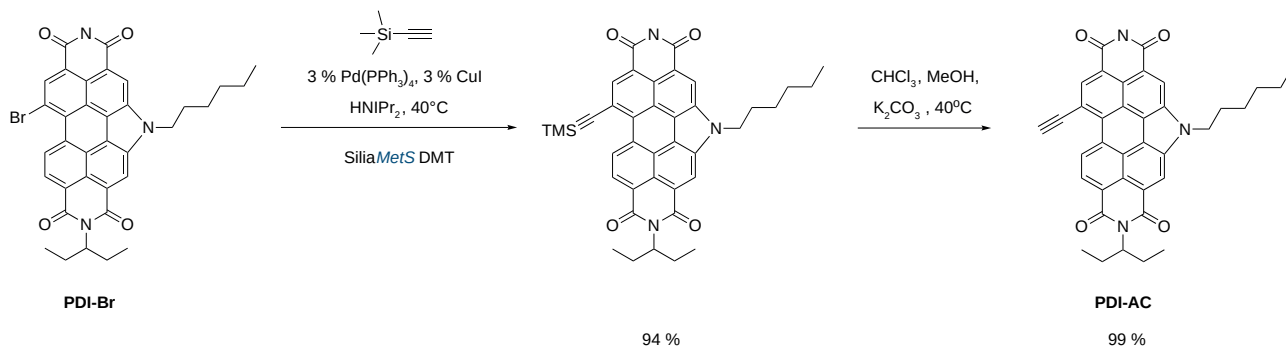
N-annulated perylene diimide dimers: controlling structural conformation & impact on physical, electronic, optical & photovoltaic properties

The geometry of organic π -conjugated small molecules can impact the morphology of blended-thin films and subsequent performance in opto-electronic devices.

The role of molecular conformation of perylene diimide (PDI) dimers designed to act as non-fullerene acceptors in organic solar cells was studied.

SiliaMetS DMT removed all traces of Pd to generate Sonogashira product in near quantitative yield.

This was mandatory in the synthesis as it was found that the subsequent deprotection to form PDI-Ac was found to be sensitive to the amount of Pd remaining in the sample.



Initial and/or residual metal content was not disclosed.

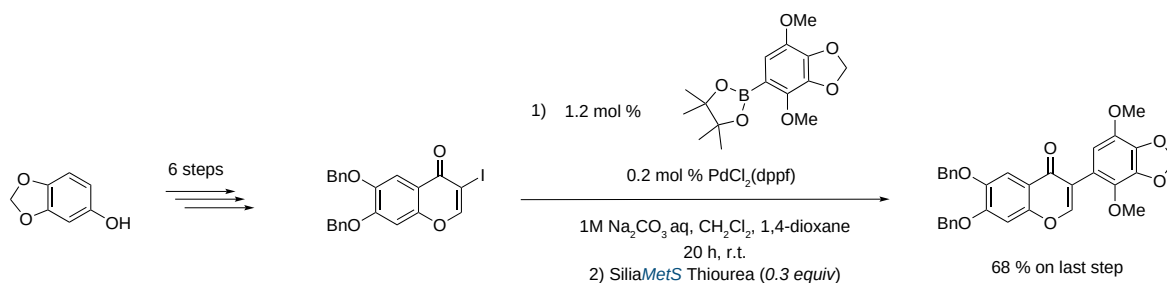
Welch, G. *et al.*, *J. Mater. Chem. C*, **2017**, *5*, 2074-2083
University of Calgary, Alberta, Canada and Dalhousie University, Nova Scotia, Canada

Suzuki-Miyaura cross-coupling synthesis of O⁶-benzyl glaziovianin A

O⁶-benzyl glaziovianin A is a potent cytotoxic substance & a potent inhibitor of α,β -tubulin polymerization. Following a Suzuki-Miyaura cross-coupling, Pd-containing O⁶-benzyl glaziovianin A was purified using SiliaMetS Thiourea.

Purification was done stirring the API with SiliaMetS Thiourea at r.t. in CHCl_3 for 12 h.

Less than 1 equiv. of SiliaMetS (0.3 equiv) was needed for scavenging!



Initial and/or residual metal content was not disclosed.

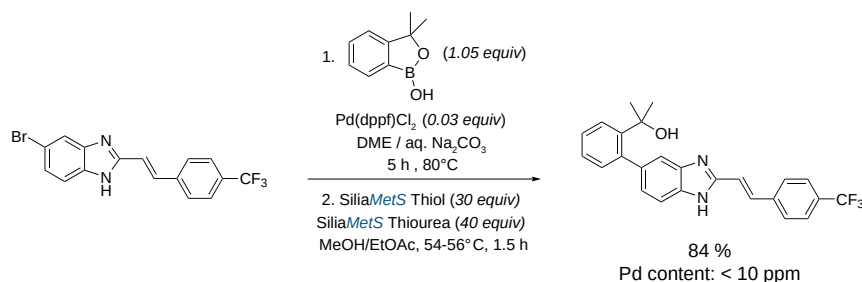
Hayakawa, I. *et al.* *Bioorg. Med. Chem.*, **2016**, *24*, 5639-5645
Okayama University, Okayama, Japan
University of Tsukuba, Tsukuba, Japan

Synthesis of Mavatrep: a potent antagonist of transient receptor potential vanilloid-1

Mavatrep, a potent transient receptor potential vanilloid-1 (*TRPV1*) antagonist, was prepared in four steps in 63% overall yield. One of the two key synthetic transformations was the last step Suzuki coupling of an imidazole with an oxaborolole moiety.

Repeated attempts to carry out the Suzuki coupling reaction under the original conditions in presence of $\text{Pd}(\text{dppf})\text{Cl}_2$ as a catalyst resulted in very poor yields (5-35 %) and formation of high levels of impurities requiring tedious purification. This poor outcome was even worse on larger scale.

After screening various experimental conditions, the best result was obtained by the use of $\text{Pd}(\text{dtbpf})\text{Cl}_2$ in DME in the presence of aqueous Na_2CO_3 which led to a remarkable improvement in both reaction rate and yield. The crude salt was obtained in 80-90% as a brownish solid that typically contained about 1400-1600 ppm of residual palladium. Out of the six screened *SiliaMetS* (*Diamine*, *TAAcOH*, *Thiol*, *Thiourea* and *Triamine*), Thiourea proved to be the most effective palladium scavenger.



However, an unexpected result was found by the synergistic effect of a combination of two *SiliaMetS*, Thiol and Thiourea when used in concert, which was not apparent from the screening array. Their use in combination left the API with less than 10 ppm of Pd.

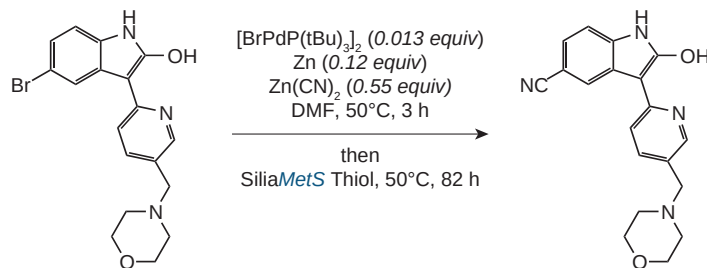
Wells, K. M. *et al. Org. Process Res. Dev.*, **2015**, *19*, 1774-1783
Janssen Research and Development, Pennsylvania, United States



An AstraZeneca case study: palladium removal using SiliaMetS Thiol

AstraZeneca published a paper on removal of palladium impurities in a pilot-scale process.

The work-up method found to work the best was a treatment with SiliaMetS Thiol (25 % w/w or ~1.4 kg) at 50°C to purify more than 6.7 kg of material. Final residual palladium concentration was as low as 1 - 2 ppm.

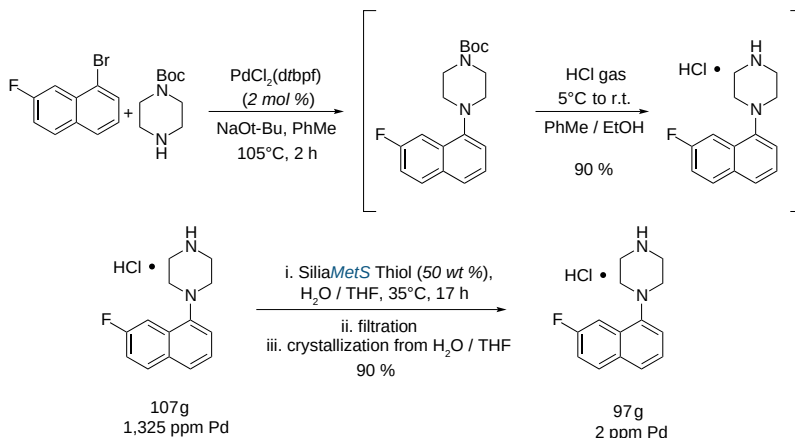


P. Ryberg *et al.*, *Org. Proc. Res. Dev.*, **2008**, *12*, 540-543
 Process Chemistry, AstraZeneca PR&D, Sweden

A Pfizer case study: palladium removal using SiliaMetS Thiol after a Buchwald-Hartwig amination

SiliaMetS Thiol was employed by researchers at Pfizer for Pd removal during the preparation of a naphthalenopiperazine HCl salt. The product from the Buchwald-Hartwig amination of naphthyl bromide with Boc-piperazine was telescoped as a toluene solution and the Boc protecting group was subsequently cleaved with HCl gas to afford the HCl salt containing over 1,300 ppm Pd.

A water / THF solution of this material was then treated with SiliaMetS Thiol (50 wt %) at 35°C for 17 h and, following crystallization from water / THF.



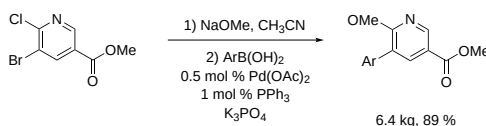
Conclusion

The HCl salt was obtained with a 90 % yield with only 2 ppm Pd. This chemistry was demonstrated on a kilogram scale.

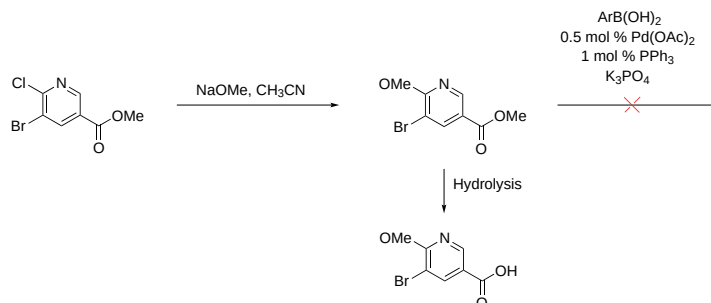
J. Magano *et al.*, *J. Synth. Commun.*, **2008**, *38*, 3631-3639
 Research API, Pfizer Global Research and Development, Connecticut, United States
 Separation Sciences, Pfizer Global Research and Development, Connecticut, United States
 Research API, Pfizer Global Research and Development, Michigan, United States
 Supply Chain API, Pfizer Global Research and Development, Michigan, United States

Circumventing an unexpected catalyst poisoning in a Suzuki coupling

In one project, ring methoxylation of a chloronicotinate was achieved by scientists at Dart NeuroScience and Accela ChemBio, followed by a one-pot Suzuki-coupling to yield a biaryl intermediate, one that was needed on a KG scale in further synthetic steps.



Consistent and excellent results were first obtained from R&D (*mg-scale*) up to a first cGMP process-scale tryout (6.4 kg). Yet, subsequent couplings on other batches gave practically no expected biaryl compound. Instead, the first methoxylation product simply hydrolyzed from its ester form to the corresponding carboxylic acid!



After investigation, the only time the team could reproduce the non-reactive behavior of the reaction was upon intentionally omitting the Pd(OAc)₂ catalyst – hence the idea of catalyst poisoning – but the reaction could still be conducted by adding some more palladium in the reaction mixture (*up to 5 %*). This also leads to downstream issues, as higher palladium loading also implies higher residual palladium, which can greatly impair subsequent reactions.

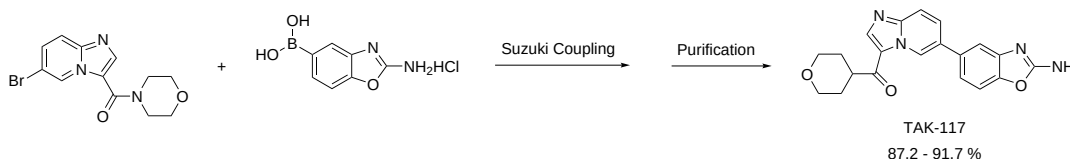
Among all metal removal strategies, it was the use of SiliaMetS Thiol that proved to be the best protocol for a simple, fast and efficient removal of palladium. The Pd levels were thus lowered below 200 ppm. The team concluded that “*The subsequent Pd removal step was carried out as planned, and the remainder of the GMP synthesis proceeded well to provide final API in the desired quantity and purity*”, as the expected biaryl intermediate was isolated in 73 % yield and 98 % purity.

Initial and/or residual metal content was not disclosed.

Liu, J. *et al. Org. Process Res. Dev.*, **2018**, *22*, 111-116
Dart NeuroScience L.L.C., California, United States
Accela ChemBio Ltd, Shanghai, China

Development and scale-up to improve an API's physicochemical and bulk powder properties

Purification process for TAK-117, a selective PI3K α inhibitor currently in Phase 1b of clinical trials, was developed and greatly improved the overall purity, recovery, physicochemical and bulk powder properties of the isolated product, which was obtained after a Suzuki coupling.



A purification process is required to control the Pd levels within International Conference on Harmonisation (ICH) guidelines.

The revised process was found to produce purified material across a total of 6 batches at 15 and 30 kg scales. Original protocol subjected TAK-117 to 2 treatments with decreasing quantities of GCB and SiliaMetS Thiol scavenger (20 wt % each then 10 wt % each). New protocol uses SiliaMetS Diamine (80 wt %) and GCB (20 wt %).

Initial and/or residual metal content was not disclosed.

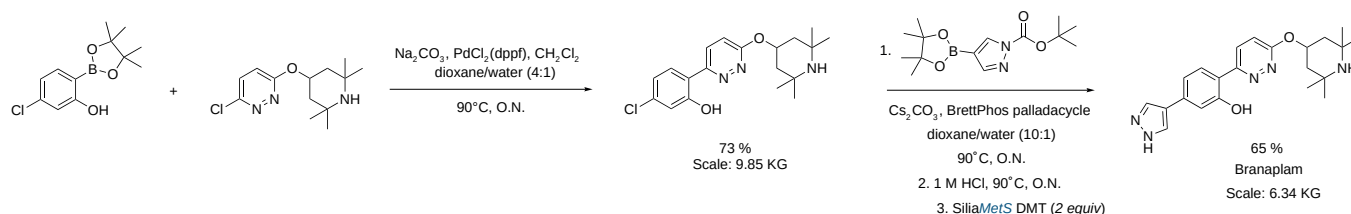
Papageorgiou, C. D. *et al. Org. Process Res. Dev.*, **2018**, *22*, 296-305
Takeda Pharmaceuticals International Co., Process Chemistry, Cambridge, United States

Discovery of small molecule splicing modulators of survival motor neuron-2 (SMN2) for the treatment of Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy (SMA), a rare neuromuscular disorder, is the leading genetic cause of death in infants and toddlers. SMA is caused by the deletion or a loss of function mutation of the survival motor neuron 1 (SMN1) gene. SMN2 (*survival of motor neuron 2*) is a closely related gene which can partially compensate for the loss of SMN1, however coding for a less stable SMN protein.

In recent years, modulating SMN2 pre-mRNA splicing has greatly improved SMA treatments by means of the discovery of LMI070 / Branaplam, a small molecule stabilizing interaction between the spliceosome and SMN2 pre-mRNA.

An efficient two-step synthesis of Branaplam (*from an advanced intermediate S2*) was developed to avoid late stage demethylation which proved challenging upon scaling. Suzuki coupling occurred between pinacol ester of (4-chloro-2-hydroxyphenyl)boronic acid and pyridazine intermediate S2 in the presence of PdCl₂(dppf), CH₂Cl₂ and sodium carbonate, followed by a second Suzuki coupling catalyzed by BrettPhos palladacycle with 1-Boc-pyrazole pinacol boronate to form the Boc protected intermediate. After stirring overnight in the presence of 1M HCl, and then treated with SiliaMetS DMT (5 mmol, 2 equiv) for 20 h, Branaplam was obtained in good overall yield (65 %).



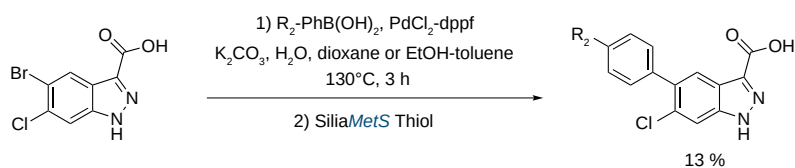
Initial and/or residual metal content was not disclosed.

Cheung, A. K. et al. *J. Med. Chem.*, **2018**, *61*, 11021-11036
Novartis Institutes for Biomedical Research & Novartis Pharmaceuticals, Cambridge, United States

Discovery and synthesis of a direct activator of AMP-Kinase PF-06409577 against diabetic nephropathy

Adenosine monophosphate-activated protein kinase (AMPK) is a protein kinase involved in maintaining energy homeostasis within cells. PF-06409577 has been discovered as an indole acid with excellent balance of properties and has now been advanced to first-in-human trials for the treatment of diabetic nephropathy. Key indazoles in the synthesis were prepared by Suzuki coupling to some commercially available 5-bromoindazoles.

SiliaMetS Thiol was used to remove remaining Pd after only 30 min of stirring.



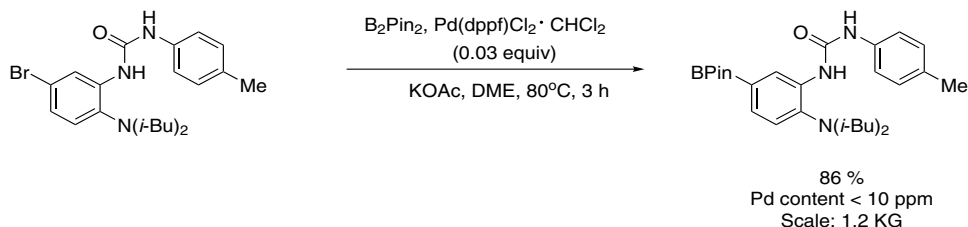
Initial and/or residual metal content was not disclosed.

Cameron, K. et al. *J. Med. Chem.*, **2016**, *59*, 8068-8081
Pfizer Worldwide Research & Development, Massachusetts & Connecticut, United States

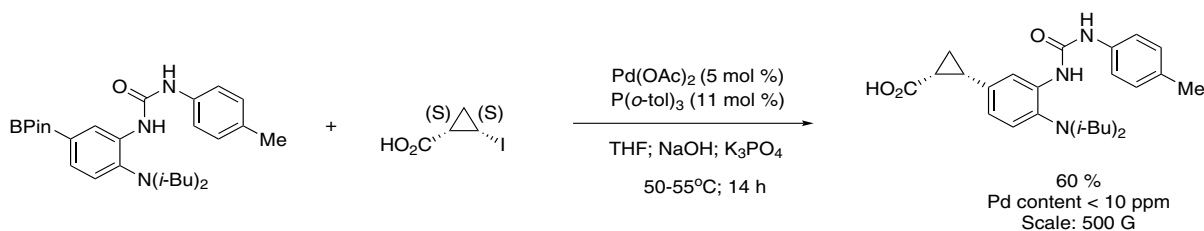
Development of a scalable synthesis of an IDO¹ inhibitor featuring a stereospecific Suzuki coupling of a cyclopropane carboxylic acid

A modified synthetic route to an IDO inhibitor was developed, which synthetic steps comprised a chemoselective nitro reduction, a Miyaura coupling (*Scheme 1*) followed by a key stereospecific Suzuki coupling (*Scheme 2*). A systematic evaluation of the Suzuki conditions led to the identification of a robust catalyst/ligand/base combination to reproducibly duplicate the coupling reaction on large scale, without recourse to chromatography given optimized purification methodology.

Post-reaction treatment included activated charcoal (*for pigments, inorganics...*) and SiliaMetS Thiol (*for residual Pd*): following the reaction work-up, the organic layer was stirred over activated charcoal (125 g) at 20 - 30°C for 2 h. SiliaMetS Thiol (1.3 kg) was charged to the mixture, and the slurry was stirred for 16 h at ambient temperature and filtered through Celite.



Scheme 1



Scheme 2

Purification of final IDO inhibitor was done by treatment with activated charcoal and SiliaMetS Thiol for removal of pigments, inorganics and residual palladium. After the work-up, the organic layer was distilled under reduced pressure, and the resultant brown viscous liquid was dissolved in MTBE (8 L).

Activated charcoal (40 g), silica gel (300 g), and SiliaMetS Thiol (300 g) were added into this solution and stirred at 20 - 30°C for 18 h. The slurry was filtered through Celite.

Overall, the API was delivered in high quality (> 99 %) and good yield (42 %, less than 10 ppm of Pd) for a 5-step synthesis.

¹ Indoleamine-2,3-dioxygenase is a heme-containing intracellular enzyme

Improved synthetic route and scale-up of GSK973 using SiliaMetS Thiol for Pd removal

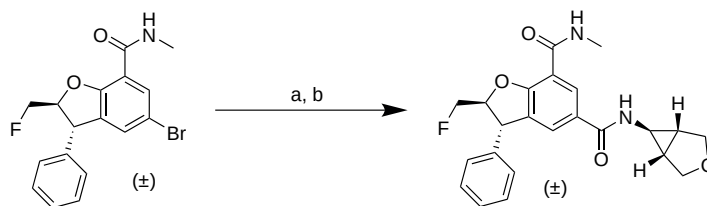
The team at GSK worked on improving the synthetic route to GSK973 for larger scale synthesis in order to provide sufficient material for pre-clinical efficacy and safety studies for oncology trials. GSK973 is an inhibitor of the second bromodomains.

Overall, this study managed to:

- Reduce the number of steps (*from 10 to 7*)
- Transform the synthesis into a more environmentally friendly, greener process due to solvent changes and total quantities
- Improve the synthesis' reliability and scalability
- Increase overall yield (*from 10 to 25 %*)
- Lower the dependency for flash chromatography at large scales

One of the objectives was to reduce the number of steps. The carbonylation/saponification/amide coupling sequence was replaced with a one-step aminocarbonylation. Basing themselves on a set of conditions previously optimized for an aminocarbonylation of another compound of interest, the researchers reused and adjusted the parameters for the synthesis of GSK973 on a 300 mg scale prior to scaling up. The adjustments were done in accordance with GSK's guidelines on green chemistry. Good yields were obtained at the small scale.

While scaling-up, lower conversions arose due to the limited solubility of the compound in the solvent used (*n-butyl acetate*). Switching the solvent to 1,4-Dioxane and increasing the catalyst loading, succeeded in converting 100 % of the starting material, with 87 % isolated yield on the 5 g scale and 95 % isolated yield on the 45 g scale.



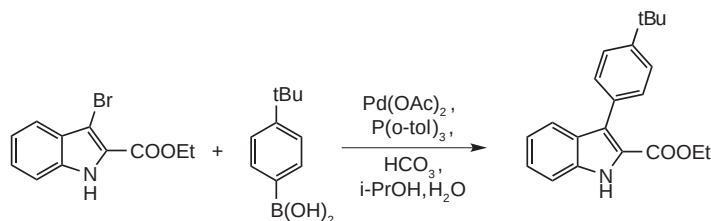
Reagents and conditions: (a) CO (1 atm), 5 mol % (Pd(OAc)₂), 5 mol % Xantos, 1.3 equiv amine·HCl, 2.5 equiv 2,6-lutidine, 1,4-dioxane, 85°C, 16 h, 95 % (97 % pure by LCMS); (b) Si thiol resin, CH₂Cl₂/MeOH, room temperature, then trituration in EtOAc, 83 %.

While the product obtained at this step was initially purified by flash chromatography, at a larger scale, flash chromatography could be avoided by scavenging the residual Pd catalyst using SiliaMetS Thiol. The recovered product was simply trituated, filtered, and concentrated under vacuum to give the resulting product with a yield of 83 % with over 99 % of purity. Both enantiomers (\pm in Figure) were finally separated by chiral preparative HPLC, and enough material was recovered for the subsequent in vivo efficacy and toxicology studies.

[Alder, C. et al. Org. Process Res. Dev., 2022, 26, 365-379](#)

Pd scavenging after a Suzuki-Miyaura coupling using a GlaxoSmithKline published reaction

A metal scavenging study was performed following the synthesis of a key synthetic intermediate obtained by the Suzuki-Miyaura coupling presented in scheme below. Various parameters were investigated including the efficiency of SiliaMetS in different formats, scavenging kinetics, intermediate recovery and purity.



Small-Scale Scavenging (Synthesis Scale ~ 5 g)

The table below shows the most efficient SiliaMetS Metal Scavenger products for the treatment of the reaction mixture after work-up in both bulk and fixed-bed mode bed (*pre-packed SPE cartridges*).

SiliaMetS Scavenging Efficiency & Intermediate Recovery Results (in %)				
Scavengers	Batch Reactor Mode (Bulk)		Fixed-Bed Mode (SPE) 6 mL / 1 g	Intermediate Recovery
	5 equiv, 4 h, 22°C	5 equiv, 4 h, 40°C		
SiliaMetS Thiol	95	> 99	98	> 99
SiliaMetS Thiourea	83	93	99	98
SiliaMetS Cysteine	84	91	97	> 99
SiliaMetS DMT	97	> 99	> 99	98
Initial Pd Concentration	179 ppm in MTBE		76 ppm in Toluene	-

Scavenging Conclusion

Addition of 5 equivalents of SiliaMetS products for 4 h at the end of the reaction reduces the residual metal concentration to single digit ppm.

Recovery & Purity Conclusion

Palladium was completely removed, while the organic compound was not sequestered by SiliaMetS products. No impurities were released.

Larger Scale Scavenging (Synthesis Scale ~ 55 g)

SiliaMetS Metal Scavengers in pre-packed SiliaSep Flash Cartridges are a great alternative for metal removal at process development scale. These cartridges offer excellent scavenging efficiency as shown by the results in associated table.

After the first run, almost all the palladium was captured.

After three runs, less than 1 ppm remained in solution.



Results

SiliaSep Scavenging Results (in %)	
Run #	Scavenging
1	97
2	99
3	> 99

Initial Pd Concentration: 700 ppm in AcOEt

Experimental Conditions

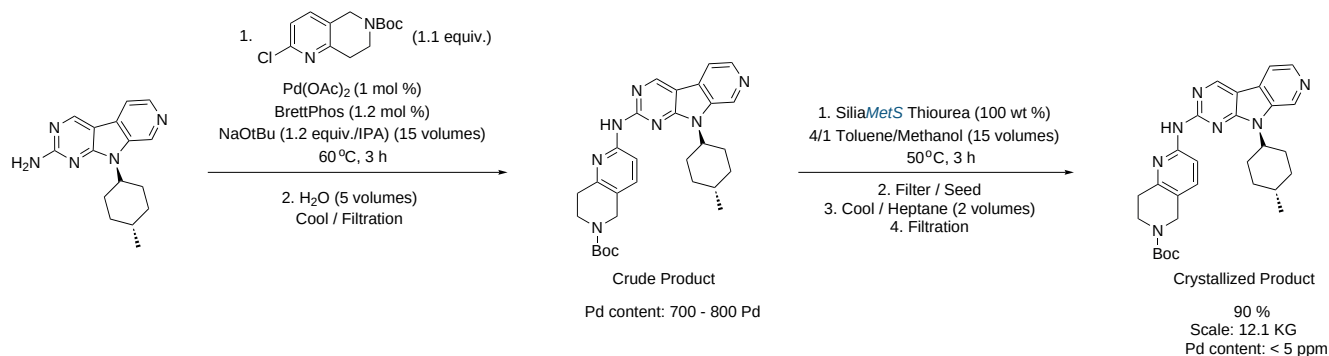
Scavenger Used	SiliaMetS Thiol
Cartridge Size	120 g
Nb. Equivalent	25 equiv
Solution Volume	1 L
Flow Rate	40 mL/min

J. F. Toczko *et al.*, *Org. Proc. Res. Dev.*, **2008**, *12*, 896-899
Chemical Development, GlaxoSmithKline, North Carolina, United States

Multi-kilo delivery of AMG 925 featuring a Buchwald-Hartwig amination and processing with insoluble synthetic intermediates

Amgen describes the development of a synthetic route to manufacture the drug candidate AMG 925 on kilogram scale. The synthetic route features a Buchwald-Hartwig amination using BrettPhos as ligand and conducted to afford 12 kg of product in a single batch.

Yet, the target levels of heavy metal in the drug substance AMG 925 were < 100 ppm, much lower than that found in the crude Buchwald-Hartwig product (700 - 800 ppm).



After the screening of potential scavengers, SiliaMetS Thiourea was selected as the scavenger of choice since it was the most effective. At 100 wt % relative to crude product, in 80 % (v/v) toluene/MeOH and a total of 15 volumes of solvent, it afforded product in 90 % with less than 2 ppm of residual Pd.

Caille, S. et al. *Org. Process Res. Dev.*, **2015**, *19*, 476-485
 Amgen Inc., Thousands Oaks, California

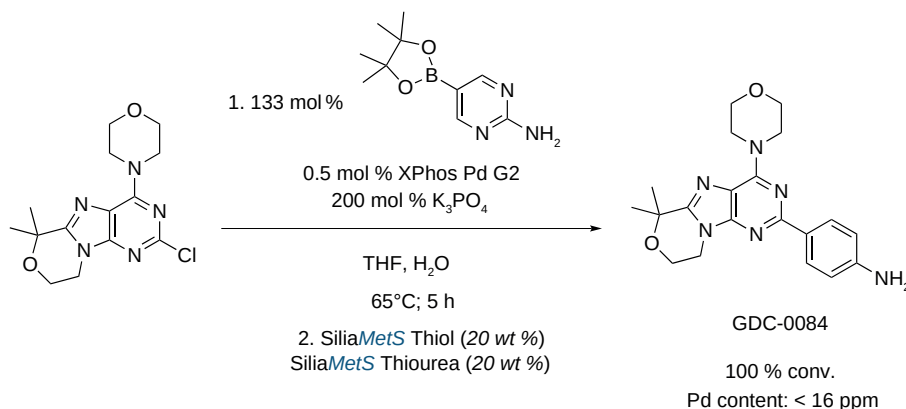
Suzuki-Miyaura cross-coupling synthesis of GDC-0084, a glioblastoma multiforme cancer inhibitor

GDC-0084 is a BBB (*Blood-Brain Barrier*)-inhibitor of the PI3K pathway, where GBM cancer cells reside.

In order to remove residual palladium from the API, a scavenging study using 40 functionalized resins, silicas & activated carbon was performed. Representative samples containing 2,400 ppm Pd were exposed to SiliaMetS Scavengers (20 wt % loading, 14 h) in a solvent mixture of THF and HOAc (67:33).

Both SiliaMetS Thiol & Thiourea were chosen for lowering residual Pd to ≤16 ppm in G-scale experiments.

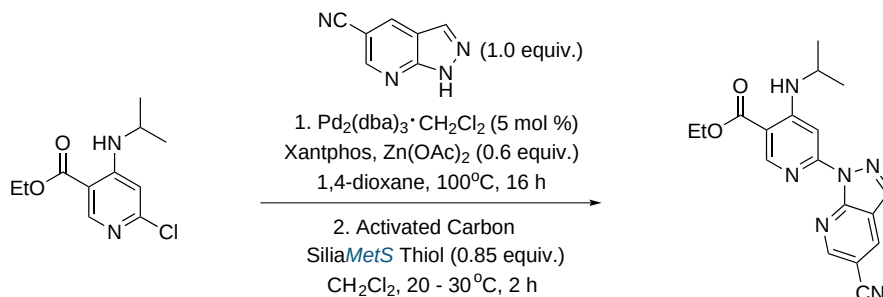
On KG-scale, a mixture of the two scavengers was used.



Stumpf, A. et al., *ACS Symp. Series*, **2016**, *6*, 147-173
 Genentech Inc., San Francisco, United States

Scalable Zn-catalyzed regioselective allylation of 1-methyl-1- α -rhamnopyranoside

The construction of C–N bonds by Pd-catalyzed cross coupling of amines with aryl halides, pseudohalides, and aryl ethers is an uncontested tool for the synthesis of functionalized diaryl amines (*widely found in pharmaceuticals, natural products and so on*).



Zinc salts have been shown to promote the Buchwald-Hartwig coupling of azaindoles and azaindazoles with heteroaryl chlorides to provide the corresponding 1-aryl-1H-azaindoles and 1-aryl-1H-azaindazoles.

The optimal Zinc salt was shown to be $\text{Zn}(\text{OAc})_2$, because of high conversion, availability, low molecular weight and cost. SiliaMetS Thiol successfully removed traces of palladium.

Initial and/or residual metal content was not disclosed.

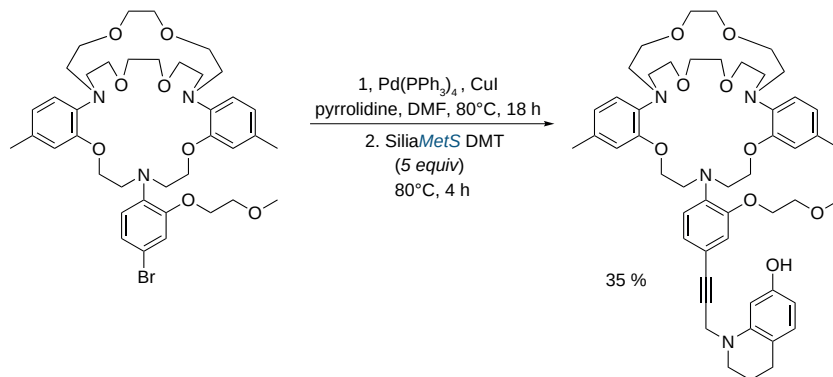
Vaidyanathan, R. *et al. J. Org. Chem.*, **2017**, *82*, 7420-7427
Chemical Development and API Supply, Bristol Myers Squibb Research and Development Center, India

Palladium-mediated synthesis of a near-infrared fluorescent K⁺ sensor

Potassium (K⁺) exits electrically excitable cells during normal and pathophysiological activity.

Currently, K⁺-sensitive electrodes and electrical measurements are the primary tools to detect K⁺ fluxes. A near-IR, oxazine fluorescent K⁺ sensor (*KNIR-1*) with a dissociation constant suited for detecting changes in intracellular and extracellular K⁺ concentrations were synthesized, via a Sonogashira coupling between a halogenated triazacryptand (TAC) and a tetrahydroquinoline. The reaction proceeded smoothly.

Remaining palladium in the resultant alkyne was removed using SiliaMetS DMT, as failure to remove all of the palladium impurities in the following reduction reaction resulted in cleavage of the tetrahydroquinoline from the TAC K⁺ binding domain during reduction.



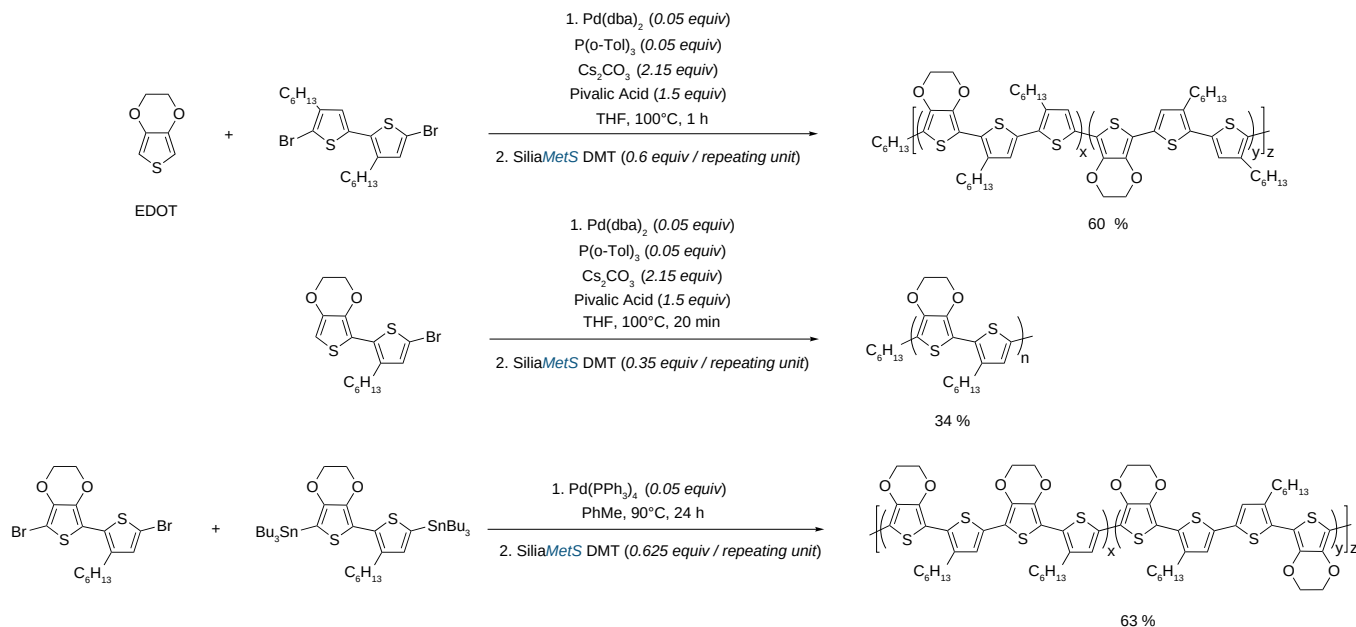
Initial and/or residual metal content was not disclosed.

Robertz, W. R. *et al. J. Org. Chem.*, **2017**, *82*, 8199-8205
University of Massachusetts Medical School, Massachusetts, United States
& Assumption College, Massachusetts, United States

Synthesis of EDOT-containing polythiophenes and their properties in relation to the composition ratio of EDOT

Polythiophenes composed of 3,4-ethylenedioxythiophene (EDOT) and 3-hexylthiophene (3HT) with different composition ratios of EDOT in the repeat unit of the polymer backbone were synthesized by polycondensation reactions. The optical, electrochemical and charge transport properties of the polymers were compared and found to be well correlated with the EDOT composition ratio.

Three kinds of polythiophenes containing 3HT and different EDOT composition ratios were synthesized by polycondensation reactions using direct C–H arylation and Stille coupling, from which Pd residues was removed with SiliaMetS DMT.



Initial and/or residual metal content was not disclosed.

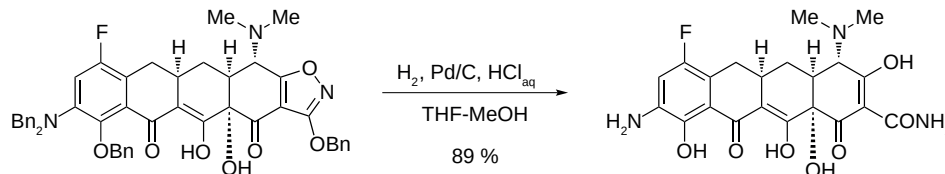
Imae, I. *et al.* *RSC Adv.*, 2015, 5, 84694-84702
Hiroshima University, Hiroshima, Japan



A Tetraphase case study: palladium scavenging in the development of the first fully synthetic fluorocycline using SiliaMetS DMT

Process research and development of the first fully synthetic broad spectrum fluorotetracycline in clinical development was reported by Tetraphase Pharmaceuticals. The key reaction was a Dieckmann condensation between a suitable substituted aromatic moiety and a cyclohexanone derivative. Subsequent hydrogenolysis was extensively studied, using a Pd/C catalyst. **Without any treatment, residual palladium levels as high as 2,000 ppm were detected.**

SiliaMetS DMT was found to be an excellent metal scavenger to reduce the residual Pd content to more than acceptable levels.



Scale-Up of Hydrogenation and Pd Scavenging Results				
Entry ¹	Hydrogenation Time (h)	Time for Slurry in EtOH / H ₂ O (h)	Yield (%)	Pd Content (ppm) (after treatment)
1	12	2	82	0.4
2	4	17	73	2
3	7	2	77	0.39
4	10	2.5	79	1.11
5	11	4	85	< 0.2

¹ 6.2 to 10 wt % Pd/C was used

Conclusion

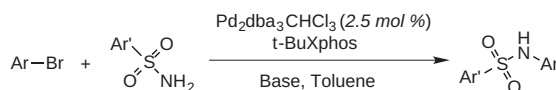
The reaction was run in THF / MeOH (3.3/10 v/v) under nitrogen with 10 wt % Pd/C. Without any treatment, residual palladium levels were as high as 2,000 ppm, but after stirring with 50 or 100 wt % SiliaMetS DMT in MeOH for 2 - 3 h, residual levels were consistently below 1.5 ppm.

M. Ronn *et al.*, *Org. Proc. Res. Dev.*, **2013**, *17*, 838-845
 Tetraphase Pharmaceuticals Inc., Massachusetts, United States

An Amgen case study: Palladium removal using various resins

Amgen published a chapter in "Catalysis of Organic Reactions" related to the use of scavengers for the removal of palladium in small to multi-kilogram production scales.

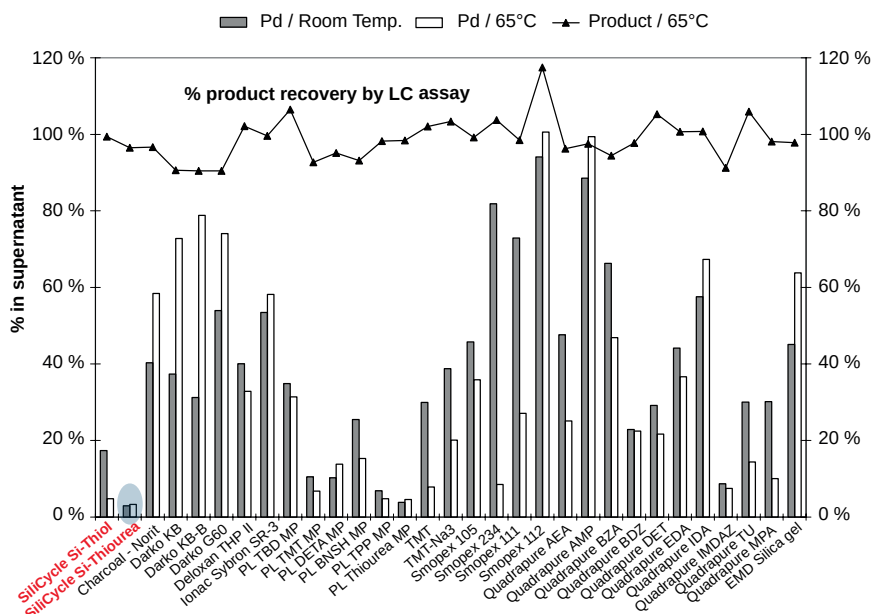
In this study, several parameters were evaluated, such as scavenging efficiency, influence of the scavenger loading and loss of product to adsorption (*recovery*). The study was based on a palladium-catalyzed sulfonamide coupling and scavenger screening was performed at both room temperature and 65°C using 31 different scavengers.



Amgen Scavenger Screening Results

Conditions: 20 mg of each scavenger (20 % w/w) were placed in 2 mL HPLC vials each containing 1 mL of crude reaction mixture containing 100 mg of product. Each vial was sealed and agitated overnight. Initial palladium concentration was 423 ppm.

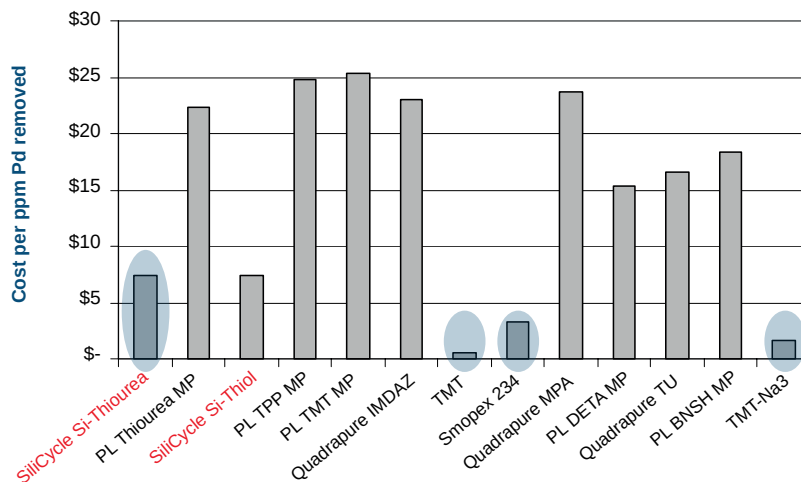
The best scavenger identified during their study was the SiliaMetS Thiourea providing the lowest Pd content (*residual palladium concentration: 3 % or < 14 ppm*) without product sequestration. They mentioned that SiliaMetS Thiourea was used extensively in early process development work.



Cost Comparison for Most Efficient Scavengers ($\geq 80\%$)

At pilot-plant scale, the optimal compromise between the cost per ppm removed and the scavenging efficiency is crucial.

Results highlighted by the graph reduced the number of options to only four candidates for further evaluation: in pole position SiliaMetS Thiourea, followed by TMT, TMT- Na_3 and Smopex 234.



Note: SiliaMetS DMT does not appear in this study because it had not been commercialized yet at the time of the study.

Top Four Scavengers Overview

A screening validation was conducted on 1-g scale purification (10 mL of solution) with 20 % w/w of the four best scavengers at 65°C overnight. After filtration, residual metal concentration was analyzed by ICP-MS and product recovery was determined by HPLC. SiliaMetS Thiourea was chosen for the large scale purification.

Scavengers	Residual Metal Concentration (ppm)			Product Recovery	Commentary from Amgen
	Screening Exp. in Solution	Validation Exp. in Solution	Validation Exp. in Solid Product		
SiliCycle Thiourea	14	11	158	102 %	Best performance
TMT	33	15	264	104 %	Fine in suspension, filterability concerns on scale
Smopex 234	36	38	496	84 %	Favorable cost but product recovery inadequate
TMT-Na3	85	81	1 555	78 %	Very basic compounds (<i>not effective with base-sensitive groups</i>) and low recovery
Initial Concentration	423 ppm	381 ppm	3,577 ppm	-	-
Purification Scale	100 mg	1 g	1 g	1 g	-

Please see Amgen's chapter for further details (*see reference below*).

Amgen's Conclusion

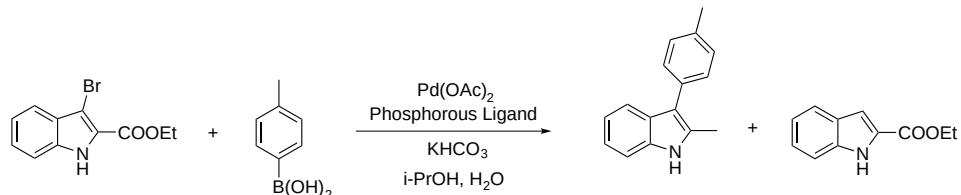
"Scavengers offer a practical and expedient option for removal of palladium from process streams to ensure quality of organic products... The screening protocol involves treatment of a candidate process stream with 20 % w/w scavenger on product at both room temperature and 65°C followed by analysis of Pd and product adsorption. High-temperature treatment increased the efficiency of Pd removal... Evaluation of process costs is key to identifying Pd removal solutions. While scavengers add cost to a process, their use is often justified by the speed to production in early phase development."

J. Allgeier *et al.*, « Application of Scavengers for the Removal of Palladium in Small Lot Manufacturing », *Catalysis of Organic Reactions*, Chapter 5., Amgen Inc., Thousand Oaks, California

The effect of variation of phosphorous ligand nature on scavenging

Even for the same metal, a variation in the scavenging efficiency can be observed depending on the nature of the products present in the solution to be treated. For example, steric hindrance and the electronic effects of the phosphorous ligands are factors influencing the removal of the metal.

The same Suzuki coupling was performed using different phosphorous ligands: three monodentate and three bidentate. For comparison purposes, scavenging screening was done by using the same two sets of conditions. No optimization was done to increase SiliaMetS performance. By experience, using longer reaction times or higher temperatures will allow better results.



SiliaMetS Scavenging Results with Monodentate Ligands (in %) with 4 equiv, 4 h						
SiliaMetS	Triphenylphosphine [PPh ₃]		Tri(o-tolyl)phosphine [P(otol) ₃]		Tri-n-butylphosphine [PnBu ₃]	
	22°C	60°C	22°C	60°C	22°C	60°C
SiliaMetS Thiol	70	97	87	96	26	85
SiliaMetS DMT	95	97	95	> 99	36	87
Initial Pd Concentration:	27 ppm in EtOAc		84 ppm in EtOAc		90 ppm in EtOAc	

SiliaMetS Scavenging Results with Bidentate Ligands (in %) with 4 equiv, 4 h						
SiliaMetS	1,1'-bis(diphenylphosphino)ferrocene [dppf]		1,3-bis(diphenylphosphino)propane [dppp]		(+/-) BINAP	
	22°C	60°C	22°C	60°C	22°C	60°C
SiliaMetS Thiol	50	69	75	90	31	56
SiliaMetS DMT	14	22	95	98	41	64
Initial Pd Concentration:	63 ppm in EtOAc		93 ppm in EtOAc		16 ppm in EtOAc	

Conclusion

In all cases, SiliaMetS DMT and Thiol remained the best scavengers throughout the study, even though there is a variation in the nature of the ligand.

As expected, scavenging was more difficult with bidentate phosphine ligands.

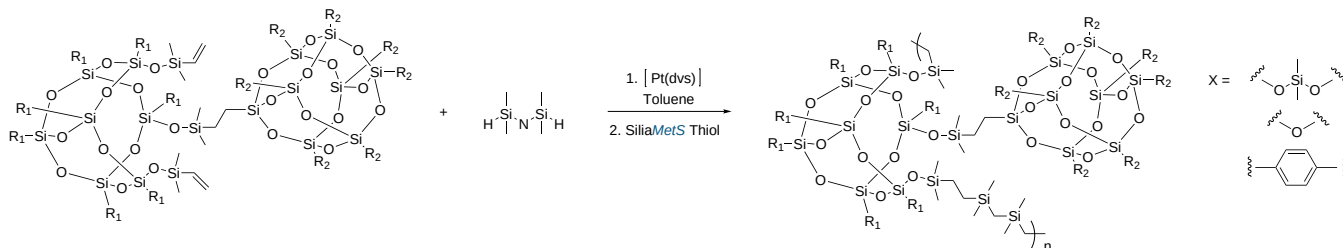
The best conditions were using 4 equiv for 4 h, at 60°C.

Polyhedral oligomeric silsesquioxanes (POSSs) are promising building blocks for organic-inorganic hybrid materials

Polyhedral oligomeric silsesquioxanes (POSSs) are promising building blocks for organic-inorganic hybrid materials, yet they have rarely been studied because the synthesis of bifunctional POSS monomers is a very difficult one in general.

In this work, a novel molecular design of a POSS monomer has been proposed and it was shown that substituents on the completely-condensed or incompletely-condensed POSSs can be widely varied. Furthermore, the resulting polymers are suitable for optically transparent materials because of their high thermal stability and transparency. The properties were controlled by the substituents on the silicon atoms of the POSSs and comonomers. The platinum-catalyzed hydrosilylation polymerization of the bifunctional POSS monomers was performed with siloxane comonomers.

For the measurement of optical properties, the obtained polymer films were fabricated according to the solution-casting method (*refer to experimental protocol*), and were approximately 50 μm thick, measured with a thickness gauge. They showed high transparency in the 380 - 400 nm range.



Experimental Protocol: A polymer (0.1 g) was dissolved in CHCl_3 (1 mL) in the presence of SiliaMetS Thiol, and the solution was filtered and cast onto a glass substrate.

Initial and/or residual metal content was not disclosed.

Naka, K. et al. *J. Polymer Sci. Part A: Polymer Chem.*, **2018**, *9*, 4108-4112
Kyoto Institute of Technology, Sakyo-Ku, Japan



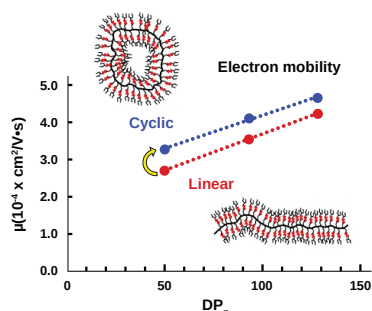
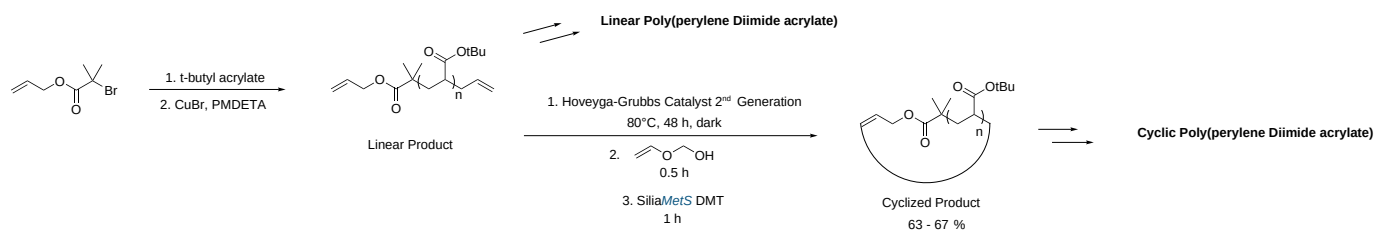
© Photo Charles O'Hara

Electrostatic self-assembly and covalent fixation (*ESA-CF*) process for the synthesis of linear and cyclic polymers and their topology effects on thin-film electron mobility

A pair of topologically contrastive, linear and cyclic polymers having densely appended perylene diimide (*PDI*) units have been prepared by means of an electrostatic self-assembly and covalent fixation (*ESA-CF*) process.

As a first step, a pair of linear and cyclic poly(sodium acrylate) of different segment lengths were prepared through an atom transfer radical polymerization, followed by the end-capping reaction and subsequent ring-closing metathesis in the presence of Hoveyda-Grubbs catalyst second generation.

Unreacted precursor as well as unassigned side products were removed by flash chromatography and Ru removal with SiliaMetS DMT.



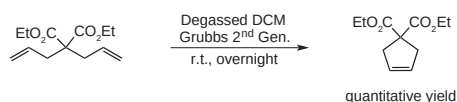
The electron-only device (*EOD*) measurement by using thin-film samples of a series of the Cyclic Poly(perylene Diimide acrylates), revealed consistently higher electron carrier mobilities in comparison with the corresponding linear counterparts, the linear Poly(perylene Diimide acrylates).

Initial and/or residual metal content was not disclosed.

Tenuka, Y. *et al. Macromolecules*, **2016**, *49*, 5831-5840
University of Calgary, Alberta, Canada
Dalhousie University, Nova Scotia, Canada

SiliaMetS vs other purification methods for ruthenium scavenging

The use of SiliaMetS to remove ruthenium catalysts after a ring-closing metathesis (*RCM*) reaction is a very effective purification method. One of its main advantages is that no product is lost during the purification step.



Scavenging Results for Various Purification Methods* (in %)

Scavenging	Scavenger SiliaMetS DMT ¹	Filtration over packed bed of ... ²			Flash Purification	
		Act. Carbon	Celite	Silica	Manual	SiliaSep Cart.
Ruthenium captation	93	73	24	58	70	73

¹ Using 4 equiv, 16 h, 22°C.

² Solution is passed directly on a packed bed of various adsorbents, which was then washed with the same quantity of solvent.

* Quantitative yield obtained for each purification method (*adjusted in function of the residual concentration of catalyst*). No impurities were generated in all cases using the different methods (*determined by NMR*).

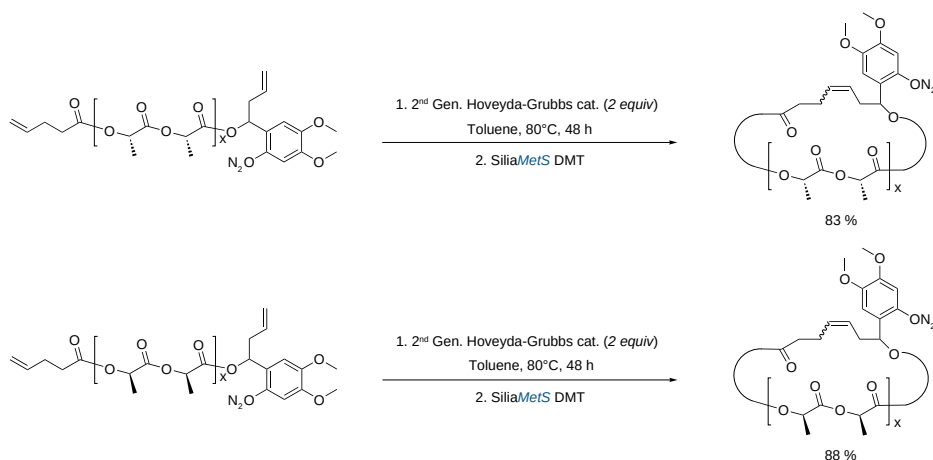
Photoinduced topological transformation of cyclized poly lactides for switching the properties of homocrystals and stereocomplexes

Cyclized poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA) incorporating an o-nitrobenzyl group as a photocleavable linker were synthesized and photoirradiated for topological transformation to form photocleaved linear poly lactides.

The o-nitrobenzyl group was chosen as it is one of the most widely used photolabile protecting groups due to its prompt removal.

Two cyclic PLLA and PDLA with this photocleavable linker were prepared via a Hoveyda-Grubbs catalyzed olefin metathesis, a polymerization known to form highly optically pure poly lactides without degradation in the stereochemistry. SiliaMetS DMT was used to remove residues of ruthenium.

It was shown that the enthalpy of the photocleaved cyclized poly lactides was much lower than that of the linear prepoly lactides, hence the crystalline-amorphous interface is more stable for the cyclized poly lactides arising from the topology.



Initial and/or residual metal content was not disclosed.

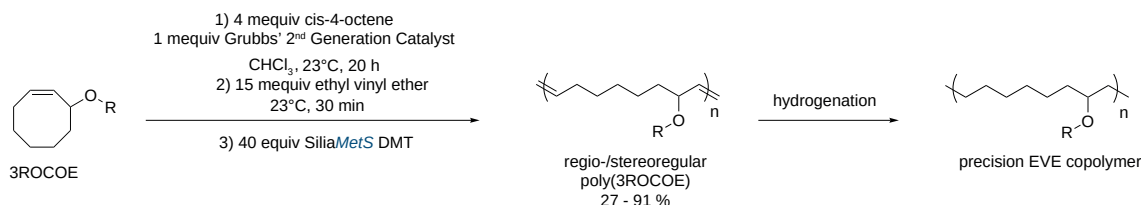
Yamamoto, T. *et al. Polym. Chem.*, **2015**, 6, 3591-3600

Regioselective ring-opening metathesis polymerization of 3-substituted cyclooctenes

Allyl-substituted cyclooctenes with various sidechains [amides, methoxy, methoxy-terminated oligo(ethylene glycol)s, and tetrahydrofurfuryloxy groups] were prepared as monomers and polymerized by ring-opening metathesis polymerization (ROMP) using Grubbs second-generation catalyst.

In all cases, the ROMP of allyl-substituted monomers proceeded in a regio- and stereoselective manner to afford polymers with remarkably high head-to-tail regioregularity with high trans-stereoregularity.

Poly(3ROCOE) were purified from contaminating Ru with SiliaMetS DMT (O.N. at 40°C)



Initial and/or residual metal content was not disclosed.

Kobayashi, S. *et al. Macromolecules*, **2016**, 49, 2493-2501

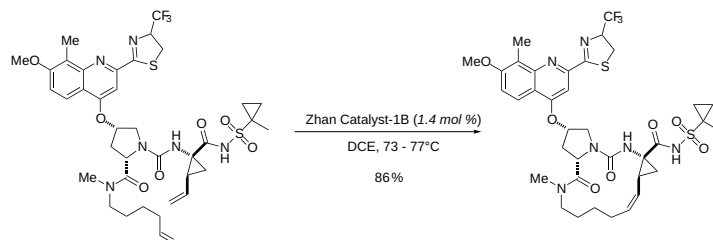
Macromolecules, **2016**, 49, 8154 - 8161

Kyushu University, Fukuoka, Japan

Yamagata University, Yamagata, Japan

An Idenix case study: ruthenium removal in the macrocyclization of dienyliureas via RCM, using SiliaMetS DMT

A novel assembly of two structurally related 14-membered ring macrocyclic hepatitis C virus protease inhibitors was reported by Idenix Pharmaceuticals. Key to their successful construction was an ultimate ring-closing metathesis step on the highly functionalized dienyliurea via Zhan Catalyst-1B (*Ru*-based catalyst).



Several methods have been reported to remove Ru by-products, and were investigated in this study with some variations, including the use of tris(hydroxymethyl)phosphine, lead tetraacetate, TPPO, DMSO followed by silica gel filtration, adsorption onto silica gel, activated carbon and silica gel chromatography, treatment with mercaptanpicotinic acid (MNA) and washing with aqueous NaHCO₃, and the use of supercritical fluid extraction. Resulting Ru levels of those methods vs SiliaMetS DMT treatment were analyzed by ICP-OES and are listed below.

Effect of Reaction Conditions and Purification on Ru Content and Yield of Protease Inhibitor				
Entry	Reaction Conditions	Ru Reduction Operation	Ru content (ppm)	Yield (%)
1	250 mL/g diene 4.9 mM 1.5 wt % catalyst	MNA / NaHCO ₃ wash ; charcoal ; silica gel filtration	14 (<i>initial</i>)	-
		1 st MeOH trituration	12	63
		2 nd MeOH trituration	7.5	58
2	250 mL/g diene 4.9 mM 1.5 wt % catalyst	Charcoal ; silica gel filtration	120 (<i>initial</i>)	-
		1 st MeOH trituration	34	81
		2 nd MeOH trituration	20	75
3	250 mL/g diene 4.9 mM 1.5 wt % catalyst	Charcoal ; silica gel filtration	120 (<i>initial</i>)	-
		1 st MeOH trituration	48	79
		5/4 v/v DCE / MeOH crystallization	4.6	61
4	80 mL/g diene 15.2 mM 1.1 wt % catalyst	Charcoal ; silica gel filtration	880 (<i>initial</i>)	-
		1 st MeOH trituration	300	84
		Toluene crystallization	22	45
5	80 mL/g diene 15.2 mM 1.1 wt % catalyst	Charcoal ; silica gel filtration	880 (<i>initial</i>)	-
		1 st MeOH trituration 2:1 v/v	300	84
		EtOAc / n-heptane crystallization	19	51
6	80 mL/g diene 15.2 mM 1.25 wt % catalyst	SiliaMetS DMT 16 h treatment + filtration	380 (<i>initial</i>)	-
			66	75
7	160 mL/g diene 7.6 mM 1.25 wt % catalyst		200 (<i>initial</i>)	-
			3.6	86
8	250 mL/g diene 4.9 mM 1.25 wt % catalyst		180 (<i>initial</i>)	-
			7.7	89

Conclusion

As one can easily note, treatment with SiliaMetS DMT gave a much lower Ru residual content conjointly with the highest final yields. Hence, low yield losses (11 - 14 %) and high purities (98 %) were achieved, together with excellent Ru levels observed (as low as 3.6 ppm), indicating the strong utility of this approach in Ru removal in the synthesis of macrocycle HCV PIs IDX316.

B. A. Mayes et al., *Org. Proc. Res. Dev.*, **2013**, *17*, 811-828
Idenix Pharmaceuticals Inc., Massachusetts, United States

Ruthenium scavenging

Ruthenium-based catalysts are commonly used in organic synthesis, mainly in olefin metathesis reactions [ROM(P) and RCM]. Grubbs and Hoveyda-Grubbs catalysts are the most popular ruthenium-based complexes in this field of application. Complete ruthenium removal can be tedious using conventional methods.

Under various conditions, several SiliaMetS are known to be excellent scavengers to obtain minimal tolerated concentrations of residual ruthenium.

A ruthenium scavenging study was conducted and various parameters were investigated in order to learn more about their influence on the scavengers' robustness as well as to establish the best experimental conditions.

Ruthenium Scavenging Results using SiliaMetS (in %)								
SiliaMetS	Grubbs 1 st Gen.		Grubbs 2 nd Gen.		Hoveyda-Grubbs 1 st Gen.		Hoveyda-Grubbs 2 nd Gen.	
	Toluene ¹	DMF ²	Toluene ¹	DMF ²	Toluene ¹	DMF ²	Toluene ¹	DMF ²
SiliaMetS Thiol	90	96	-	99	97	93	-	-
SiliaMetS Thiourea	-	98	-	96	97	98	-	-
SiliaMetS DMT	95	99	> 99	99	> 99	98	98	99
SiliaMetS Diamine	99	99	91	94	> 99	98	-	90

Notes: SiliaMetS Cysteine and Imidazole were not screened in this study. Only SiliaMetS results higher than 90 % are presented in this table.

Experimental Conditions

Nb. Equivalent: ¹ 8 equiv of SiliaMetS, 16 h, 80°C

² 4 equiv of SiliaMetS, 16 h, 80°C

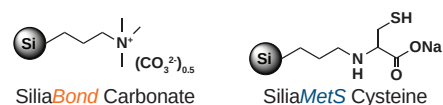
Initial Concentration: 500 ppm for all ruthenium-based catalysts

Conclusion

For all Ru-catalyzed reactions, the best scavenging was achieved using SiliaMetS DMT. For most experiments, little or no difference was observed when using toluene or DMF.

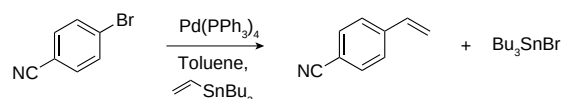
Tin scavenging using SiliaBond Carbonate vs SiliaMetS Cysteine

SiliCycle also provides a quaternary ammonium salt grafted on silica to which a carbonate group is ionically bounded. The latter has shown to be an excellent alternative for tin retrieval from organic mixtures.



Stille Reaction

Tin scavenging was demonstrated on a Stille coupling in which Bu₃SnBr is the major tin by-product. In each test, residual Pd was scavenged in its entirety (from 24 mg/L to < 0.1 mg/L).



Tin Scavenging (in %)		
Scavenger	4 h, 8 equiv, 22°C	4 h, 16 equiv, 22°C
SiliaBond Carbonate	91	99
SiliaMetS Cysteine	77	99

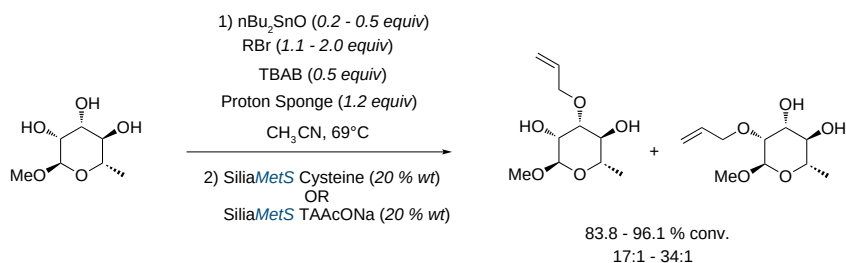
Conclusion

Scavenging yields were excellent with both scavengers. Hence, SiliaBond Carbonate was found to be of the same high efficiency as SiliaMetS Cysteine to scavenge tin compounds of R₃SnX type.

Tin acetate-promoted Buchwald-Hartwig couplings of heteroaromatic amines

Regioselective manipulation of hydroxyl groups in polyols has been critical to carbohydrate chemistry.

A robust selective allylation of 1-methyl-L- α -rhamnose was developed using $n\text{-Bu}_2\text{SnO}$ as the catalyst and proton sponge as optimal base for high regioselective control. The optimized condition afforded the 3-O-allylated rhamnose in excellent regioselectivity ($> 20:1$) and 82 % isolated yield on a 50 g scale.



A scalable isolation/purification process was developed which afforded the desired product in 72 % yield with 1530 ppm of Sn.

The residual Sn level can be further reduced to < 20 ppm by treatment with SiliaMetS Cysteine & TAAcONa.

Residual Sn (ppm)			
Experimental Step	Starting Level	End Level	Recovery (%)
Extractive Work Up	-	1,530	72
1st treatment 20 wt % with SiliaMetS Cysteine	1,530	273	92
2nd treatment 20 wt % with SiliaMetS Cysteine	273	31.9	93
1st treatment 20 wt % with SiliaMetS TAAcONa	1,530	267	91
2nd treatment 20 wt % with SiliaMetS TAAcONa	267	19.5	95

This catalytic system also showed outstanding potential in the selective benzylation of the same substrate.

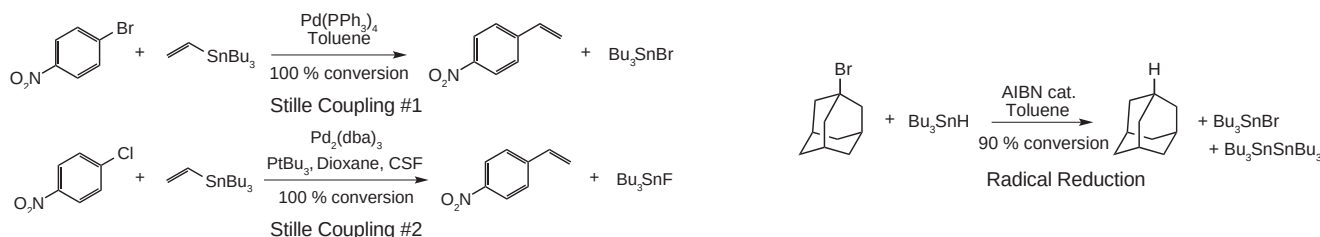
The isomeric purity remained unchanged after the scavenger treatment.

Li, X. *et al. Org. Process Res. Dev.*, 2017, 21, 1653-1658
 Process Development & Process Chemistry, DOW AgroSciences, Michigan & Indiana, United States

Tin scavenging using SiliaMetS Cysteine & TAAcONa

The removal of tin residues can often be an issue due to the high toxicity of this metal. Traditional removal methods for this impurity are treatment with an aqueous solution of KF, NH_4OH or NaOH, or with bases such as DBU. However, the efficiency of these methods can vary and may be inapplicable for some particular compounds.

Both SiliaMetS Cysteine & TAAcONa can be used to efficiently remove tin residues from organic mixtures, as demonstrated below.



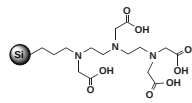
Tin Scavenging using SiliaMetS Cysteine & TAAcONa (in %)						
Reactions	Initial Concentration	SiliaMetS Cysteine		SiliaMetS TAAcONa		
		4 equiv, 4 h, 22°C [2 treatments]	8 equiv, 4 h, 22°C	4 equiv, 4 h, 22°C [2 treatments]	8 equiv, 4 h, 22°C	4 equiv, 16 h, 22°C
Stille coupling #1 ¹	3,385 ppm	99	64	96	62	-
Stille coupling #2 ¹	981 ppm	90	66	66	50	-
Radical Reduction	4,090 ppm	92	88	90	90	90

¹ Pd residues were completely removed after only one treatment with SiliaMetS Cysteine.

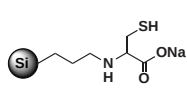
Uranium XAFS analysis of kidney from rats exposed to uranium

The kidney is the critical target of uranium exposure because uranium accumulates in the proximal tubules and causes tubular damage, but the chemical nature of uranium in kidney, such as its chemical status in the toxic target site, is poorly understood. In this study, micro-X-ray absorption fine-structure (*mXAFS*) analysis was used to examine renal thin sections of rats exposed to uranyl acetate.

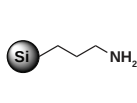
In the preparation of uranium standards for XAFS analyses, uranium adsorbed on 6 different metal scavengers were prepared: SiliaMetS TAAcOH, SiliaMetS Cysteine, SiliaMetS Amine, SiliaMetS DMT, SiliaMetS Imidazole & SiliaMetS Thiol.



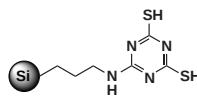
SiliaMetS TAAcOH



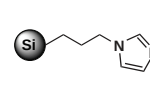
SiliaMetS Cysteine



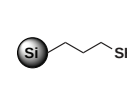
SiliaMetS Amine



SiliaMetS DMT



SiliaMetS Imidazole



SiliaMetS Thiol

Uranium Concentrations	
Scavenger	Uranium concentration ($\mu\text{g/g}$)
SiliaMetS TAAcOH	149,000
SiliaMetS Cysteine	77,640
SiliaMetS Amine	37,400
SiliaMetS DMT	87,530
SiliaMetS Imidazole	74,400
SiliaMetS Thiol	22,500

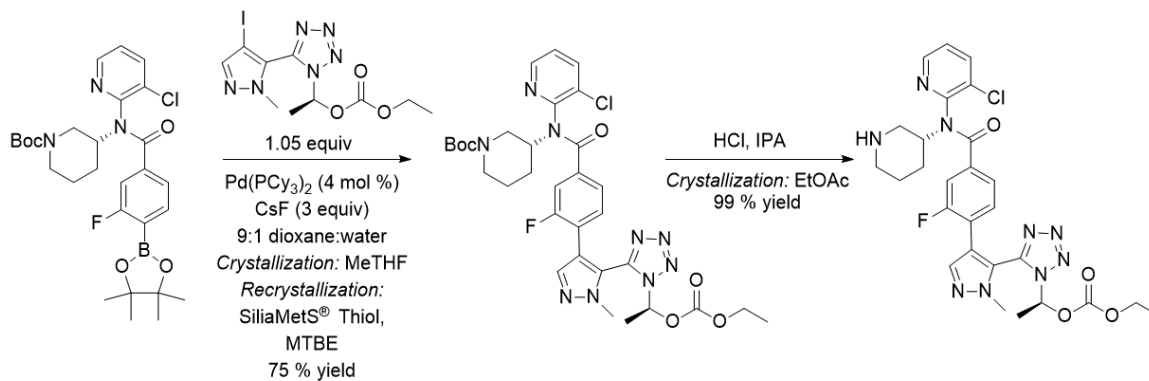
The concentrations of uranium bound to the functionalized resin were above 15,000 $\mu\text{g/g}$.

Homma-Takeda, S. *et al.*, *J. Synchrotron Rad.*, **2017**, *24*, 456-462
National Institute for Quantum and Radiological Science and Technology, Chiba, Japan
Japan Synchrotron Radiation Research Institute, Hyogo, Japan

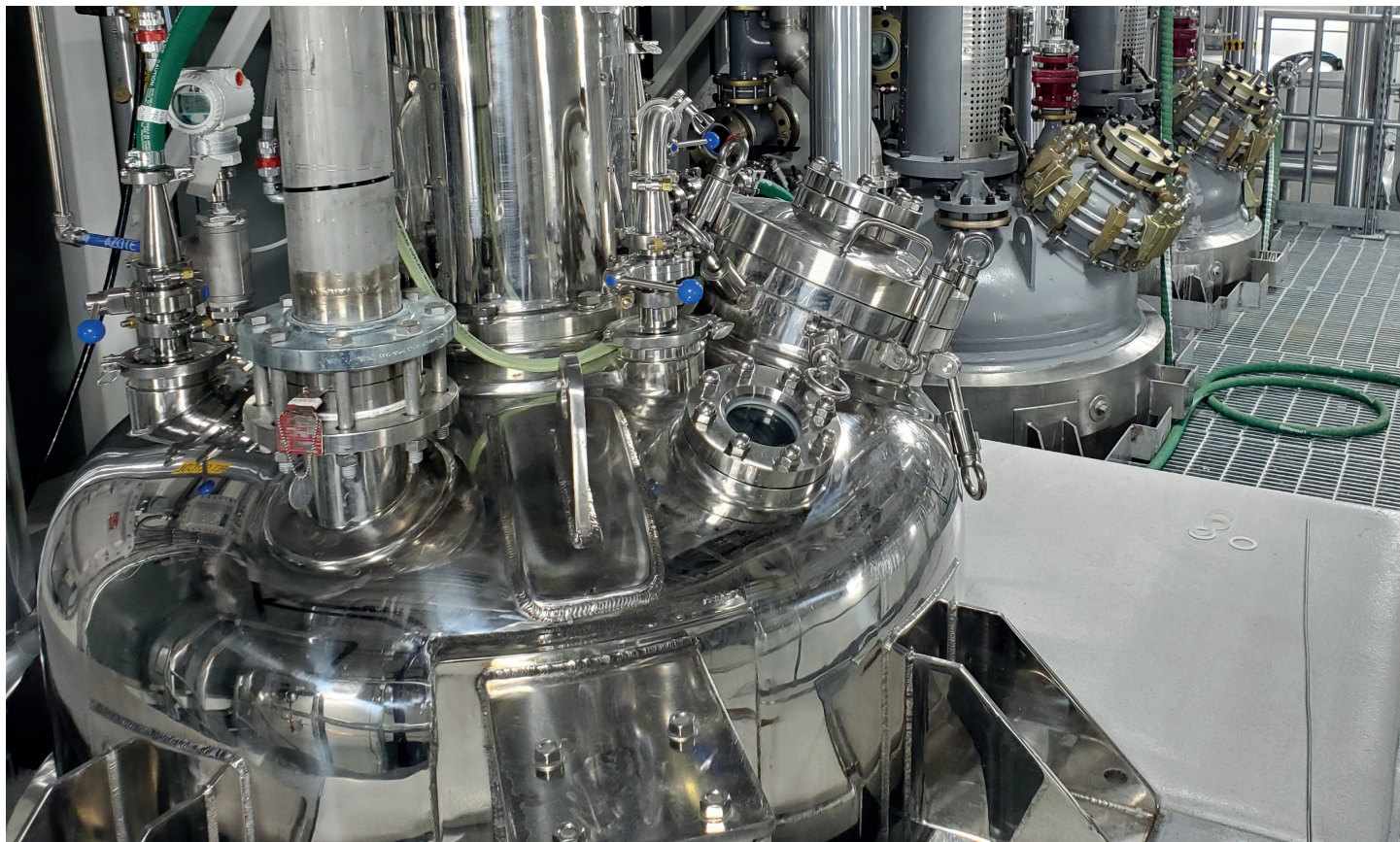
Enantiomer N-1 substituted tetrazole prodrug synthesis

The authors of the study performed a regioselective tin-mediated alkylation to access the N-1 alkylated tetrazole isomer. A highly selective enzymatic hydrolysis provided the desired prodrug enantiomer. For the final fragment union, a Suzuki-Miyaura coupling was employed, leading to the need to eliminate both tin and residual palladium catalyst from the API in multikilogram quantities.

Purification was done adding 10 kg of SiliaMetS Thiol to 18.9 kg of the crude product solubilized in 2-MeTHF. The suspension was heated to 60°C for 2 h, then cooled to 2°C to isolate the compound. A 83 % yield was achieved with 99.1 % purity, having less than < 2 ppm of Sn and 9 ppm of Pd.



Akin, A. et al. *Org. Process Res. Dev.* 2019, 23, 8, 1167 - 1777
Pfizer Groton



A Genentech case study: palladium and ruthenium removal in the synthesis of AKT inhibitor Ipatasertib using SiliaMetS Thiol (multi-kilogram scale)

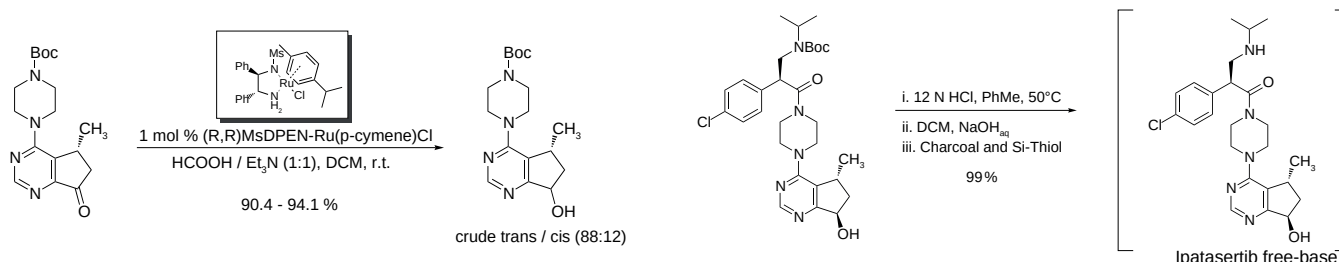
The first-generation process to manufacture Akt inhibitor Ipatasertib through a late-stage convergent coupling of two challenging chiral components on a multi-kilogram scale was reported by Array BioPharma.

A carbonylative esterification and subsequent Dieckmann cyclization was developed to forge a cyclopentane ring in the target. A second key chiral component, a β -amino acid, was produced using an asymmetric aminomethylation (*Mannich*) reaction.

Upon scale-up, the deprotection of the Boc-API for the preparation of the Ipatasertib mono-HCl salt was easily completed in toluene in 12 N HCl.

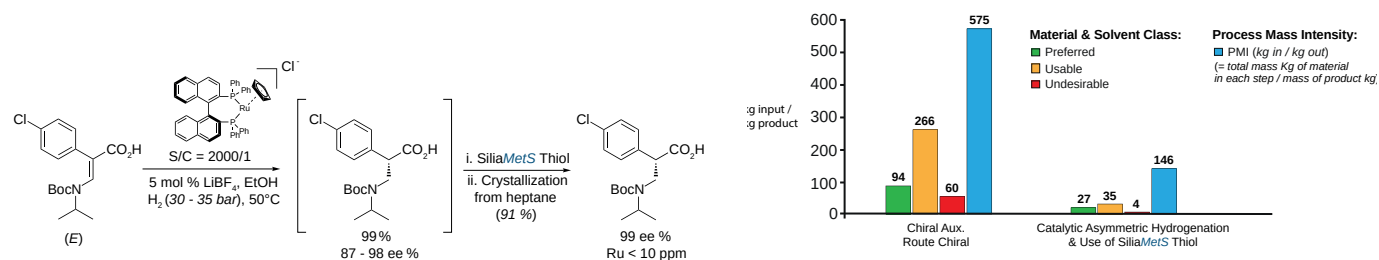
The aqueous layer was then basified to pH ≥ 12 with aqueous NaOH in order to extract the Ipatasertib free-base with DCM. The DCM solution was subsequently treated with charcoal and SiliaMetS Thiol to remove colored impurities and trace heavy metals resulting from previous synthetic steps.

These metals consisted in Palladium (*Pd/C catalyst in a Noyori Asymmetric Transfer Hydrogenation of ketone*), Ruthenium [(*R,R*) MsDPEN-Ru(*p*-cymene)Cl] catalyst for asymmetric ketone reduction] and Titanium (*TiCl₄ catalyst in asymmetric Aldol addition*).



In Akt inhibitor synthesis, Genentech describes a scalable catalytic asymmetric hydrogenation process for the multi-kilogram scale production of a β -amino acid, the last building block. An extensive catalysis screening and optimization study was done and identified a simple Ru-BINAP catalyst system to directly afford the *S* product in high enantiomeric excess and yield was reported.

The final process enabled the multi-kilogram production in > 99 % ee to be used as a key component for one of their clinical candidates.



Conclusion

For 138 kg of the crude amino acid, 8.3 kg of SiliaMetS Thiol were necessary. Filtration of the DCM solution over Celite® resulted in a 99 % yield of Ipatasertib free-base with a ruthenium content of less than 5 ppm (*ICP-OES*).

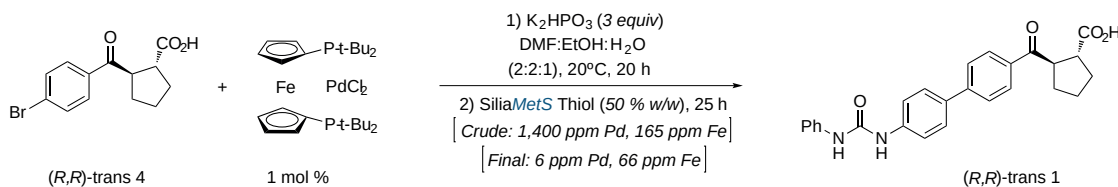
J. Lane, T. Remarchuk *et al.*, *Org. Proc. Res. Dev.*, **2014**, *18*, 1641-1651
Small Molecule Process Chemistry, Genentech, Inc., a member of the Roche Group, California, United States
Array BioPharma Inc., Colorado, United States

T. Remarchuk *et al.*, *Org. Proc. Res. Dev.*, **2014**, *18*, 1652-1666
Small Molecule Process Chemistry, Genentech, Inc., a member of the Roche Group, California, United States
Array BioPharma Inc., Colorado, United States

T. Remarchuk *et al.*, *Org. Proc. Res. Dev.*, **2014**, *18*, 135-141
Small Molecule Process Chemistry, Genentech Inc., A member of the Roche Group, California, United States
Catalysis and Chiral Technologies, Johnson Matthey, Cambridge United Kingdom
WuXi AppTec Co., Ltd., Shanghai, China

An Abbott Laboratories case study: palladium and iron removal using SiliaMetS Thiol

Abbott Laboratories published a paper on removal of palladium and iron impurities using SiliaMetS Thiol (50 % w/w). Thus, palladium and iron levels were 6 ppm and 66 ppm respectively. Although this final iron concentration was sufficient for the herein study, a much lower residual iron concentration can be achieved by optimizing the purification experimental conditions.

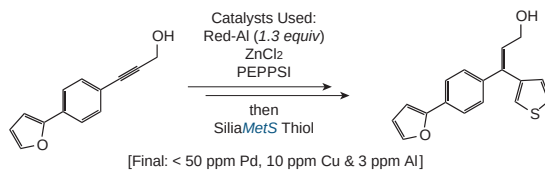


M. M. Ravn *et al.*, *P. Org. Proc. Res. Dev.*, **2010**, *14*, 417-424

Global Pharmaceutical R&D, Process Research & Development and Discovery, Abbott Laboratories, Chicago, Illinois, United States

A Johnson & Johnson case study: Sonogashira reaction & metal scavenging of various metals

Johnson & Johnson, in collaboration with Solvias, published a paper in which a mild Sonogashira reaction was developed using various metal catalysts. Treatment with SiliaMetS Thiol simultaneously removed Pd, Cu & Al. Residual concentrations were below 50, 10 and 3 ppm respectively, in the isolated product 3.



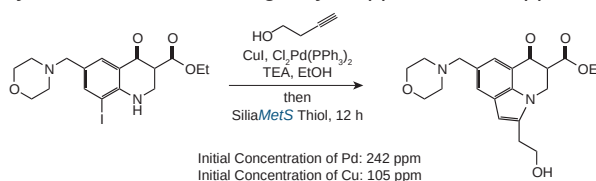
Note: copper comes from a previous synthesis step.

I. N. Houpis *et al.*, *Org. Proc. Res. Dev.*, **2009**, *13*, 598-606

Johnson & Johnson PRD, API Development, Belgium, and Solvias A.G., Synthesis and Catalysis, Switzerland

A Pfizer Global R&D case study: palladium and copper removal on a large scale batch using SiliaMetS Thiol

Pfizer published a paper on removal of palladium & copper impurities from a 20 kg pilot-plant batch. They made two subsequent treatments using SiliaMetS Thiol (20 % + 7 % w/w) at room temperature for 12 hours. After scavenging with SiliaMetS Thiol, the desired product was obtained with a yield of 76 %, containing only 17 ppm Pd and 1 ppm Cu.



An alternative method was also tried using 80 % w/w of Deloxan THP (*Degussa AG*) overnight followed by basification with Na_2CO_3 . Residual metal concentration with this method was higher compared to that of SiliaMetS and the yield was lower.

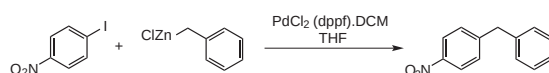
Scavengers	Residual Metal Concentration (ppm)		Yield (%)
	Pd	Cu	
Degussa Deloxan THP	20	2	60 - 70
SiliCycle SiliaMetS Thiol	17	1	76

SiliaMetS allows lower residual metal concentration & higher yield with fewer manipulations!

R. L. Dorow *et al.*, *Org. Proc. Res. Dev.*, **2006**, *10*, 493-499
Pfizer Global Research and Development, Michigan, United States

Multiple metal scavenging

SiliaMetS can be used to remove multiple metals in the same reaction with excellent efficiency.



The Negishi coupling presented in scheme above was performed to show that SiliaMetS can be used to simultaneously remove residual palladium, iron and zinc present after the reaction.

SiliaMetS	Pd	Fe	Zn
SiliaMetS Cysteine	95	> 99	98
SiliaMetS DMT	83	93	99
SiliaMetS Imidazole	84	91	97
SiliaMetS TAAcONa	97	> 99	> 99
Initial Concentration (in THF)	188 ppm	110 ppm	6 ppm

Conditions: 4 equiv of SiliaMetS (relative to palladium), 4 h, 22°C.

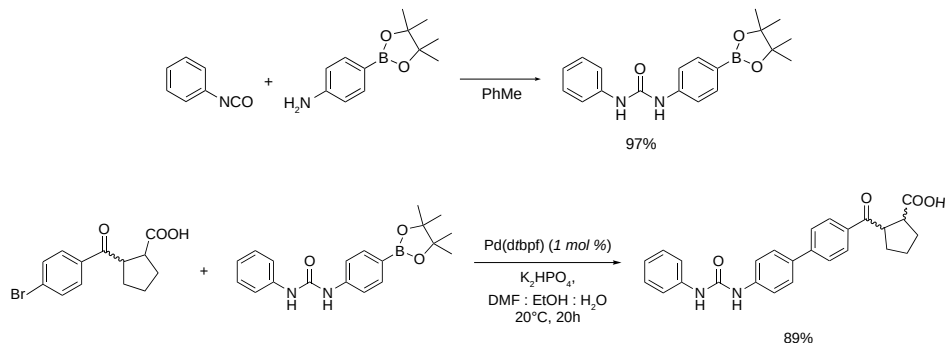
For Zinc removal, all tested scavengers gave excellent results. Overall, for multiple removal scavenging results, SiliaMetS Cysteine and TAAcONa showed to be the most versatile scavengers.

Scavenging of Pd(dtbpf) in Suzuki coupling for the synthesis of a DGAT-1 inhibitor

Diacyl glycerolacyltransferase-1 (*DGAT-1*) is one of two known isoforms that catalyse the final step of triglyceride biosynthesis and hence could play a role in the development of obesity and insulin resistance.

In a *DGAT-1* inhibitor synthesis project, a kilogram-scale Suzuki-Miyaura reaction was described by Abbott researchers in 2010.

This synthesis was reproduced in SiliCycle's labs and the resulting contaminated mixtures were treated with our most promising scavengers.



Effect of Time in the Scavenging Efficiency with 4 equiv. at 22°C (in %)

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
SiliaMetS Thiol	53	19	72	31	90	67
SiliaBond Tosic Acid	11	54	24	92	22	95

Effect of Time in the Scavenging Efficiency with 8 equiv. at 22°C (in %)

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
SiliaMetS Thiol	69	12	86	37	96	69
SiliaBond Tosic Acid	24	91	33	91	17	92

Effect of Time in the Scavenging Efficiency with 4 equiv. at 45°C (in %)
Treatment with 2 Scavengers Simultaneously: SiliaMetS Thiol & SiliaBond Tosic Acid

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
SiliaMetS Thiol & SiliaBond Tosic Acid	78	81	91	81	96	81

Conclusion

In this case again, it was SiliaMetS Thiol that proved to be the preferred scavenger for palladium under any conditions. As for iron, SiliaBond Tosic Acid was, again and by far, the most effective.

Scavenger combinations can achieve, in some cases, even higher removal of both metals. The best conditions were using 4 or 8 equiv at 22°C for 16h.

M. Ravn *et al.*, *Org. Proc. Res. Dev.*, **2010**, *14*, 417-424

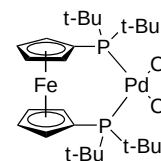
D. Barnes *et al.*, *Org. Proc. Res. Dev.*, **2009**, *13*, 225-229

Abbott Laboratories, North Chicago, Illinois, United States

Scavenging of Pd-118 using SiliaMetS metal scavengers

Some of SiliaMetS Metal Scavengers have a particularly powerful scavenging behavior toward reagent Pd-118.

Pd-118, or Pd(dtbpf)Cl₂ is a strong, homogeneous catalyst that has been shown to be very stable and active for all coupling reactions, especially aminations, reductive carbonylations and Suzuki couplings. Nevertheless, metals from this active catalyst can act as severe contaminants and be tricky to get rid of.



Pd-118 Complex

Behavior of SiliaMetS Metal Scavengers Toward this Specific Complex (*catalyst only in solvent*)

Scavengers	Scavenging Efficiency of Preliminary Screening (<i>in %</i>)									
	DMF, 22°C		DMF, 60°C		Methyl-THF, 22°C		Methyl-THF, 60°C		DCM, 22°C	
	Pd	Fe	Pd	Fe	Pd	Fe	Pd	Fe	Pd	Fe
SiliaMetS DMT	76	45	97	51	85	63	97	47	96	83
SiliaMetS Thiol	51	28	72	34	50	50	88	64	36	48
SiliaMetS Cysteine	59	49	67	49	70	60	93	52	53	50
SiliaBond Tosic Acid	25	47	8	54	70	69	85	83	80	78

Conditions: Palladium complex solutions were made in DMF, methyl-THF and dichloromethane, and shaken with 4 equiv. of metal scavengers for 4 hours, at room temperature or 60°C.

Scavenging Conclusion

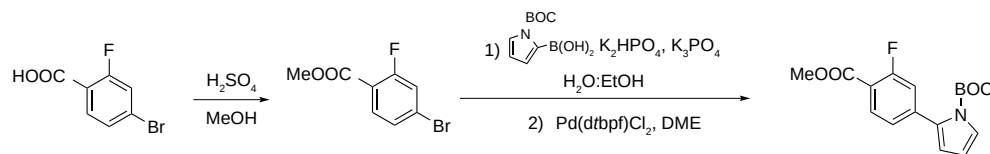
SiliaMetS DMT and Cysteine proved to be the preferred scavengers for Palladium (*Pd*) in this application.

As for Iron (*Fe*), SiliaBond Tosic Acid (SCX) was the best scavenger.

Furthermore, very good removal of both metals could be achieved through a combination of both scavengers.

Scavenging of Pd(dtbpf)Cl₂ in Suzuki coupling for the preparation of arylpyrrolidines

Abbott Laboratories has used Pd(dtbpf)Cl₂ for the preparation of arylpyrrolidines resulting in a final mixture contaminated with Pd and Fe.



SiliaCycle has used this latter synthesis as a control reaction to study the effect of our Metal Scavengers on such contamination. The final crude mixtures were treated with the most promising metal scavengers and further optimization was carried out.

Overview of Metal Residues Scavenging Efficiency (*in %*) in Various Experimental Conditions of a Suzuki Coupling for the Preparation of Arylpyrrolidines

Effect of Time in the Scavenging Efficiency with 4 equiv at 22°C (<i>in %</i>)						
Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
SiliaMetS DMT	78	44	89	51	98	35
SiliaBond Tosic Acid	34	65	34	70	36	86

Effect of Time in the Scavenging Efficiency with 8 equiv at 22°C (<i>in %</i>)						
Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
SiliaMetS DMT	90	53	94	56	96	47
SiliaBond Tosic Acid	31	85	32	89	33	91

Effect of Time in the Scavenging Efficiency with 4 equiv at 45°C (<i>in %</i>)						
Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
SiliaMetS DMT	81	57	90	58	95	34
SiliaBond Tosic Acid	27	81	28	85	29	89

Scavenging Conclusion

Clearly, SiliaMetS DMT proves to be the preferred scavenger for palladium. As for iron, SiliaBond Tosic Acid was by far the best reagent. A combination of scavengers can achieve, in some cases, stronger removal of both metals. The best results were obtained using 8 equiv of each scavenger at 22°C for 16 h.

M. Ravn *et al.*, *Org. Proc. Res. Dev.*, **2010**, *14*, 417-424
 D. Barnes *et al.*, *Org. Proc. Res. Dev.*, **2009**, *13*, 225-229
 Abbott Laboratories, North Chicago, Illinois, United States

SiliaMetS in aqueous conditions

Along with growing importance of sustainable chemistry and catalysis, SiliaMetS compatibility in aqueous conditions needed to be evaluated. As a preliminary exploration, palladium nitrate scavenging was tested at four different pH in various acidic medias. In purely aqueous conditions, SiliaMetS TAAcOH was the most compatible and efficient scavenger. However, in acidic conditions, apart from SiliaBond Tonic Acid, all scavengers showed good to excellent removal capability. Scavenging activity can either be driven by H₃O⁺ concentration (*pH*), or its counter-ion.

Scavenging (<i>in %</i>) of Pd(NO ₃) ₂ in Various Aqueous Conditions, 4 equiv at 22°C, 4 h				
Scavengers	H ₂ SO ₄ (1 M)	HNO ₃ (1 M)	AcOH (1 M)	H ₂ O
SiliaMetS Diamine	43	23	> 99	5
SiliaMetS DMT	> 99	> 99	> 99	15
SiliaMetS Imidazole	> 99	> 99	> 99	36
SiliaMetS TAAcOH	98	98	98	98
SiliaMetS Thiol	> 99	> 99	> 99	77
SiliaMetS Thiourea	> 99	> 99	> 99	35
SiliaBond Tonic Acid	19	6	76	28
SiliaMetS Triamine	55	49	96	10

Results illustrate well that the counter-anion (*and counter-cation*) plays a determinant role in the affinity of the resin toward palladium.

Experimental Conditions: an aqueous 250 ppm solution of Pd(NO₃)₂ was prepared in a volumetric flask. 8 mL of this solution was introduced in 10 mL polypropylene tube charged with four molar equivalents of a metal scavenger. All scavengers were treated identically. The tubes were shaken on the SiliCycle MiniBlock® orbital shaker for four hours. All solutions were filtered on separate tubes, and the remaining palladium was measured.

Other complexes were tested using the same method described as above for scavenging of Pd(NO₃)₂.

Various Metallic Complexes Scavenging (<i>in %</i>) & Concentrations in Aqueous Conditions, 4 Equiv at 22°C, 4 h					
Scavenger	RuCl ₃ [150 ppm]	K ₃ PtCl ₆ [250 ppm]	FeCl ₃ [250 ppm]	RhCl ₃ [250 ppm]	Pd(NO ₃) ₂ [250 ppm]
SiliaMetS Diamine	11	71	25	94	5
SiliaMetS DMT	0	97	6	68	15
SiliaMetS Imidazole	0	91	6	59	36
SiliaMetS TAAcOH	63	0	> 99	5	98
SiliaMetS TAAcONa	47	87	98	7	77
SiliaMetS Thiol	0	57	7	0	35
SiliaMetS Thiourea	0	92	9	34	28
SiliaBond Tonic Acid	52	87	> 99	98	99
SiliaMetS Triamine	14	61	13	92	10

Various Metallic Complexes Scavenging (<i>in %</i>) & Concentrations in Aqueous Conditions, 4 Equiv at 22°C, 4 h					
Scavenger	AgNO ₃ [250 ppm]	Ni(NO ₃) ₂ [250 ppm]	Sn(OTf) ₂ [250 ppm]	CuSO ₄ [250 ppm]	ZnSO ₄ [250 ppm]
SiliaMetS Diamine	74	43	47	93	58
SiliaMetS DMT	> 99	40	60	86	51
SiliaMetS Imidazole	90	25	39	64	39
SiliaMetS TAAcOH	> 99	84	93	99	86
SiliaMetS TAAcONa	97	96	73	94	95
SiliaMetS Thiol	96	6	6	0	0
SiliaMetS Thiourea	79	1	17	14	3
SiliaBond Tonic Acid	86	90	95	88	81
SiliaMetS Triamine	76	33	58	44	58

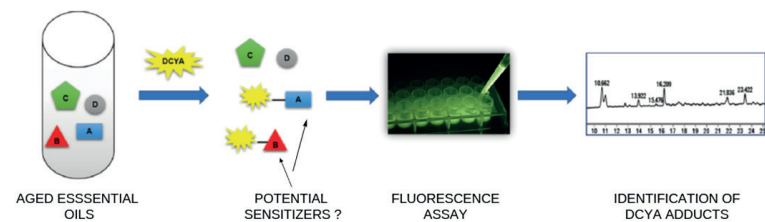
Conclusion

SiliaMetS TAAcONa has shown to have very good scavenging efficiency in aqueous media. SiliaMetS TAAcOH and SiliaBond Tonic Acid were also efficient. Generally speaking, many metal scavengers have demonstrated excellent performance in aqueous environment, even when bearing hydrophobic moieties.

SiliaBond trapping agent in the evaluation of tea tree essential oils as skin sensitizers

Authentic Tea Tree Oils (*especially aged ones*) have been identified as potential skin sensitizers. Thiols were used as trapping agents (DCYA) for isolation, characterization and identification of several possible DCYA-adducts, which can be used to deduce the structure of the candidate reactive species.

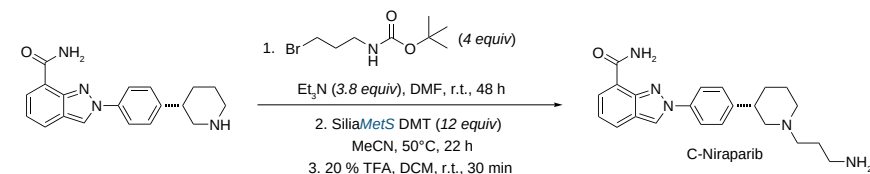
SiliaBond Maleimide was used to quench excess of thiols. Both SiliaBond Maleimide and Tosyl Chloride were tested, but SiliaBond Maleimide was found to be more selective in their experimental procedures.



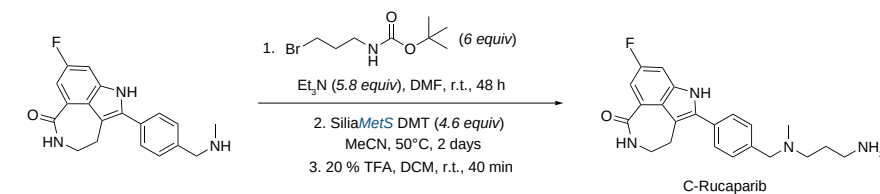
Further studies on detection and identification of potential ingredients of concern for skin sensitization were later conducted using SiliaBond Maleimide as a thio-scavenger in HTS-DCYA assays.

- I. Khan, I. et al. *Chem. Res. Toxicol.*, **2016**, *29*, 1108-1117
 - II. Khan, I. et al. *Chem. Res. Toxicol.*, **2016**, *29*, 1488-1492
 - III. Khan, I. et al. *Toxicol. in Vitro*, **2018**, *46*, 237-245
- University of Mississippi, Mississippi, United States

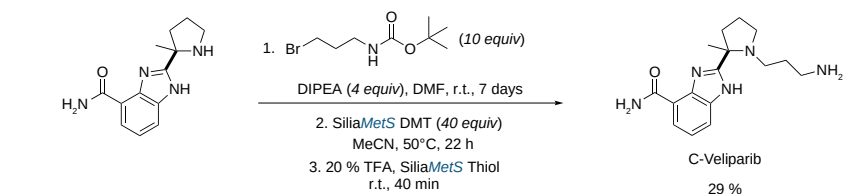
Proteome-wide profiling of clinical PARP inhibitors to reveal compound-specific secondary targets



Scheme 1



Scheme 2



Scheme 3

- Rix, U. et al. *Cell. Chem. Biol.*, **2016**, *23*, 1490-1503
- H. Lee Moffitt Cancer Center & Research Institute, Tampa, United States
University of California, Los Angeles, United States
University of South Florida, Tampa, United States

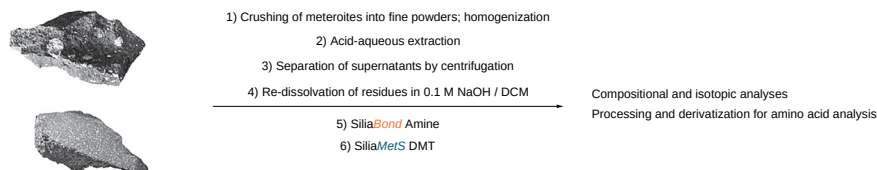
Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) are a promising class of targeted cancer drugs, but their individual target profiles beyond the PARP family, which could result in differential clinical use or toxicity, are unknown.

Using an unbiased, mass spectrometry-based chemical proteomics approach, a comparative proteome wide target map of four clinical PARPi was generated. SiliaMetS DMT and Thiol were useful as organic scavengers for three out of the four PARPi: Niraparib (scheme 1), Rucaparib (scheme 2) and Veliparib (scheme 3).

Aliphatic amines in Antarctic CR2, CM2, and CM1/2 carbonaceous chondrites amines

Meteoritic water-soluble organic compounds provide a unique record of the processes that occurred during the formation of the solar system and the chemistry preceding the origins of life on Earth. Hence, molecular, isotopic, and enantiomeric compositions of amines in Antarctic carbonaceous chondrites were studied.

SiliaMetS DMT & SiliaBond Amine were used to purify the organic compounds from carbonaceous chondrites.



Results provided information on the prebiotic synthesis of amines and amino acids and on the origins of homochirality on Earth.

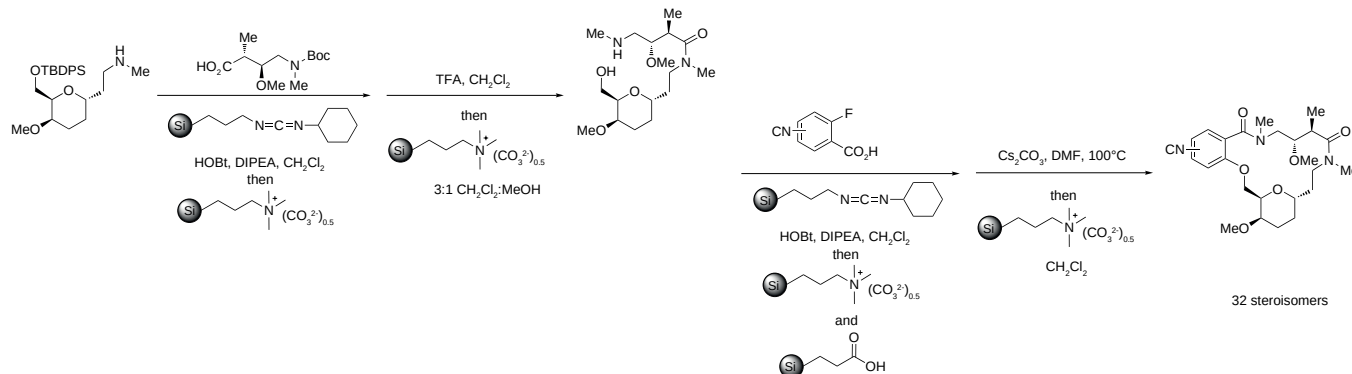
Aponte, J. C. *et al. Geochimica et Cosmochimica Acta*, **2016**, *189*, 296-311
Solar System Exploration Division, NASA Goddard Space Flight Center, Maryland, United States

A Broad Institute case study: ionic scavenging of acids with SiliaBond carbonate & scavenging of amines with SiliaBond carboxylic acid

In the context of the synthesis of a library of highly complex macrocycles with a pyran core, SiliaBond Carbonate (Si-CO₃) and SiliaBond Carboxylic Acid (Si-WCX) were used in the purification process.

In the reaction below, SiliaBond Carbonate was used to remove excess of the acidic acylating reagent, and used again in the next step to remove excess benzoic acid. Then, SiliaBond Carboxylic Acid was added to remove any excess N,N-Diisopropylethylamine or potential o-acylation by-products.

Purities of various macrocycles were between 70-92 %, with an average purity of 87 %.



General Procedures

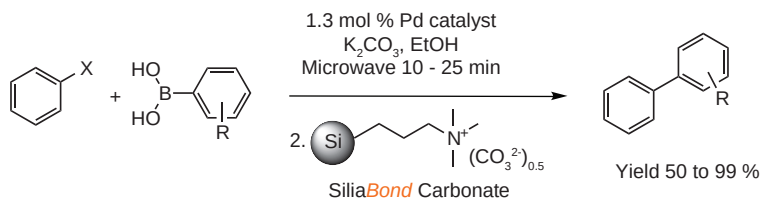
Acylation: The crude amino alcohols, cyano-fluorobenzoic acid 4-o or 4-p (0.14 mmol; 1.0 equiv), SiliaBond Carbodiimide (Si-DCC) (0.19 mmol; 1.4 equiv) and DIEA (0.090 mmol; 0.7 equiv) were combined in 2 % dimethylformamide (DMF / DCM 3.0 mL), and stirred at room temperature overnight. In cases where acylation is slow, additional Si-DCC (0.19 mmol; 1.4 equiv) and a solution of HOBT (0.03 mmol; 0.2 equiv) in DMF / DCM (1.0 mL) and DIEA base (0.03 mmol; 0.2 equiv) were added. After acylation was deemed complete, reactions were scavenged with Si-CO₃ (0.18 mmol; 1.4 equiv) and Si-WCX (0.18 mmol; 1.4 equiv) for 30 min and then filtered and evaporated for 4 h.

SNAr Macrocyclization: All crude products from above were dissolved in DMF (4.0 mL) and heated at 110°C with Cs₂CO₃ (approximately 0.61 mmol; 4.5 equiv for 4 h). Reaction mixtures were filtered through Celite, washed with DCM, and solvents evaporated. Crude products were dissolved in DCM and treated with Si-CO₃ (0.18 mmol; 1.4 equiv) and Si-WCX (0.18 mmol; 1.4 equiv) for 30 min, and then filtered through Celite and concentrated.

E. Comer *et al., Proceedings of the National Academy of Sciences of the United States of America*, **2011**, *108*, 6751-6756
Chemical Biology Platform, Broad Institute, Cambridge, MA 02142

An Abbott case study: ionic scavenging of boronic acids with SiliaBond carbonate

An efficient Suzuki coupling protocol was developed and excess boronic acids were rapidly removed using solid-phase extraction and SiliaBond Carbonate to yield clean product.



General Procedure

A Smith Process vial was charged with a stir bar, 4-bromobenzonitrile, p-tolylboronic acid and 2 mL of ethanol. A solution of 1 M K₂CO₃ was added followed by the Pd catalyst. The reaction vessel was sealed and heated to 110°C for 10 minutes under microwave irradiation.

After cooling, the reaction mixture was transferred to a pre-packed column of SiliaBond Carbonate which had been conditioned with MeOH / CH₂Cl₂ (1:1), and the eluent was collected via gravity filtration.

The column was then washed with MeOH / CH₂Cl₂ (1:1) (3 × 3 mL).

The eluents were combined, concentrated and purified by flash chromatography to yield a purified compound.

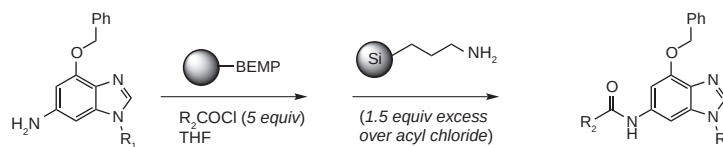
Scavenging Boronic Acids Results (<i>in</i> %)				
# of Equiv				
10	> 97	> 97	> 97	> 97

Y. Wang, D. R. Sauer *et al.*, *Org. Lett.*, **2004**, *6*, 2793-2796

High-Throughput Organic Synthesis Group, Global Pharmaceutical R&D, Abbott Laboratories, Illinois, United States

A Roche case study: nucleophilic scavenging of acyl chlorides with SiliaBond Amine

The guanine synthesis started with the simple and direct acylation of O-benzyl-2-aminopurine with polymeric BEMP. This convenient acylation approach using polymeric base was attempted in order to avoid the laborious Mitsunobu reaction introducing N9 substituents and tedious aqueous work-up steps. SiliaBond Amine was used to sequester the excess acyl chloride instead of using polystyrene-based trisamine resins.



General Procedure

SiliaBond Amine (1.5 equiv) was added to the reaction mixture and stirred for 1 h at room temperature.

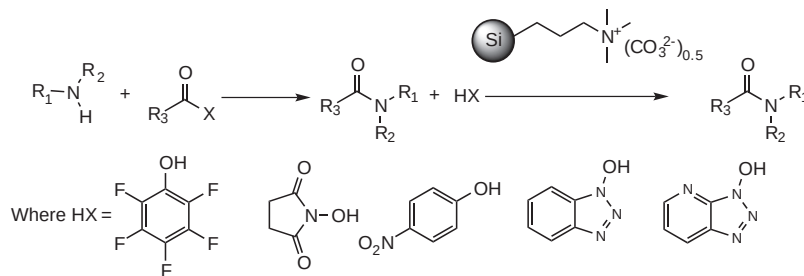
The SiliaBond Amine scavenger with bound acyl chloride was then filtered off and rinsed with solvent (e.g.: MeOH) to yield an acyl chloride-free solution.

K. Kim *et al.*, *Tett. Lett.*, **2000**, *41*, 3573-3576

Roche Research Center, Hoffmann La-Roche, Inc., Nutley, NJ, USA

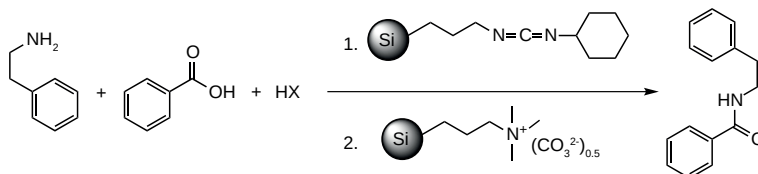
Ionic scavenging of phenols and acids with SiliaBond carbonate

The efficiency of SiliaBond Carbonate as a scavenger of various coupling reagents (HX) - including pentafluorophenol, N-hydroxysuccinimide (HOSu or NHS), 4-nitrophenol, 1-hydroxybenzotriazole (HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt) - was studied, as well as a comparison with two suppliers of polymer-supported carbonate.



Phenol Scavenging Results (in %)						
HX	SiliaBond Carbonate		Polymer 1		Polymer 2	
	5 min	60 min	5 min	60 min	5 min	60 min
Pentafluorophenol ¹	98	98	92	95	85	94
N-Hydroxysuccinimide	93	> 95	41	64	40	42
4-Nitrophenol	94	96	89	95	77	88
1-Hydroxybenzotriazole ²	88	96	68	92	26	96
1-Hydroxy-7-azabenzotriazole ²	97	97	72	96	30	92

Initial concentration: 5,000 ppm - 3 equiv of SiliaBond Carbonate. Analyzed by UV. 1 Analyzed by GC-MS, 2 in THF.



Benzoic Acid Scavenging Results (in %)		
HX	Yield	Purity
No Catalyst	35	95
N-Hydroxysuccinimide ¹	67	98
1-Hydroxybenzotriazole ²	99	98
1-Hydroxy-7-azabenzotriazole ²	100	99

Note: 1.0 equiv of amine, 1.5 equiv acid, 1.7 equiv catalyst (HX), 2.0 equiv SiliaBond Carbodiimide, 7.0 equiv SiliaBond Carbonate. Yield refers to the mass of isolated product. Purity was determined by GC-FID. 1 in DCM, 2 in THF.

Conclusion

For each of the various experimental conditions / coupling reagents that were tested, SiliaBond Carbonate yielded better to much better scavenging results than its polymer-bound Carbonate equivalents.

SiliaBond Carbonate was also very useful in the scavenging of benzoic acid, in the following amide coupling, using SiliaBond DCC as a coupling reagent.

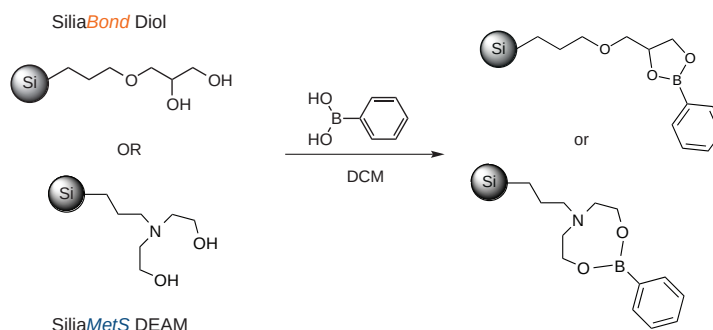
Nucleophilic scavenging of boronic acids with SiliaBond Diol, SiliaBond Carbonate and SiliaMetS DEAM

Boronic acids and their derivatives are one of the most widespread intermediates and reagents in organic and medicinal synthesis. On-the-market drugs have even been adding boron atoms to enhance compatibility, selectivity and potency to their target molecules.

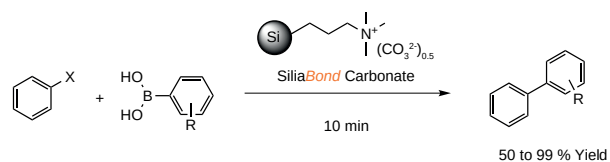
Up to very recently, boronic acids had always been reported as lacking apparent toxicity, mutagenic activity or in vivo instability issues. New studies have raised objections about this safe toxicological profile, both based on experimental and clinical data.

This is major in the chemical and pharmaceutical industry, as more and more studies denounce the genotoxicity of boronic acids. Today, in view of new data concerning boronic acids, there is pressure building on the ICH steering committee to assess boron compounds as potential genotoxic impurities (PGIs) per ICH M7.

Scavenging Boronic Acids Results			
Scavengers	# Equiv	Time	Efficiency (%)
SiliaMetS DEAM	4	1 h	> 99
SiliaBond Diol	4	1 h	> 99



Scavenging Boronic Acids Results				
Scavenger	# Equiv	Boronic Acid	Time	Efficiency (%)
 SiliaBond Carbonate	10		10 min	> 99
	10			> 99
	10			> 99
	10			> 99



All % of scavenging are determined by GC-MS

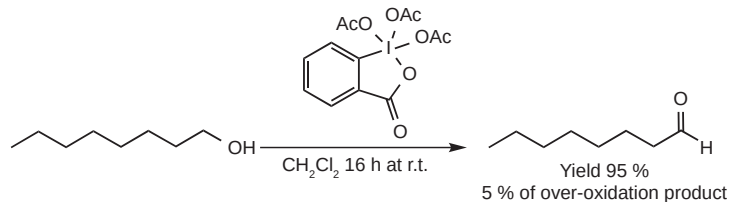
Depending on ones' needs, all three scavengers gave excellent scavenging results and showed to be an efficient and fast method for the removal of boronic acids.

SiliaMetS DEAM and SiliaBond Diol are both excellent scavengers for Catch & Release: i.e., when the molecule of interest is temporarily bound either ionically or covalently to a functionalized silica and subsequently released, once all undesirable impurities were washed out.

Ionic scavenging of 2-iodobenzoic acid with SiliaBond TMA Acetate and SiliaBond Carbonate

Dess-Martin Periodinane (DMP) is a mild and chemoselective oxidant. It is readily accessible, environmentally benign and has a good shelf-life. Furthermore, the ease of handling, simple reaction work-up, product purification and good yields obtained with DMP make it a valuable reagent in organic synthesis.

2-Iodobenzoic acid is the degradation product from DMP formed during the work-up. Most of it can be removed with a basic work-up, but sometimes, it can be difficult to get rid of all this side product.



General Procedure

A solution of 1-octanol (1.00 mmol; 1.0 equiv) in CH_2Cl_2 (6 mL) at room temperature, was added to DMP (1.10 mmol; 1.1 equiv). The reaction mixture was stirred for 16 h, then diluted with 35 mL of MTBE and poured in 20 mL of an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (25 %). The mixture was stirred for 10 min. Another portion of 35 mL of MTBE was added for the liquid-liquid extraction. The MTBE phase was then washed with water and a saturated aqueous solution of NaCl (10 mL) and dried on MgSO_4 .

Scavenging was done using SiliaBond TMA Acetate or Carbonate, both in bulk (1 g) and SPE cartridge (6 mL / 1 g) for comparison purposes. Each sample was washed or eluted with a fresh portion of MTBE (8 mL) and then the 2-iodobenzoic acid concentration was monitored by GC-MS against an internal standard. The over-oxidation product (carboxylic acid) was successfully scavenged using all products and formats.

Scavenging of 2-Iodobenzoic Acid Results (in %)		
Scavenger	Bulk	SPE
SiliaBond TMA Acetate	100	100
SiliaBond Carbonate	100	100

Have a Scavenger Success Story?

Interested in sharing your scavenging application as one of our customer success stories? We would love to hear from you!

To get started, simply send us an email at scavengers@silicycle.com with your project details. Details can include project title, challenges faced, project info such as a procedure and results, and of course how SiliaMetS made an impact. Bullet point is fine and the more details the better!

A member of our team will then contact you to get more information if needed and send over a first draft of your Case Study for you to review plus provide any feedback. Once you are satisfied and have approved the final draft, we will then share it for others to learn from!

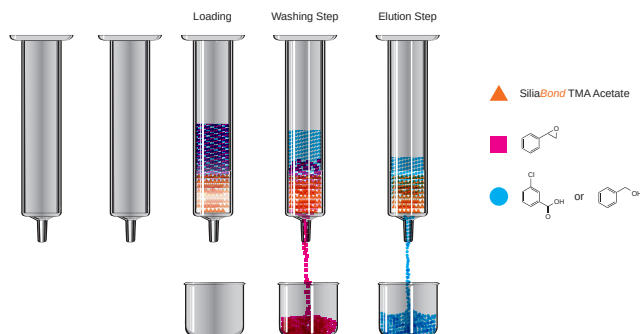
Carboxylic acids purification with SiliaBond TMA Acetate

SiliaBond TMA Acetate is an ion exchange media useful to extract organic anions from organic or inorganic matrices. It is less selective than SiliaBond TMA Chloride. The acetate anion being more labile than the chloride, it therefore retains more easily acidic compounds with pK_a in the range of 4 - 5, such as carboxylic acids.

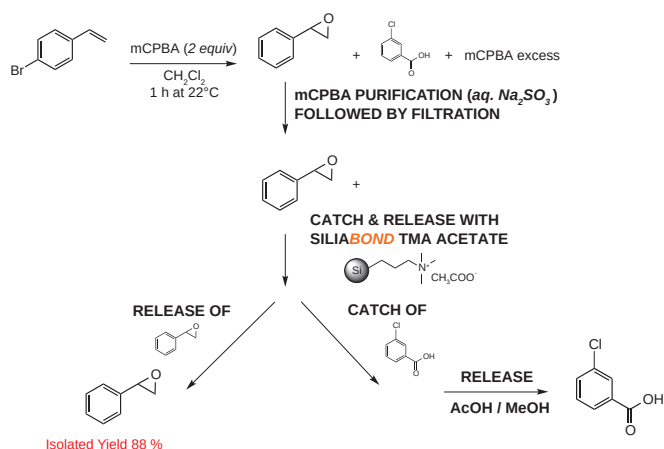
12 mL cartridges were filled with 2 or 4 g of SiliaBond TMA Acetate (loading of 1 mmol/g, for an equivalent of about 4 mmol of active function). They were tested with quantities of 1 and 2 mmol of each selected acid.

General Procedure for Catch & Release Purification

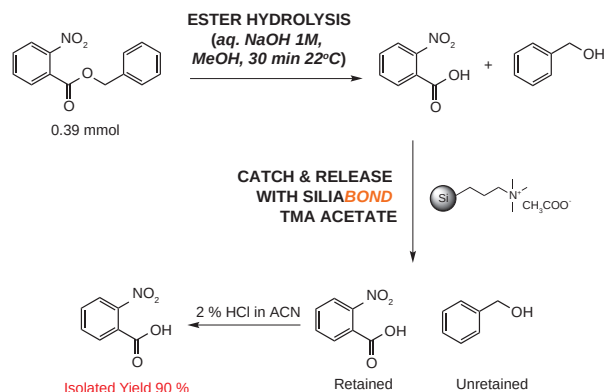
- 12 mL cartridges (2 or 4 g of SiliaBond TMA Acetate) were conditioned with 6 mL of MeOH.
- Compound was dissolved in 1 - 2 mL of MeOH and loaded onto the cartridge.
- Column was washed with 15 mL of MeOH.
- Compound was released with a solution of AcOH / MeOH : 2/98.
- Solvents were evaporated and final compound weighted.



3-Chlorobenzoic Acid Purification Via Catch & Release



Ester Hydrolysis Purification Via Catch & Release



Conclusion

Epoxidation reactions with 3-chloroperbenzoic acid (*mCPBA*) often yield after treatment of the reaction a certain undesirable amount of 3-chlorobenzoic acid, which can sometimes be difficult to separate from the desired product.

In the present example, 4-bromostyrene was treated with *mCPBA*, and the reaction medium is then treated with an aqueous solution of sodium sulfite. The latter allows to destroy excess reagent and eliminates much of the 3-chlorobenzoic acid correspondent. After extraction with dichloromethane and evaporation, the product was loaded on a 12 mL TMA Acetate SPE cartridge of 2 or 4 g. A simple elution with methanol made it possible to isolate 88 % of the desired epoxide product. Similarly, the same strategy was applied for the purification of 2-nitrobenzoic acid after hydrolysis of benzyl-2-nitrobenzoate, to yield the former molecule in a 90 % final yield.

In conclusion, SiliaBond TMA Acetate is very useful for the purification of carboxylic acids. Conversely, it may free the reaction media from compounds having a pK_a lower than 5.

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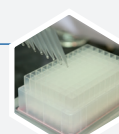
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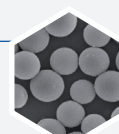
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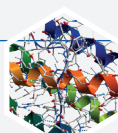
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