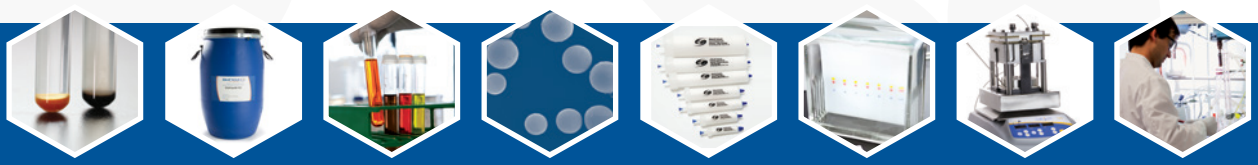
GUIDE FOR CHEMICAL SYNTHESIS & PURIFICATION



SILICYCLE Inc.®
UltraPure SILICA GELS

SiliCycle Guide for Chemical Synthesis & Purification

About SiliCycle

We provide solutions to the global chemical industry.

Founded in 1995, SiliCycle® Inc. is a worldwide leader in the development, the manufacturing and the commercialization of high-value silica-based and specialty products for organic chemistry, chromatography and analytical chemistry. Our business extends to more than seventy five countries and our customer portfolio includes companies in a wide range of markets.

At SiliCycle, we are at the forefront of the chromatography industry, owing to the extraordinary purity of our silica gels and polymeric sorbents, combined with our capacity to rapidly adapt our products to meet the specific requirements of scientists worldwide. Our customers benefit from our expanded global footprint, with international sales offices & warehouses (*Canada, United States, China, India, France & Germany*).

We lead the way in offering innovative first-rate *UltraPure* products. Our automated manufacturing processes are continuously optimized to ensure high purity and a low percentage of fine particles, thereby guaranteeing optimal performance. With our multi-ton manufacturing capacity, we are your partner of choice for all your metal removal, catalysis, synthesis, analysis and purification requirements.

SiliCycle is also a firm believer in the importance of investing in scientific discovery and people. This is why we created an accelerator center for businesses growth and mentorship. We are proud to be part of an ecosystem that's dedicated to innovation in chemistry.

SiliCycle is also a leading service provider, offering turnkey solutions based on its expertise in organic chemistry, material science and analytical chemistry to name only a few. With state of-the-art instrumentation in the areas of chromatography, spectroscopy and manufacturing combined to an applications support laboratory, we are devoted to extend your R&D and make your project a success.

We are committed to providing you with the highest quality products and services in the industry.

Information about SiliCycle is available at www.silicycle.com

Follow us and get our news, updates and promotions!

https://www.facebook.com/silicycle
@SiliCycle_Inc
https://www.linkedin.com/company/silicycle

Photo: Stéphane Groleau

Word from the President

« We are proud to present you our new catalog designed for the pharmaceutical industry. It was specifically tailored for the players in the fields of synthetic organic chemistry, combinatorial synthesis, medicinal drug discovery, drug development and drug manufacturing. »

Dear valued customers,

Hugo St-Laurent
President & CEO

2015 marked the anniversary of the first 20 years of SiliCycle. WOW! So many roads traveled and paths crossed since 1995. We've lived through our share of failures and successes, of fires and explosions, of discoveries and patents, of unexpected sales and non-quality returns, of hiring amazing people and sometimes having to dismiss others, of relocations and the construction of our manufacturing facility, of starting sales in Europe and in Asia and hiring our first US employees, of sales to universities followed by sales to a few biotechs and then to all the pharmaceutical industry. What joy it has been to build our company from A to Z!

Actually, that's not true, we have not reached Z yet! But know that we are incredibly proud of SiliCycle, a manufacturing company that today sells its products and services in over 75 countries. And this pride, we owe to you, dear customers, who show your confidence in SiliCycle products with every purchase and every time you refer a customer to us, or when you allow us to grow and improve ourselves through your suggestions, ideas and testimonials.

All our worldwide offices (*Canada, U.S.A., Europe, India and China*) are managed by local, Ph.D.-level staff on hand to better serve you in real time. From Toronto to Seoul, from San Francisco to London or Tokyo, at SiliCycle, we are committed to delivering the same quality products and services, no matter where you are. Our ISO 9001:2008 certification is a testimony to the importance we place on quality. In response to our international growth and to support the consequent increasing demand, we are increasing our manufacturing plant which was inaugurated in March 2009. We are thrilled to announce that this expansion should be completed by the end of 2016.

Following our acquisition of BTR Separation, a previous asset of LGSQ, in 2012, SiliCycle also acquired Chromatography Sciences Company (*CSC*) Inc., a Canadian pioneer in the manufacturing of HPLC columns in North America. With this acquisition, all manufacturing operations, equipment and know-how of CSC were transferred to SiliCycle, including key personnel of CSC and its President. This has enabled us to truly polish our HPLC expertise and manufacturing capabilities, as well as consolidate our position in the analytical business segment. Thanks for showing us your confidence by ordering a prep or analytical HPLC column.

As a partner of choice for your metal removal, purification, catalysis, analysis and synthesis needs, we offer you a full range of products available in all the formats requested by the industry, making us a true *"One stop shop"*. In this catalog, you will find all the information you need to choose the right products for your applications.

Yet, SiliCycle is so much more than just products. SiliCycle's laboratories and production facility offer high-throughput, high quality R&D services catering to several areas - but not limited to: metal & organic scavenging screenings, immobilization of molecules, development on new synthetic routes, development of scalable processes for APIs, new analytical method development, HPLC packing services, extraction / purification of natural products, customized mesostructured materials and so on. Whatever stage you are at in the product development process, it is never too early or late to benefit from our input to ensure that things are on track. Trust SiliCycle as your very specialized CRO / CMO.

Hopefully, you will enjoy this new catalog and it will become a reference tool for you, which was the goal we set for ourselves when we designed it. Finally, and most of all, I want to thank you for your trust and business over all these years, your loyalty, your suggestions, your comments and your encouragement; they allow us to grow year after year and differentiate ourselves in a positive way.

Sincere thanks from the bottom of our hearts!

Hugo St-Laurent
President & CEO

Word from the Vice-President, R&D

Dear fellow scientists,

François Béland
Ph.D., Chemist,
Vice-president, R&D

I am proud to present our new catalog. The making of which is an enormous job in itself, thanks to Ms. Geneviève Gingras (*Marketing Director*) and her team. But there is also a lot of work involving the R&D group. We have worked hard to develop new products and applications that we are sure will be of help to you. They were developed by listening to you, our partners and customers.

For all of the researchers, chemists, students and other scientists in drug discovery, drug development and production, and University laboratories, we have silica-based products that will meet and exceed your chromatography, purification and synthesis needs.

Over the years, we have developed extensive knowledge of silica gel and the ways it can be modified to meet the demands of diverse applications. From chromatography phases for your most demanding separations to metal scavengers used in the selective removal of spent catalysts from active pharmaceutical ingredients and our new Silia*Cat* catalysts, we have products that make running your applications easier.

We are also able to make custom phases for you. We have already anchored small molecules, peptides, sugars and even enzymes for different customers. If your project would benefit from special silica-bound materials, contact us; we are up to the challenge!

Finally, beside our products and applications that you will find in this catalog, we offer a wide range of R&D services. We can develop chromatographic methods, purify compounds, identify impurities, screen and remove spent catalysts (*Pd and other metal traces*) from APIs, synthesize small molecules, etc., and we offer a wide range of analytical services. If you require help on a project, please contact me and give us a chance to help you.

All my best,

François Béland
Ph.D., Chemist,
Vice-president, R&D

SiliCycle, your Partner from R&D to Commercialization

As a worldwide supplier of premium silica-based products for research & production, SiliCycle has become a value-added, strategic sourcing partner for its customers. At SiliCycle, we truly understand the needs and challenges you encounter when trying to satisfy both the regulatory requirements and the need for economical validated manufacturing. Listed below are some of the solutions SiliCycle provides to better serve you.

- **On-time Delivery**
  As a critical component supplier, SiliCycle understands the importance of maintaining and managing its inventory. As a manufacturer of hundreds of tons of silica-based products, you can feel confident that we will deliver your product on-time.

- **Batch Reservations**
  For our customers that do not have the storage capacity, SiliCycle can reserve specific batches of finished product and ship upon request.

- **Packaging sizes**
  The wide range of available packaging sizes and formats help eliminate waste and reduce release testing.

- **Batch Sizes**
  SiliCycle's proprietary manufacturing processes can easily be scaled-up to meet the batch size requirements of its customers.

- **Customized Products**
  Since SiliCycle controls the manufacturing process, we can customize the particle size distribution, loading, defined water content and any other specification our customers require.

- **Regulatory Filing**
  SiliCycle will work with your quality team to provide the necessary documentation and specific analytical testing needed for your regulatory filings.

- **R&D Services**
  Under a Non-Disclosure Agreement (*NDA*), we will screen a customer's metal contaminated reaction mixture against our Silia*MetS*® Metal Scavengers to determine the best scavenger and conditions. We can also help you with your synthesis or purification challenges. A full report is included, which provides all the data necessary to select the best option based on your project's requirements and constraints.
  For more information please consult the R&D Services chapter page 287.

A Global Presence

On time and fast delivery of raw materials is crucial and is a key of success to ensure project's timeline. SiliCycle has a dedicated procurement team and over the time, we developed an extensive sourcing network around the world.

SiliCycle as Your Worldwide Supplier

Having a local presence wherever our customers are is important. With direct sales and distributors all over the world, SiliCycle can ensure that every customer receives the best service and support possible.

All our products are available worldwide.

If you want to get the contact of your area's sales manager, go to http://www.silicycle.com/contact-us

SiliCycle has sales offices in America, Europe, India and China. Our representatives are always available for any technical request, sale inquiry or for a meeting.

Furthermore, SiliCycle optimizes its delivery time through its distributors' logistics and by establishing its own storage facility in Europe.

At SiliCycle, our team of local representatives, international account managers and technical support work together as a connected network to offer the best customer experience possible.

SiliCycle Inc. Worldwide Headquarters and Factory

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SiliCycle European Office & Storage Facility

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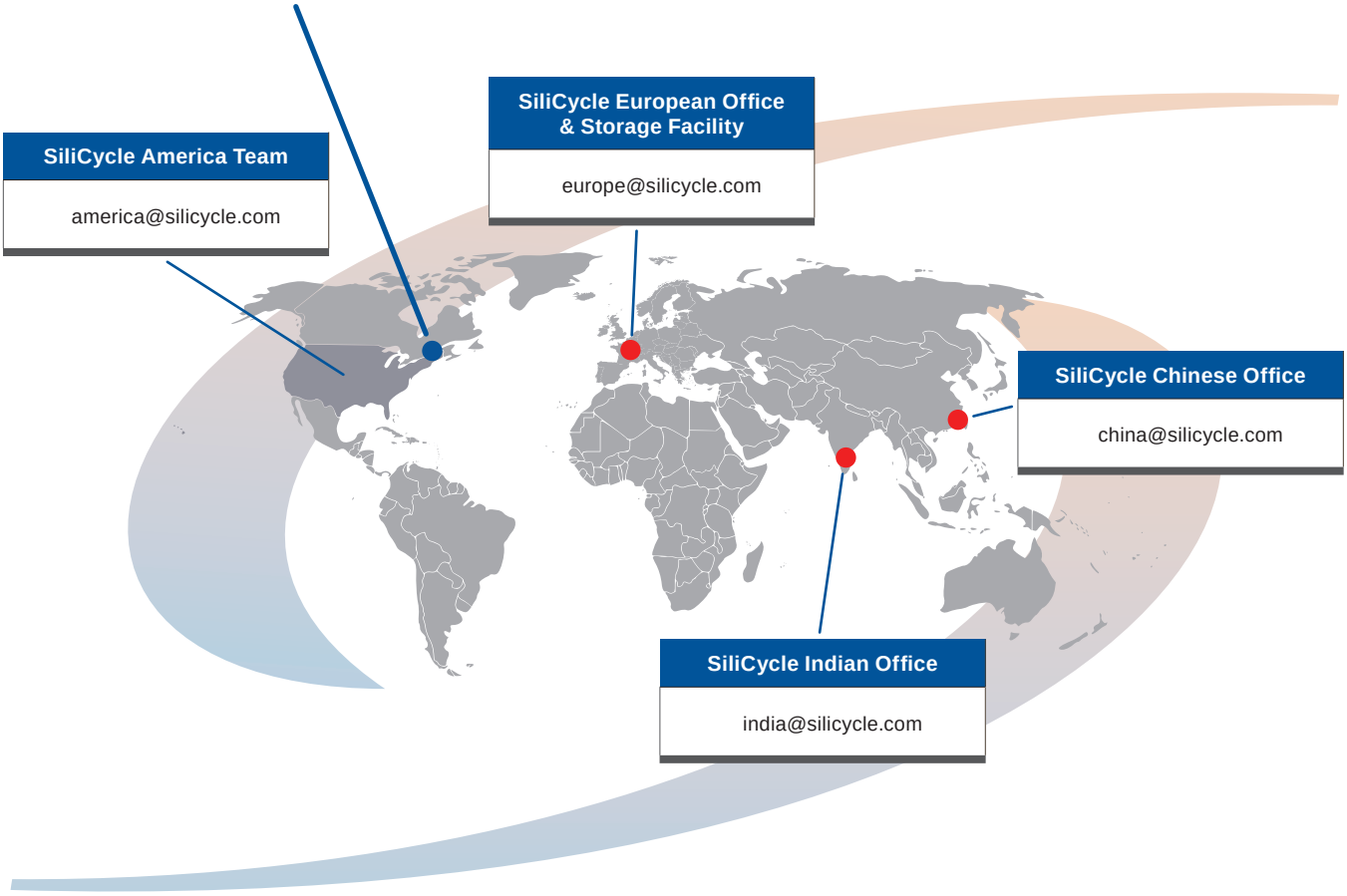


SiliCycle Chinese Office

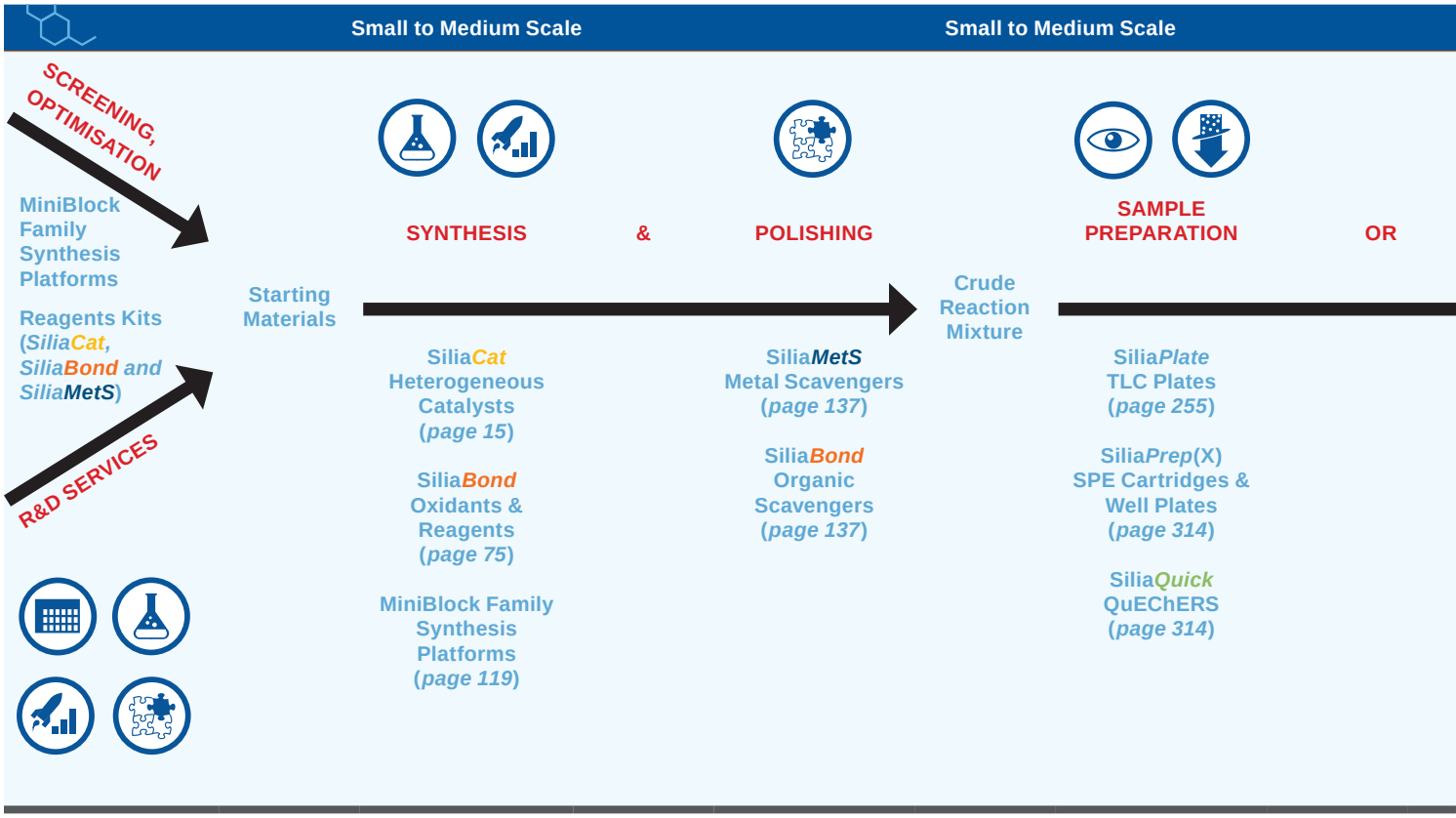
china@silicycle.com

SiliCycle Indian Office

india@silicycle.com

SiliCycle's Spheres of Activity

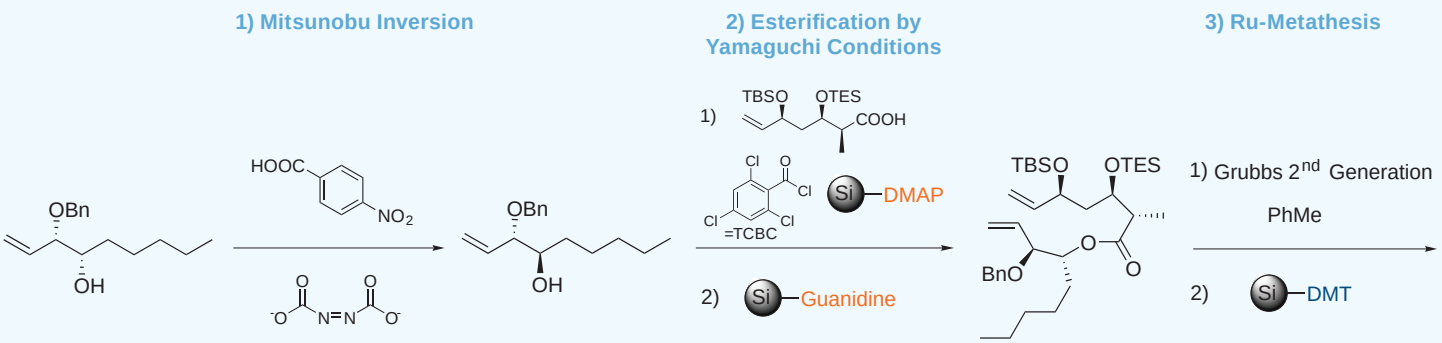
See how SiliCycle's products can help you at every step of your synthesis.



Screening | Chemical Reaction | Catalysis | Scavenging

Example of Reaction You Could Conduct With Our Products

Total Synthesis of Cytospolide P (*Anti-Cancerous Properties*)



SiliaBond DMAP: Heterogeneous Reagent

SiliaBond Guanidine: Scavenger of TCBC

SiliaMetS DMT: Scavenger of Ru

Small to Medium Scale

PURIFICATION

SiliaFlash (Irregular) & SiliaSphere PC (Spherical) Silica Gels (page 213)

SiliaBond Chromatographic Phases (page 225)

SiliaSep Flash Cartridges (page 225)

→ Pre-Purified Sample

ANALYSIS

SiliaChrom HPLC Columns (page 316)

→ Compound of Interest (mg scale)

Large Scale

INDUSTRIAL PROCESS

SiliaSep BT Process Flash Cartridges (page 247)

SiliaSphere Spherical Silica Gels (page 315)

SiliaChrom Preparative Columns (page 316)

→ Compound of Interest (g to kg scale)

CONFIRMATION

→ Analytical Services (page 300)

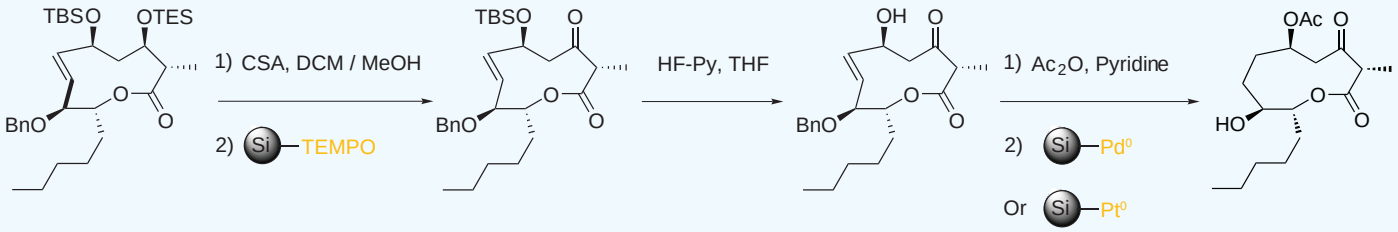
Monitoring | Purification | Identification

Total Synthesis of Cytospolide P (*Anti-Cancerous Properties*)

4) Cleavage of TES
5) Oxidation

6) Cleavage of TBS

7) Acetylation
8) Hydrogenation



SiliaCat TEMPO: Heterogeneous Catalyst

SiliaCat Pd⁰ or Pt⁰: Heterogeneous Catalysts

Importance of Quality Control

The Quality Control Department's objective is to provide default-free products. In light of this goal, we have determined the critical points that need to be addressed for each product line. These points are based on customers' and account managers' recommendations as well as on our employees' scientific knowledge and industry standards.

Each product family has its own quality control procedures, which are strictly adhered to. QC test results are checked and confirmed before being cleared for shipping. Complete procedures for each product line are available upon request.

SiliCycle is committed to high quality standards. Every product meets or exceeds the quality specifications our customers demand. All products are shipped with the following information, and a sample from every batch is kept for subsequent analysis:

- Certificate of Analysis (*molecular loading, surface coverage, volatile content, etc.*)
- Material Safety Data Sheet (*MSDS*)
- Technical information

Furthermore, all products can also be shipped with the following information, when requested:

- BSE / TSE Declaration (*non animal-derived*)
- GMO-Free Certificate
- Melamine-Free Certificate

Please do not hesitate to contact us if you have any questions or concerns about the product you have received.

Bare Silica Gel

The backbone of most of SiliCycle's products is Silia*Flash* F60 (*40 - 63* µm, *60 Å*) silica gel. It provides superior performance for chromatographic applications due to its narrow particle size distribution and high purity.

Before functionalization, every silica is rigorously characterized and analyzed by the procedures listed below to ensure lot-to-lot reproducibility.

Functionalized Silica Gel

The process for functionalizing the silica is highly dependent on the group being attached. In most cases, it is possible to functionalize 90 % of the surface, verified by ^{29}Si MAS NMR. The remaining 10 % of the surface may be endcapped to provide a completely inert support. After being functionalized, the product is submitted to further analysis and quality control as outlined.

Regulatory Support File

SiliCycle can work with you to fill and provide customized regulatory documents, including specific analytical tests in line with your needs.

Our Regulatory Support Files (*RSF*) are documents that include both proprietary and non-proprietary information on performance, chemical / thermal / mechanical stabilities, extractable & leachable compounds, SOPs, scale-up procedures, batch history, analytical methods and even more. RSF documentation can be obtained through a Non-Disclosure Agreement (*NDA*).

For any inquiries, please contact:
regulatorysupport@silicycle.com

Quality Control	
Type of Analysis	**Performed by:**
Bare Silica Gel	
Carbon, nitrogen & sulfur content	Elemental analyzer
Total trace metal	ICP-OES, ICP-MS
Surface area & porosity	Nitrogen adsorption analyzer
Particle size distribution	Laser light diffraction, sieving
Tapped density analysis	Density measurement
Water content	Moisture balance
pH	pH-meter
Functionalized Silica Gel	
Residual solvent content	Moisture balance
Specific reactivity analysis	GC-FID, GC-MS, LC-MS/MS, ICP-OES
Organic function signature	Infrared spectroscopy
Purity analysis	GC-MS

Analysis Descriptions

Elemental Analysis of Organic Compounds

Silia*Flash* silica gel has a very low organic content. All lots are subjected to elemental analysis to determine the carbon, nitrogen and sulfur levels.

Total Trace Metal Analysis

To improve the quality of the separation, SiliCycle manufactures silica gels with very low trace of metal content. All silica gels are analyzed for more than 45 metals by ICP-MS down to ppm and reach up to 99.4 % silica purity. This minimizes any issues from metal oxides that may act as Lewis acids and prevents «tailing» of most polar compounds (*frequently ionizable*) that can be caused by silica with a high metal content.

Surface Area and Porosity Analysis

The efficiency and reliability of silica gel depend on its surface condition. We use the Brunauer, Emmet and Teller analysis to determine the surface area, and the Barret-Joyner-Hatenda method to determine the pore diameter and pore volume. A larger surface area results in more contact or interaction with the analyte, thereby increasing the segregation of different products. Pore diameter and pore volume permit semi-exclusion chromatography where smaller molecules fit into pores more easily than larger ones. This justifies the use of several types of silica to achieve better discrimination in chromatographic separations.

Particle Size Distribution Analysis

Particle size distribution is determined by laser diffraction or sieving. Usually, more than 90 % of the silica gel is within the appropriate range.

Water Content Analysis (*silica gel activity*)

The amount of water on the silica's surface affects chromatographic performance. An anhydrous silica gel will be extremely polar, while a wetted one will be considerably less polar. Every batch is carefully adjusted to a specific percentage of water content.

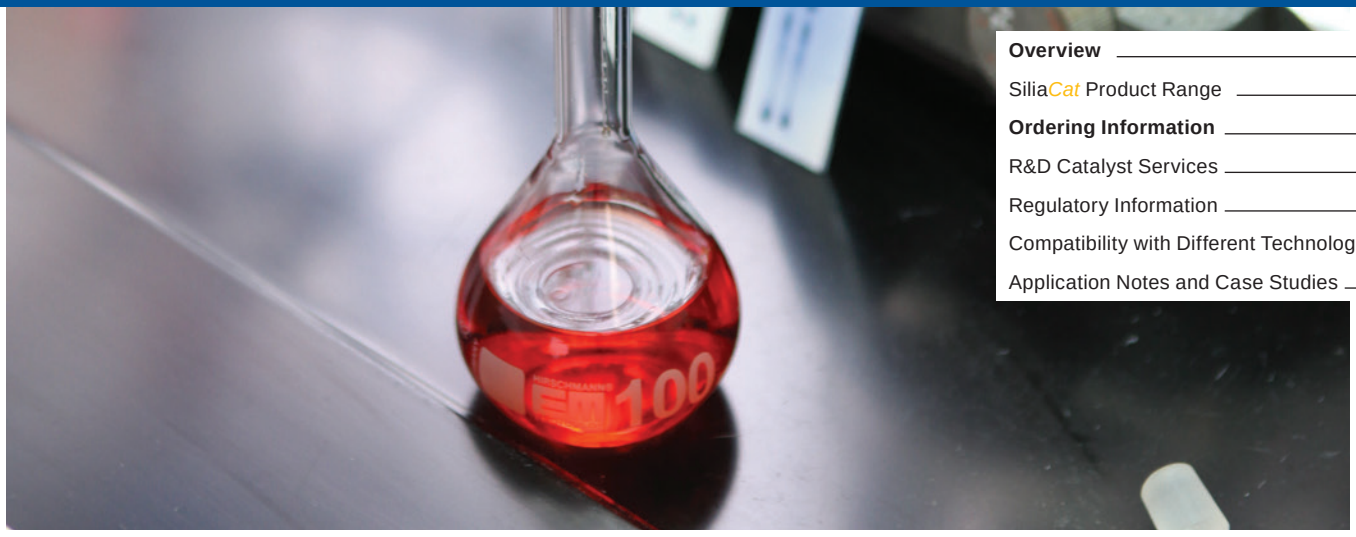
pH Analysis

The pH can increase the retention of some ionizable compounds. However, some products can become hydrolyzed or rearranged when in contact with acidic silica. A neutral pH, with a range between 6.5 and 7.5, is the most important factor in determining the reliability and inert behavior of the silica. This pH test involves suspending the silica gel in pure water (*5 % w/w*).


Synthesis

Heterogeneous Catalysis

SiliaCat® Silica-Supported Catalysts



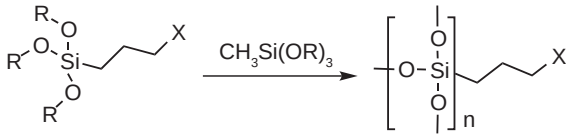
Catalytic Reactions with Silia*Cat*®

Advantages of using Silia*Cat* heterogeneous catalysts over traditional methods include:

- High stability and accurate loading
- Rigid & porous structure
- Compatibility with a wide range of solvents
- Ease of use: no swelling or static charge
- Minimal leaching
- Fast kinetics

The Silia*Cat* Matrix

Inspired by the ORganically MOdified SILica (*ORMOSIL*) technology, the Silia*Cat* family is composed of new and innovative catalysts. Resulting from the co-condensation of two organosilane monomers by the sol-gel process, the hybrid organic-inorganic materials present the highest stability and reactivity available with heterogeneous catalysts. Furthermore, the highly cross-linked framework presents a better resistance compared to post-functionalization process.

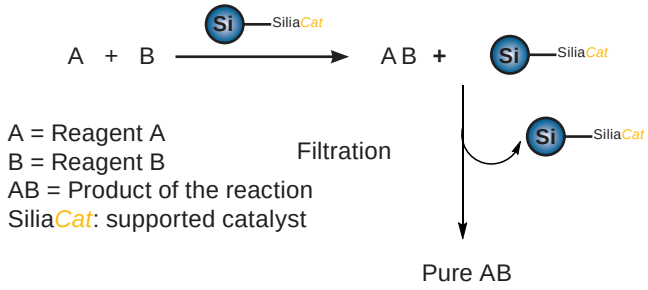


X = DPP, TEMPO

What is Silia*Cat* Heterogeneous Catalyst?

Usually, heterogeneous catalysts supported on a silica matrix are immobilized by post-modification of the inorganic support. These supports, however, present a high degree of leaching due to the poor stability of the immobilized phase. For example, with Silia*Cat* the ligand is directly cross-linked in an organic-inorganic framework. This results in a high degree of stability of the catalysts. Compared to homogeneous catalysts, Silia*Cat* exhibits a good reactivity and selectivity with one of the major advantages being that the catalyst is eliminated from the reaction mixture by a simple filtration. Forget your purification problems with our Silia*Cat* catalysts family.

What is Silia*Cat* Heterogeneous Catalyst?



Features and Benefits of Silia*Cat* Catalysts

Features & Benefits of Silia*Cat*	
Features	**Benefits**
Reagent concentrated at the surface of the material	Reproducible synthesis with high conversion and yield
Robustness	High thermal and mechanical stability
Rigid and porous structure	No swelling, solvent independent and air stable (*no inert conditions required*)
Minimal leaching of organoceramic matrix	Easier purification
High and accurate catalyst loading	Less catalyst required over competitive products
High turnover number (*TON*)	Low catalytic amount required (< *1 mol %*)
Reusability	Multi-uses possible
Ease of handling and purification	Free flowing, no static charge Easily removed by simple filtration
Ease of scalability	Scalable from mg up to multi-ton scale
Available in bulk quantities	Can be delivered in large quantities and always in stock

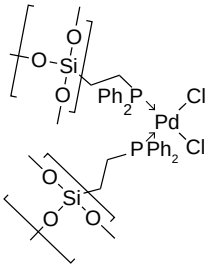
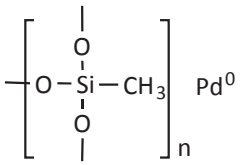
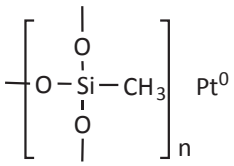
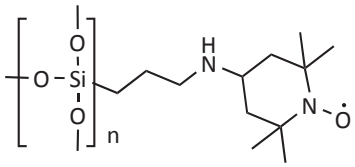
Silia*Cat*: A Versatile Catalyst Series for Organic Chemistry

Silia*Cat* catalysts can be used in a wide range of applications, and to manufacture products such as active pharmaceutical ingredients (*API*), *cis*-only hydrogenated fats, silanes, anilines, fragrances and emollients.

Silia*Cat*
a Versatile Catalyst Series
for Synthetic Organic Chemistry

- ► Multiple C-C cross coupling reactions (*Suzuki-Miyaura, Mizoroki-Heck, Sonogashira, etc.*)
- ► Selective oxidation of alcohols to carbonyls or carboxylic acids
- ► Highly efficient continuous flow C-C for cross coupling and oxidation reactions
- ► Full hydrogenation of terpenes
- ► Chemoselective hydrogenation of nitroarenes
- ► Isomerization-free hydrogenation of vegetable oils

Silia*Cat* Heterogeneous Catalysts Product Range

Silia*Cat* Heterogeneous Catalysts Portfolio			
Silia*Cat* Name	**Product Number**	**Structure**	**Brief Description**
Silia*Cat* DPP-Pd	R390-100		Silia*Cat* DPP-Pd is a unique diphenylphosphine palladium (II) heterogeneous catalyst made from a leach-resistant organoceramic matrix.
Silia*Cat* Pd^0	R815-100		Silia*Cat* Pd^0 is a new series of patent-protected sol-gel-entrapped Pd nanocatalysts. It is made from highly dispersed Pd nanoparticles (*uniformly in the range 2.0 - 6.0 nm*) encapsulated within an organosilica matrix. It is a safer alternative for hydrogenation over Pd/C.
Silia*Cat* Pt^0	R820-100		Silia*Cat* Pt^0 is made of organosilica physically doped with nanostructured platinum (0), and is both stable and efficient. Pt nanoparticles (*uniformly in the range 1.5 - 6 nm*) are encapsulated via an alcohol-free sol-gel process typical of enzyme sol-gel encapsulation.
Silia*Cat* TEMPO	R723-100		Silia*Cat* TEMPO is an oxidizing catalyst made from a proprietary class of organosilica-entrapped radicals. This encapsulation process confers enhanced reactivity and properties. The leach-resistant organoceramic matrix makes Silia*Cat* TEMPO highly efficient and selective compared to homogeneous TEMPO. It also has a superior performance compared to polymer-supported TEMPO in terms of both selectivity and stability. With Silia*Cat* TEMPO, no activation is required prior to use and selective aldehyde vs acid oxidation is possible.

All catalysts are available in the following format sizes:
5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc.

SiliaCat Heterogeneous Catalysts Portfolio							
Typical Applications	SiliaCat Typical Characteristics						SiliaCat Name
	Color	Endcapping	Loading / Metal	Typical Tap Density	Solvent Compatibility	Prolonged Storage	
Suzuki, Heck, Negishi, Borylation, Sonogashira, Kumada, Stille	Orange	Yes	0.2 - 0.3 mmol/g (*2.1 - 3.2 % Pd*)	0.300 - 0. 400 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*) and dry	SiliaCat DPP-Pd
Selective debenzylation, Selective hydrogenation, Suzuki, Heck Sonogashira, Kumada, Stille	Black	Yes	0.2 - 0.3 mmol/g (*2.1 - 3.2 % Pd*)	0.300 - 0. 400 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*), dry and under argon	SiliaCat Pd^0
Selective reduction of nitroarenes, Hydrosilylation	Black	Yes	0.15 - 0.25 mmol/g (*2.9 - 4.9 % Pt*)	0.300 - 0. 400 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*), dry and under argon	SiliaCat Pt^0
Oxidation of alcohols or aldehydes	Orange	Yes	≥ 0.70 mmol/g	0.550 - 0.650 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*) and dry	SiliaCat TEMPO

Available Kits

Because all reactions are unique, and that small differences can influence the catalysis efficiency, doing a screening is often recommended, especially if you are new to this technology. This is why we created a special kit containg our four catalysts.

This kit is available in 5 g, 10 g, 25 g, 50 g and 100 g formats (*custom formats are also available, contact us for more details*).

SiliaCat Heterogeneous Catalysts Kit		
Kit Name	Kit PN	Composition
SiliaCat Heterogeneous Catalysts Kit	K305-100	DPP-Pd, Pd^0, Pt^0 & TEMPO

Catalyst Services

CONFIDENTIALITY GUARANTEED

You can take advantage of SiliCycle's expertise in catalysis and our R&D team can assist you in your catalysis challenges. Our Catalyst Services provide a turnkey solution with an easy technology transfer.

Working with the substrates you identify, our chemists can quickly develop the most efficient catalysis process or optimize an existing one, test the feasibility of a new one, understand metal-catalyzed reaction, etc.

As a catalyst designer & manufacturer, our skilled and competent catalysis group can investigate any reaction parameter (*catalyst nature and loading, solvent, ligand, base / additive nature, concentration, temperature, time, etc.*) to maximize yields and purities as well as to reduce waste and cost.

Our most popular catalysis services include the following:

- Catalyst evaluation, testing and screening services
- Catalytic process optimization
- Scale-up of catalytic reactions
- Tailor-made catalyst development to fit your requirements
- Scavenging of residual metal catalyst

Contact us to discuss how we can help you reach your goals.

Silia*Cat* - Regulatory Information

Silia*Cat* are more and more used in GMP pharmaceutical, biotechnology and fine chemical industries as well as contract research and manufacturing organizations. Many have run their own analysis proving Silia*Cat* can safely be used without compromising the purity of their compounds.

SiliCycle is committed to high quality standards and strives to provide default-free products. All products are manufactured in an ISO 9001:2008 compliant facility and submitted to stringent quality control. Every lot must meet the quality specifications to be released and a sample from every batch is stored as reference for subsequent analysis. All products are shipped with the following information:

- Certificate of Analysis
    - Purity (*leachables and extractables*)
    - Molecular loading of active metal
    - Surface coverage
    - Volatile content
- Material Safety Data Sheets (*MSDS*)
- Relevant technical information

Note: BSE / TSE Declaration (*no animal origin*) available under request.

Need specific data for your regulatory files?
SiliCycle can work with you to fulfill your requirements.
We can provide custom regulatory documentations that include specific analytical tests in line with your needs.

Beyond the Basics

This section is a step-by-step guide for the most common technical questions that you might have when using our Silia*Cat* catalysts in your synthesis.

Every catalyst is different and the way you use it has an influence on the performance. It is highly recommended to use our typical experimental procedure presented at the end of each reaction as a starting point from which you can optimize conditions for optimum yields & purity in your own experimental conditions.

If you want we can determine for you the best conditions for your reaction in our labs with our catalyst services.

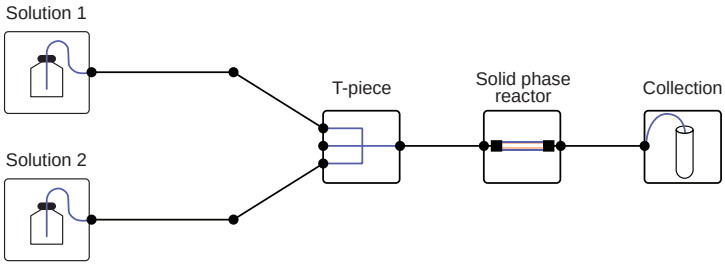
If you need a custom supported-catalyst to run your synthesis, we can also develop it for you.

Compatibility with Different Technologies

Silia*Cat* Catalysts in Flow Chemistry

Silia*Cat* works wonders in flow chemistry as it is non-leaching, very stable & will last for many runs. Simply place the heterogeneous catalyst inside the solid-phase reactor provided with your flow system (*e.g.: in a Syrris Asia® Solid Phase Chemistry Reactors*) and letting the catalytic reaction run. Multiple reactors can be placed in serie and can be heated to obtain optimum conversions and yields.

Please refer to the applications presented in the following section identified with this logo for various examples. Detailed experimental procedure are described inside each publication.

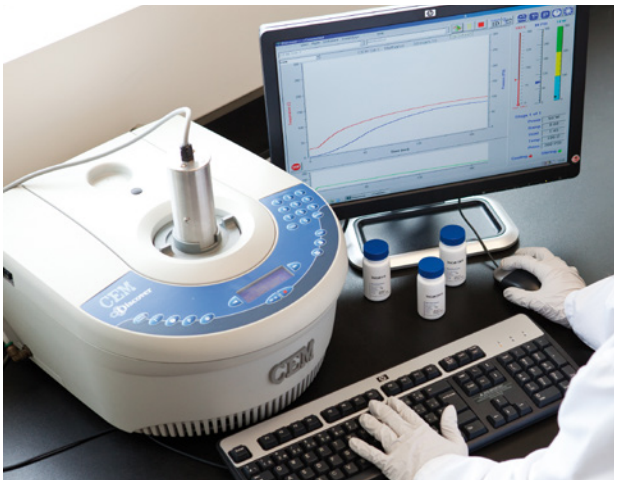


Silia*Cat* Catalysts in Microwave-Assisted Chemistry

Reactions catalyzed with Silia*Cat* can also be done under microwave irradiation to provide excellent yields in just minutes. Add all products listed for each procedure (*see following pages*) to a microwave tube equipped with a magnetic stirrer and set microwave conditions to:

- Power: 150 W
- Pressure: 150 psi
- Temperature: 75 - 150°C
- Reaction Time: 5 - 15 min

Some optimization can be required but these settings are a good starting point. Use the same work-up conditions provided for each procedure.



Applications developed in microwave are identified by this logo (*refer to related publications for details*).

Typical Apparatus

Under Magnetic Stirring for Screening or Small-scale Synthesis

Advantages	Disadvantages
• Very small scale • Screening tests	• Possible catalyst attrition due to grinding • Possible metal leaching

Typical apparatus:
100 mL three-neck round-bottom flask equipped with a condenser, a magnetic stir bar and a digital temperature controller.

Under Mechanical Stirring for Reusability or Large-scale Synthesis

Advantages	Disadvantages
• Superior catalyst reusability • Catalyst morphology is not altered, easily removed by filtration	• Higher quantity of reagents needed (*half of the flask needs to be filled with solvent*)

Typical apparatus #1:
100 mL three-neck round-bottom flask equipped with a condenser, a mechanical stirrer and a digital temperature controller.

Typical apparatus #2:
High pressure reactor (*bomb reactor*) for **hydrogenation** reactions.

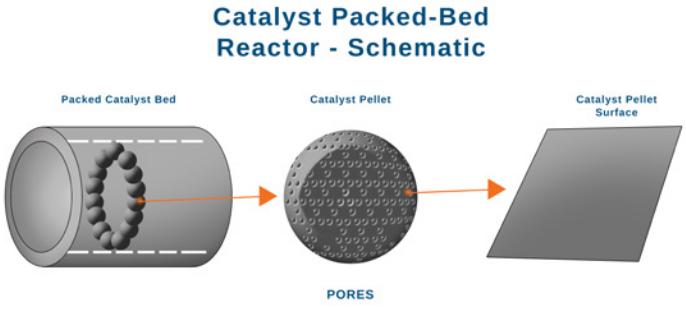
Heterogeneous Catalytic Reactions Basics

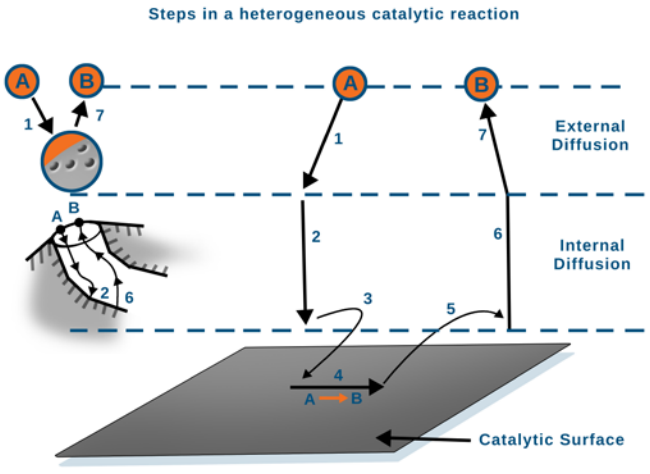
To maximize reaction rate on a porous catalyst, it is essential to maximize accessibility of all reactants to the active catalytic sites, which are dispersed through the internal pore structure of the catalyst.

Imagine a reactant **A** flowing through a bulk liquid and a bed of a heterogeneous catalyst and reacting on the catalytic surface to form a species **B**.

Schemes at right present the physical and chemical steps that must occur to **A** to convert to **B**:

1. Mass transfer (*diffusion*) of the reactant(s) (*e.g. species A*) from the bulk liquid and a separate liquid film surrounding each suspended catalyst particle to the external surface of the catalyst particle.
2. Diffusion of the reactant from the pore mouth through the catalyst pores to the immediate vicinity of the internal catalytic surface.
3. Adsorption of reactant A onto the catalyst surface.
4. Reaction on the surface of the catalyst (*e.g. A → B*).
5. Desorption of the products (*e.g. B*) from the surface.
6. Diffusion of the products from the interior of the pellet to the pore mouth at the external surface.
7. Mass transfer of the products from the external pellet surface to the bulk fluid.





Application Notes and Case Studies

We have selected a few applications to help you understand how our catalysts can be introduced in your daily synthesis routine.

Application Notes

You can read through our “Application Notes” section to learn more about different SiliCycle applications that were developed in our labs.

In the following section, applications notes are identified by this logo:

Case Studies

Don’t take our word for granted. Discover and learn what some of our customers are doing with our heterogeneous catalysts in the “Case Studies” section. Visit regularly our website to get the entire publication portfolio available.

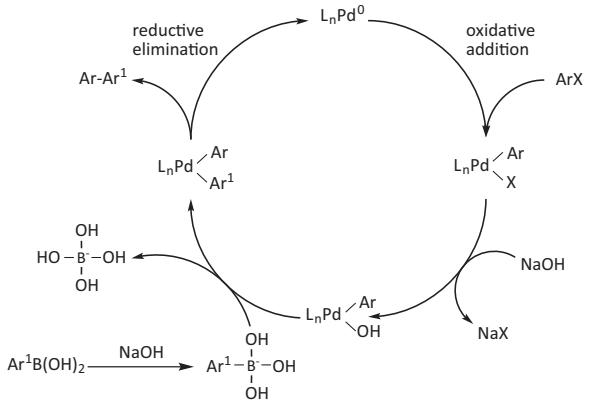
In the following section, customers’ case studies are identified by this logo:

Nothing speaks more than lab examples!

Suzuki Coupling Using Pd-based Silia*Cat*

The Suzuki coupling (*also called Suzuki-Miyaura reaction*) is the reaction between a boronic acid and a halide, catalyzed by a palladium (0) catalyst. At first, only aryl and vinyl substrates could undergo Suzuki coupling. Now, catalysts are becoming so powerful that the substrate scope has broadened to include: alkyl-, alkenyl- & alkynyl-halides, triflates and organoboranes, trifluoroborates or borate esters.

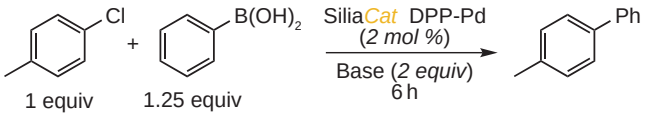
Note: detailed experimental procedure can be found at page 36.



Solvent and Base Effects

The choice of solvent and base play an important part in the Suzuki reaction. Different solvents and bases were tested to find the most suitable combination. Total conversion was obtained in both ethanol and propanol. With THF, dioxane, toluene and DMF, the kinetics were lower.

As for the base, potassium carbonate (K_2CO_3) is the best. However, in some cases, sodium carbonate (Na_2CO_3) and sodium acetate (*NaOAc*) can also be used.



Solvent and Base Effects

Solvent	Temp. (°C)	Conversion / Selectivity (%)					
		K_2CO_3	Na_2CO_3	KOAc	NaOAc	K_2HPO_4	Et_3N
MeOH	64	74 / 95	69 / 99	63 / 98	63 / 98	73 / 100	72 / 93
EtOH	77	100 / 98	100 / 97	82 / 99	85 / 100	79 / 100	77 / 93
EtOH / H_2O (*15 %*)	77	100 / 100	82 / 100	78 / 100	88 / 100	86 / 98	89 / 95
1-PrOH	90	100 / 95	70 / 97	90 / 99	91 / 99	15 / 100	20 / 95
2-PrOH	77	100 / 100	43 / 93	90 / 99	72 / 100	50 / 100	20 / 100
THF	64	30 / 93	15 / -	45 / 89	35 / 94	37 / 95	5 / -
MeTHF	77	40 / 95	33 / 100	39 / 100	56 / 100	30 / 97	4 / -
Dioxane	90	50 / 90	30 / 93	56 / 93	35 / 94	20 / 90	No reaction
Toluene	90	47 / 98	23 / 87	49 / 96	10 / 90	65 / 95	No reaction
DMF	90	50 / 100	30 / 100	15 / 100	17 / 100	7 / 100	No reaction

Catalyst Concentration Effect

Decreasing the mol % of the Pd catalyst lowers the kinetics of the reaction, but the total conversion can still be achieved by increasing reaction time.

In this example, the addition of water significantly improves catalyst activity even if the catalyst amount is reduced significantly.

(*Conditions: $PhB(OH)_2$ (1.1 equiv), K_2CO_3 (1.5 equiv) RT*).

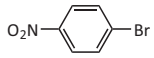
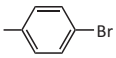
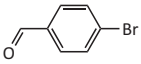
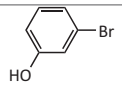
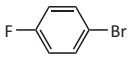
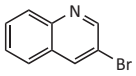
Silia*Cat* DPP-Pd Concentration Effect

mol % Pd	Molar Concentration (*M*)	Time (*h*)	Conv. (%)
0.2	EtOH (*0.05*)	0.5	100
0.1	EtOH (*0.05*)	1	100
0.01	EtOH / H_2O (*0.08*)	2	100
0.002	EtOH / H_2O (*0.08*)	16	100

Pd-Based Silia*Cat* Catalytic Performance Comparison and Reusability

The table below presents the best conditions for bromo-substrates. It can be seen that even with half the catalyst amount, Silia*Cat* Pd^0 is the most active catalyst. For substrates with electron-withdrawing groups, Silia*Cat* can be reused more than 5 times with a minimal leaching and loss of activity. For substrates containing an electron-donating group, Silia*Cat* can be used up to 3 times with only a small effect on activity. The reaction can also be done using boronic acid pinacol esters.

Pd-Based Silia*Cat* Catalytic Performance Comparison and Reusability

	Substrate (*R*)	Silia*Cat* Performance Comparison [*Conversion / Selectivity (%)*] DPP-Pd (*1 mol %*)[a-b]	Silia*Cat* Performance Comparison [*Conversion / Selectivity (%)*] Pd^0 (*0.5 mol %*)[c]	Reusability [*Conversion / Selectivity (%)*] Pd & Si Leaching (*ppm*)[1] Run 2	Run 3	Run 4	Run 5
Electron-Withdrawing		100 / 100 Pd: 0.1, Si: 2	100 / 99	100 / 100 Pd: 0.05, Si: 1	100 / 100 Pd: 0.08, Si: 1.5	100 / 100 Pd: 0.1, Si: 3	99 / 98 Pd: 0.1, Si: 3.5
		100 / 97 Pd: 0.1, Si: 3	99 / 97	98 / 99 Pd: 0.1, Si: 8	98 / 99 Pd: 0.07, Si: 5	100 / 99 Pd: 0.1, Si: 6	99 / 98 Pd: 0.1, Si: 5
		100 / 97 Pd: 0.1, Si: 6	95 / 98	99 / 90 Pd: 0.2, Si: 7	97 / 92 Pd: 0.2, Si: 8	99 / 98 Pd: 0.1, Si: 4	98 / 97 Pd: 0.1, Si: 5
Electron-Donating		100 / 99 Pd: 0.9, Si: 5	83 / 100	100 / 100 Pd: 0.6, Si: 9	100 / 98 Pd: 0.4, Si: 7	60 / 97 Pd: 0.05, Si: 6	-
		100 / 80 Pd: 0.07, Si: 3	98 / 99	99 / 99 Pd: 0.04, Si: 1.5	98 / 98 Pd: 0.1, Si: 2	81 / 94 Pd: 0.06, Si: 2	73 / 95 Pd: 0.03, Si: 7
		100 / 99 Pd: 2.1, Si: 10	97 / 95	88 / 90 Pd: 0.3, Si: 7	75 / 95 Pd: 4, Si: 9	87 / 99 Pd: 0.6, Si: 10	68 / 96 Pd: 04, Si: 11

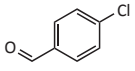
[a] Corresponds to "Run 1" in the reusability study.
General exp. cond.: 1 equiv substrate, 1.2 equiv $PhB(OH)_2$, 2 equiv K_2CO_3;
[b] MeOH (*0.1 M*), 2 h, 65°C;
[c] EtOH (*0.12 M*) 2 h, 77°C.

[1] Using Silia*Cat* DPP-Pd as catalyst under the same conditions previously described. Run #1 is the result presented in the performance comparison section of the table.

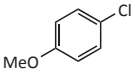
Suzuki Coupling in Microwave and Flow Chemistry

The performance of Silia*Cat* DPP-Pd for Suzuki coupling was also compared in microwave assisted experiments for brominated and chlorinated substrates. After only 5 minutes, 100 % of the product is obtained in most experiments with excellent selectivities.

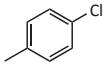
The Silia*Cat* DPP-Pd can also be used for Suzuki coupling with chlorinated substrates in both conventional and microwave conditions. Conversion and yield (*in %*) results are presented below.



Conv.: 98 %
Yield: 93 %

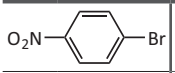
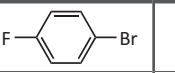
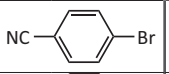
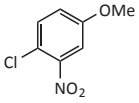
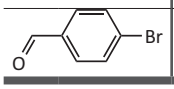


Conv.: 98 %
Yield: 96 %



Conv.: 99 %
Yield: -

Catalytic Performance in Microwave (*MW*)

Substrate	Conversion / Yield (%)	Substrate	Conversion / Yield (%)
	100 / 99.5		98 / 97.3
	100 / 99.4		Batch: 100 / 98
	100 / 88		MW: 100 / 95

General exp. cond.: 0.5 mol % of Silia*Cat* DPP-Pd, 1 equiv substrate, 1.1 equiv $PhB(OH)_2$, 1.5 equiv K_2CO_3; [a] MeOH (*0.2 M*), 5 min, 75°C, 150 W, 150 psi; [b] MeOH (*0.2 M*), 5 min, 75°C, 200 W, 200 psi

Suzuki Coupling in Flow Chemistry

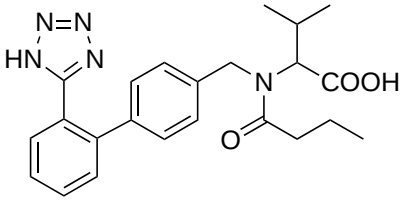
The Suzuki coupling in flow chemistry was also investigated on various substrates using the Silia*Cat* DPP-Pd with diluted and more concentrated solutions. Usually, complete conversion is obtained in less than 3 min, whereas the analogous conversion under batch requires up to 6 h.

Reactions were scaled-up from 6 mmol up to 275 mmol with high conversions and selectivities. For all results and substrate scope, please consult the following publication: *Org. Proc. Res. Dev.*, **2014**, *18*, 1550-1555

Greening the Valsartan Synthesis Using Silia*Cat* DPP-Pd

Angiotensin receptor blockers such as valsartan (*also called Diovan*) belong to a relevant therapeutic class called sartans, widely employed since the late 1980s to treat high blood pressure and congestive heart failure.

The Valsartan patent expired in 2012, opening the route to the introduction of generic alternatives. This section presents the study of the heterogeneous Suzuki-Miyaura coupling reaction in batch conditions between 2-chlorobenzonitrile and 4-tolylboronic acid, a key step in valsartan synthesis, to produce 4′-methyl-2-biphenylcarbonitrile over the Silia*Cat* DPP-Pd catalyst in ethanol under reflux.
See *Tet. Letters*, **2013**, *54*, 4712-4716 for all details.



Valsartan

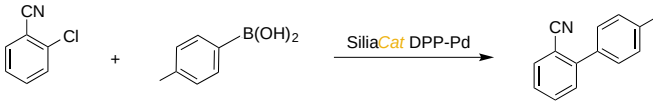
Solvent Concentration and Base Effects

Different concentrations of aryl halide were tested over 1 mol % of Silia*Cat* DPP-Pd, with the aim to identify the optimal molar concentration required for the scale-up.

Complete conversion was obtained after 30 min for concentration from 0.12 M to 1 M. Raising the concentration to 1.5 M resulted in 92 % aryl halide conversion after 1 h (*increase in the viscosity of the reaction which results in diffusion problem*).

Different bases (K_2CO_3, Na_2CO_3, $NaOAc.3H_2O$, KOAc, NaOH, KOH, $KHCO_3$) were tested and potassium carbonates were by far the most suitable ones.

*Conditions: 2-chlorobenzonitrile (1 equiv), 4-tolylboronic acid (1.1 equiv), Base (1.5 equiv), Silia*Cat* DPP-Pd (1 mol %)*



Solvent Concentration and Base Effects

Base (*1.5 equiv*)	Conc. (*M*)	Time (*h*)	Conv. / Yield (%)
K_2CO_3	0.12 / 0.25 / 0.5	0.5	100 / 98
	1.0	0.5	100 / 99
	1.5	0.5	81 / 99
		1.0	92 / -
$KHCO_3$	0.5	0.5	100 / 99
	1.0	1.0	85 / 99

Reaction Scale-Up

Using the established optimized conditions, the reaction was scaled up from 6 to 720 mmol of aryl halide. Even if the amount of aryl halide was increased to 720 mmol, complete conversion was obtained. At that scale, the quantity of catalyst can also be decreased for cost consideration.

*Conditions: 2-chlorobenzonitrile (1 equiv), 4-tolylboronic acid (1.01 equiv), K_2CO_3 (1.1 equiv), Silia*Cat* DPP-Pd, EtOH (0.5 M)*

Reaction Scale-Up Results

Aryl Halide scale	Catalyst (*mol %*)	Time (*h*)	Conv. / Yield (%)
6 mmol (*0.8 g*)	1	0.5	100 / 98.0
72 mmol (*10 g*)	1	0.5	100 / 97.5
360 mmol (*50 g*)	1	0.5	100 / 97
720 mmol (*100 g*)	0.7	1	100 / 98

Reaction Scope

To investigate the scope of the method, reactions were done using the following protocol: 1 equiv of aryl halide, 1.1 equiv of 4-tolylboronic acid, 1 mol % Silia*Cat* DPP-Pd, 1.5 equiv of K_2CO_3 in EtOH (*0.5 M*) under reflux. Several aryl halides with electron with drawing (*nitrile and carbonyl*) or electron-donating (*methoxy, methyl, phenol and amine*) groups along with various heterocycle aryl halides (*such as pyrazole, pyridine, indole and quinoline*) were tested.

The results show that usually more than 90 % yields were obtained after 0.5 - 2 h, except for the aryl halides in entries 8 and 12, which required 2 mol % catalyst to achieve more than 80 % yield.

We also found that the position of the functional group had an influence on the reactivity. For example, with a nitro in ortho position (*entry 6, 4-chloro-3-nitroanisole*), complete conversion was obtained after 2 h over 1 mol % catalyst, whereas in meta position (*entry 7, 4-chloro-2-nitroanisole*) gave only 53 % yield after 2 h (*the amount of the biphenyl product generated was significant*). To increase the conversion in the desired product, 2 equiv of 4-tolylboronic acid was needed to achieve 81 % yield after 2 h.

Steric hindrance of aryl halides (*entries 5 and 14*) does not affect conversion, with almost complete conversions obtained after 0.5 - 2 h over 1 mol % of Silia*Cat* DPP-Pd.

Conclusion

The study of the scale-up (*from 1 to 100 g of aryl halide*) of the heterogeneous Suzuki-Miyaura coupling reaction in batch between 2-chlorobenzonitrile and 4-tolylboronic acid over Silia*Cat* DPP-Pd catalyst at 77°C was succesfully achieved. We have also shown that the method is general, as it enables the heterogeneous conversion of an ample variety of different aryl halides.

Related Publications for Suzuki Coupling

Top. Catal., **2010**, *53*, 1059-1062

Catal. Sci. Technol., **2011**, *1*, 736-739

Org. Proc. Res. Dev., **2012**, *16*, 117-122

RSC Adv., **2012**, *2*, 10798-10804

Tet. Letters, **2013**, *54*, 1129-1132

Tet. Letters, **2013**, *54*, 4712-4716

Org. Proc. Res. Dev., **2013**, *17*, 1492-1497

Reaction Scope

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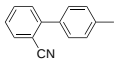
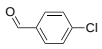
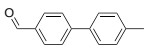
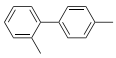
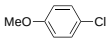
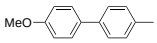
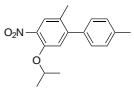
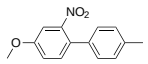
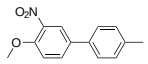
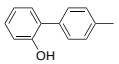
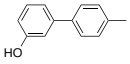
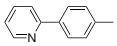
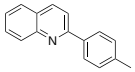
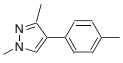
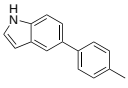
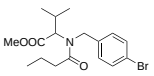
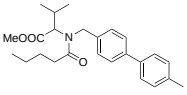
1		0.5		100
2		2.0		92
3		2.0		100
4		2.0		95
5		0.5		99
6		2.0		97
7		2.0		81
8		2.0		88
9		0.5		100
10		2.0		95
11		2.0		100
12		2.0		90
13		2.0		91
14		1.0		99

Conditions: 1 equiv of Ar-X, 1.1 equiv of 4-tolylboronic acid, 1 mol % Silia*Cat* DPP-Pd, 1.5 equiv of K_2CO_3 in 0.5 M EtOH under reflux.

Comparison of Various Heterogeneous Pd-Catalysts

The effectiveness of Silia*Cat* DPP-Pd for the Suzuki coupling were investigated and compared with other catalysts (*heterogeneous and homogeneous*) available on the market. **It is very important to note that for all reactions, all catalysts were used in the manufacturer's optimized conditions and not just SiliCycle's** in order to be able to make relevant conclusions.

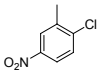
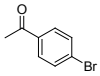
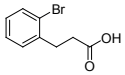
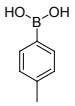
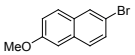
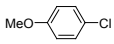
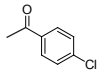
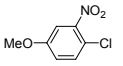
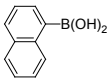
Note: results using EnCat40 are not presented here due to extremely low conversion obtained (< *10 %*).

Conclusion

In conclusion, for brominated compounds, Silia*Cat* DPP-Pd presents excellent results and compared favorably with a homogeneous catalyst. The PhosphonicS' catalyst was also effective, but showed heavy Pd leaching compared to Silia*Cat*.

For chlorinated compounds, Silia*Cat* was by far superior to all competing products.

Suzuki Coupling Conversion Comparison (*in %*)

Aryl Halide	Boronic Acid	Silia*Cat* DPP-Pd	FibreCat	PhosphonicS	$Pd(PPh_3)_4$
		**100**	0	**100**	87
		**98**	0	49	3
		**100**	0	81	**100**
		**100**	83	**100**	**100**
		**100**	**100**	**100**	96
		**100**	0	**100**	-
		**100**	5	51	68
		**95**	0	1	0
		**92**	0	14	1
		**97**	0	0	0
		77	0	1	0
		**93**	82	84	87

Experimental conditions

- Protocol with Silia*Cat* DPP-Pd was drawn from *Org. Proc. Res. Dev.*, **2013**, *17*, 1492-1497 [*1 mol % Silia*Cat* DPP-Pd; K_2CO_3; EtOH; 77°C; 30 min*]
- Protocol with PhosphonicS was drawn from *Journal of Molecular Catalysis A: Chemical*, **2008**, *293*, 25-28 [*0.1 - 0.2 mol % Si-ethylphosphatrioxaadamantane; EtOH:H_2O:DME (1:2:4); 130°C; 30 min*]
- Protocol for Johnson-Matthey FibreCat 1001 was drawn from *Topics in Catalysis*, **2008**, *48*, 91-98 [*1 mol % FibreCat 1001; K_2CO_3 / Toluene; 81°C, 2 h*]
- Typical protocol with the homogeneous catalyst: 1 mol % $Pd(PPh_3)_4$; K_2CO_3; EtOH / H_2O; 80°C; 30 min

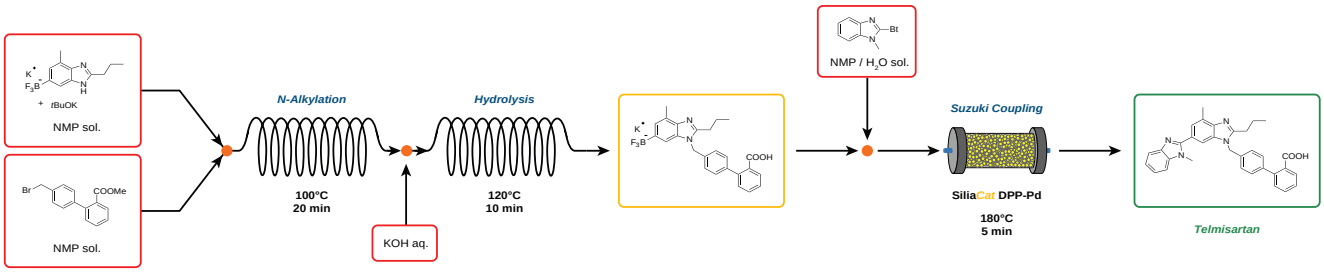
Case Study: Suzuki Cross-Coupling Using SiliaCat DPP-Pd in the Synthesis of Telmisartan

Authors: Gupton (*Virginia Commonwealth University*) *et al.*
Publication: *Org. Proc. Res. Dev.*, **2016**, *20*, 2-25

Overview

Telmisartan is the API present in the antihypertensive drug Micardis. It is an angiotensin receptor antagonist and, compared to other similar drugs, has several advantageous: longer half-life, higher protein binding affinity and lower daily dosage.

Gupton and co-workers developed a continuous flow convergent multistep synthesis of telmisartan which did not require any intermediate purification nor switch of solvent. Suzuki cross-coupling took place using SiliaCat as the metal catalyst, with a residence time of 5 min only. Upon acid-base workup, telmisartan was isolated in an overall yield of 81 % (*97 % HPLC purity*).



Conclusion

This fully automated process represents a significant improvement over traditional batch procedure since it reduces waste and unit operations.

Case Study: SiliaCat DPP-Pd in Suzuki Coupling for the Synthesis of Anti-Stroke Therapies Products

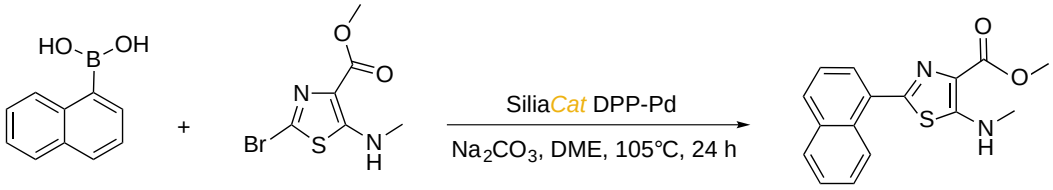
Authors: Leyen (*Massachusetts General Hospital*), Maloney (*NIH*), Holman (*University of California*) and coworkers
Publication: *Journal of Medicinal Chemistry,* **2014***, 57,* 4035-4048

Overview

Because of the broad implications of 12/15-Lipoxygenase (*12/15-LOX*) in stroke regulation, Leyen, Maloney, Holman and coworkers highlighted the need for small molecule inhibitors that could effectively cross the blood brain barrier.

Their 2014 publication represents the first report of a selective inhibitor of human 12/15-LOX with demonstrated in vivo activity in proof-of-concept mouse models of stroke.

In the synthesis of various analogues, one intermediate was prepared from 1-naphthyl boronic acid using a classical Suzuki reactions, which yield limited success. Yet, this same Suzuki coupling reaction much more successful using SiliaCat DPP-Pd under reflux conditions over 24 h.



Case Study: Suzuki-Miyaura Coupling Using SiliaCat DPP-Pd

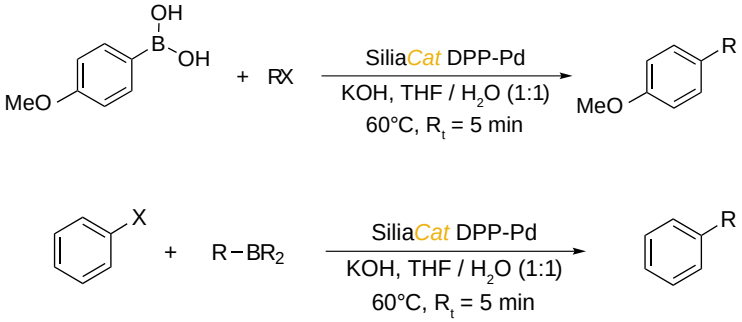
Authors: Alcázar (*Janssen Research and Development*) *et al.*
Publication: *Advanced Synthesis and Catalysis,* **2012**, *354*, 3456-3460

Overview

Alcázar's research group at Janssen Research and Development used SiliaCat DPP-Pd as a silica-supported catalyst to develop a mild, clean and high yielding procedure for Suzuki-Miyaura cross-coupling in a single pass. SiliaCat DPP-Pd could be used in more than 30 reactions and for more than 8 hours of continuous flow without any observed decrease in activity. This was possible due to the non-leaching nature of SiliaCat DPP-Pd. The lab team describes a reliable method, easily scalable, with commercially available instrumentation for mild and clean Suzuki-Miyaura coupling in single pass.

As stated in their publication: *"Within the field ot heterogeneous catalyst a broad range of solid supports were developed such as monolithic supports, polymer beads and PdEnCat™.* ***However swelling and denaturalization of the polymer supports, gradual leaching of the catalytic active palladium, the need to perform several passes through the catalyst to get full conversion, and the replacement of the cartridge after performing a limited number of reactions as well as the need to synthesize the supported catalyst in the cartridge limit their general use in organic and medicinal chemistry****"*.

The scope of the reaction was studied both between different aryl bromides and boronic acid, and between other boronic acids & organoboranes and boromobenzene or phenyltriflate.



Conclusion

In conclusion, the authors obtained good to excellent yields using SiliaCat DPP-Pd. Extremely low level of leaching were detected (*10 - 20 ppb in reaction*). They also reported that *"****silica-supported catalyst offer better chemical and thermal stability as well as rigid but porous structure devoid of swelling properties that makes it compatible with a range of solvents****."*

Case Study: SiliaCat DPP-Pd in the Synthesis of Organic Photovoltaics, using Suzuki Coupling

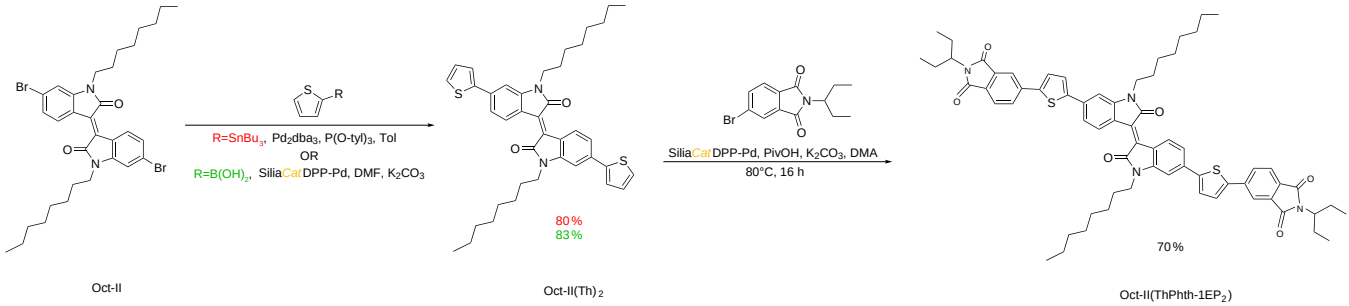
Authors: Welch (*Dalhousie University*) *et al.*
Publication: *ChemPhysChem*, **2015**, *16*, 1190-1202

Overview

More and more, soluble organic small molecules seem to represent a highly advantageous & promising alternatives vs more traditional polymer-fullerenes in the field of organic photovoltaics (*OPVs*). SiliaCat DPP-Pd was chosen as a heterogeneous catalyst for the synthesis of Oct-II(Th)$_2$, a small molecule with unique morphologies, as a fullerene alternative in OPVs. In this context:

- For the coupling between the brominated alkylisoindigo core and a 2-tributystannyl thiophene, both a Stille coupling catalyzed by Pd_2dba_3 and a Suzuki coupling catalyzed by SiliaCat DPP-Pd were considered as synthetic strategies.
- For the last step, a direct heteroarylation was chosen in order to obtain the target molecule.

Case Study: SiliaCat DPP-Pd in the Synthesis of Organic Photovoltaics, using Suzuki Coupling (*con't*)



Oct-II — Oct-II(Th)$_2$ — Oct-II(ThPhth-1EP$_2$)

Conclusion

In the synthetic step for Oct-II(Th)[2], both Stille and Suzuki couplings gave similar good yields. Yet, two points favour the Suzuki coupling using SiliaCat DPP-Pd as a catalyst:

1. Despite the two couplings giving similar yields, the two purification needs were very different, For the Stille reaction, in order to remove the toxic organotin residue, a flash chromatography was needed. For the Suzuki coupling, an aqueous work up could get rid of most impurities.
2. Moreover, Suzuki couplings involve environmentally benign boronic acids, whereas Stille couplings involve toxic organotin reagents.

Direct heteroarylation somehow represent the apex of atom economy for C-C bond forming reactions, since they do not require tin or boron extra organic material as Stille or Suzuki couplings do. This last step did not require any air sensitive manipulation.

Case Study: Comparative Investigation Between Most Common Immobilized Pd catalysts

Authors: Kappe (*University of Graz, Austria*) et al.
Publication: *ACS Catalysis,* **2015**, *5*, 1303-1312

Overview

When choosing a heterogeneous Pd catalyst for cross-coupling reactions, for all the benefits they bring in comparison with homogeneous catalysts, the key parameters of concern are the overall efficiency, the leaching resistance and the recyclability character of the catalyst. In this report, a comparative investigation of some of the most common and popular immobilized phosphine based Pd catalysts, namely SiliaCat DPP-Pd, Pd Tetrakis (*polymerbound*), FiberCat 1001 and EnCat TPP30, was performed.

Comparative results & Conclusions

- *"**Except for SiliaCat DPP-Pd**, the Suzuki-Miyaura cross-coupling produced a much higher amount of metal leaching and catalyst degradation than the Mizoroki-Heck reaction"*.
- *"In the case of the Pd EnCat TPP30, a constant drop in conversion was observed when EtOH as solvent in combination with TBAOAc as base were utilized for the Mizoroki-Heck reaction"*.
- *"**SiliaCat DPP-Pd** combined with THF / EtOH / H_2O as solvent and K_2CO_3 as base **gave the best results** regarding catalyst efficiency and leaching resistance"*.
- *"Notably, the **SiliaCat DPP-Pd** system described herein has shown superior leaching resistance and stability with respect to the other three cases studied"*.

Typical Experimental Procedure: Suzuki Couplings over Silia*Cat* DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*).
Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Reaction in flow

- Solution Preparation:
  - Solution 1: aryl halide (*1 equiv*) in THF (*0.8 M*)
  - Solution 2: boronic acid (*1.25 equiv*) and base *(1.5 equiv*) in EtOH / H_2O
- Both solutions are pumped using the flow system and mixed in a T-piece device, are driven through a preheated glass column reactor with an adjustable end (*0.785 cm ID × 6.5 cm length*) packed manually with the Silia*Cat* DPP-Pd.

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.
  For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

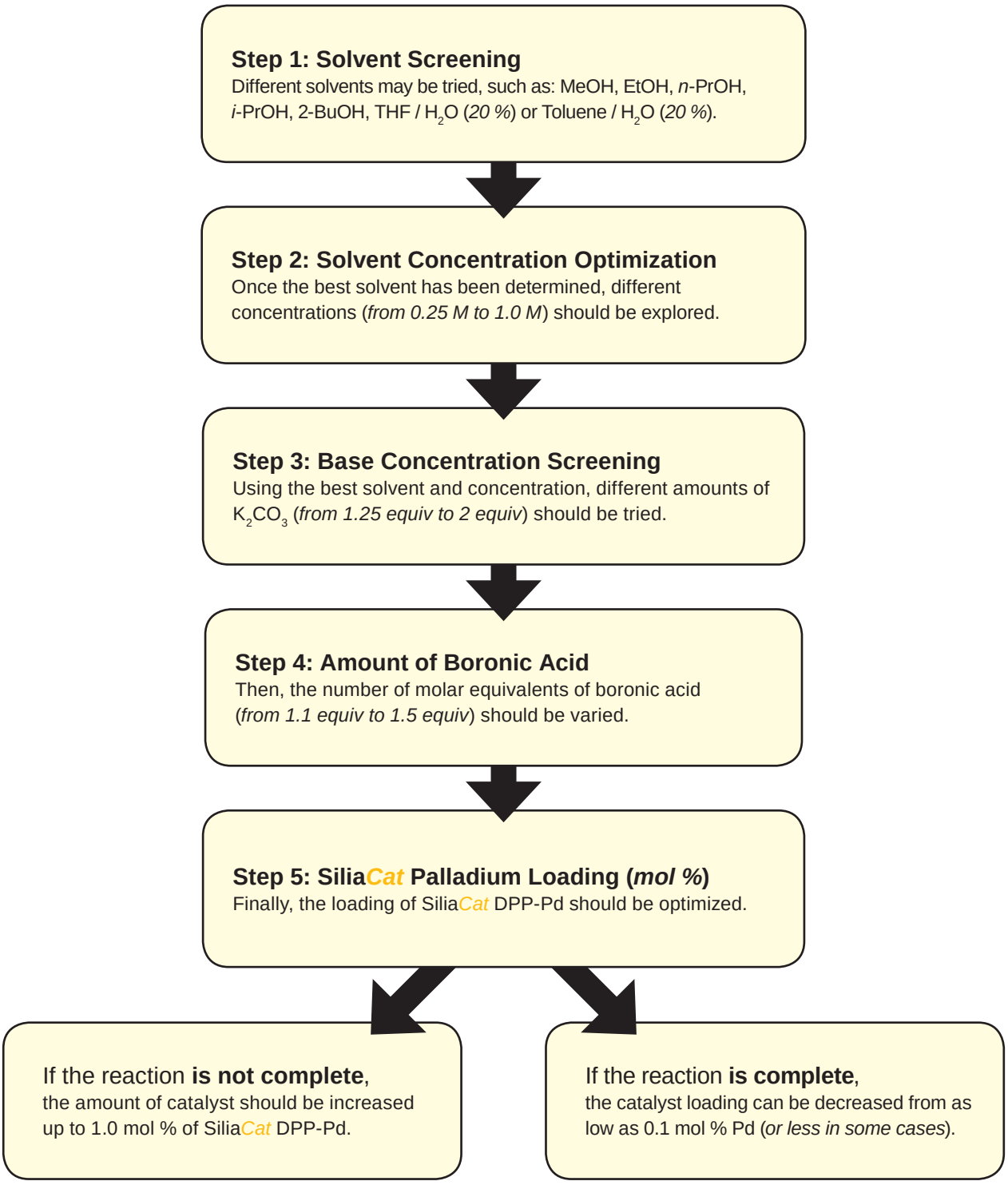
Suzuki Coupling Reactions over Silia*Cat* DPP-Pd			
Substrates	**Aryl-Iodide (*1 equiv*)**	**Aryl-Bromide (*1 equiv*)**	**Aryl-Chloride (*1 equiv*)**
Boronic Acid	1.2 equiv		
Base [K_2CO_3]	1.5 equiv [*alternate bases: Na_2CO_3, $KHCO_3$, $NaHCO_3$, NaOH, KOH, NaOAc, KOAc*]		
Silia*Cat* Loading	≤ 0.5 mol % Pd		≤ 1.0 mol % Pd
Best Solvents & Temperature	MeOH or EtOH	EtOH	
	[*alternate solvents: n-PrOH, i-PrOH, 2-BuOH, THF / H_2O (20 %), Toluene / H_2O (20 %)*] ; 1 - 2°C *under boiling point*		
Reaction Time	0.5 - 2.0 h		
Typical Scale	• Under Magnetic Stirring for Screening: 6 mmol scale of aryl halide in 12 mL solvent. • Under Mechanical Stirring for Reusability: 25 mmol scale of aryl halide in 50 mL solvent.		

Suzuki Coupling Reactions in Flow over Silia*Cat* DPP-Pd	
Substrates	***Solution 1*: Aryl-Halide 0.79 M in THF (*HPLC grade*)**
Boronic acid	*Solution 2*: Boronic acid (*1.25 equiv*) and base K_2CO_3 (*1.5 equiv*) in EtOH / H_2O (*1:1.15, v/v, 0.45 M in regards to boronic acid*)
Silia*Cat* Catalyst	Preheated glass column reactor with an adjustable end (*0.785 cm ID × 6.5 cm length*) charged with Silia*Cat* DPP-Pd.
Temperature	70°C
Residence Time	2.85 min
Flow Rate	For 0.75 mL/min: *solution 1:* 0.25 mL/min & *solution 2:* 0.50 mL/min

Optimization Steps

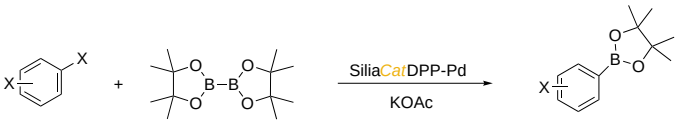
If the reaction fails or if the conversion of the aryl halide is not complete, optimization steps can be undertaken. The example below (written for Suzuki coupling using SiliaCat DPP-Pd) presents the pathway (order) you need to follow to optimize your reaction.

Always using 1.0 mol % SiliaCat DPP-Pd:



Borylation of Aryl Halides Using SiliaCat DPP-Pd

The borylation reaction is a fast and clean synthesis of boronic acid pinacol esters starting from aryl halides and bis-(pinacolato)diboron (B_2Pin_2) or bis(catecholato)diborane (B_2Cat_2). SiliaCat DPP-Pd can be used to heterogeneously catalyze this reaction with largely enhanced reaction rate and catalyst stability. The borylation can either be done under standard condition or flow chemistry. A few examples of the scope of this reaction are presented here but all results can be found in the related publications.



X = I, Br, Cl

Base and Solvent Nature Effects

The reaction conditions were optimized by using 4-bromobenzonitrile as a substrate. Stronger bases, such as K_3PO_4 or K_2CO_3, promoted further reactions of the arylboronic esters thus formed with the haloarenes resulting in contamination by a substantial amount of dimer (*36 - 60 % yield*). Milder KOAc base was unexpectedly the best basic species. Best results in terms of conversion and selectivity were obtained by performing the reaction in alcohol (*i-PrOH, n-BuOH, 2-BuOH*) and alcohol mixtures such as *n*-PrOH / MeOH. The use of anhydrous solvent generally increases the selectivity. Results presented in this table were obtained using 1 mol % of catalyst for the coupling of B_2Pin_2 and 4-bromobenzonitrile.

Base and Solvent Nature Effect

Entry	Solvent	t [*h*]	Conv. (*Select.*)* [%]
1*	anhydrous EtOH	1	100 (82)
2	*n*-PrOH HPLC	1	97 (63)
3	anhydrous *n*-PrOH	1	99 (90)
4	*i*-PrOH HPLC	1	100 (80)
5	anhydrous *i*-PrOH	1	100 (99)
6	*n*-BuOH HPLC	1	96 (62)
7	anhydrous 2-BuOH	1	100 (85)
8	anhydrous DMF	1	94
		2	100 (85)
9	anhydrous DMF / *i*-PrOH	1	100 (84)
10	anhydrous DMSO	1	69
		2	71 (84)

Experimental conditions: Substrate (*5 mmol, 1 equiv*), KOAc (*2 equiv*), solvent (*20 mL; 0.5 M, molar concentration with respect to the reagents or substrate*), SiliaCat DPP-Pd (*0.2 g, Pd loading 0.25 mmol/g*), 1 h at 82°C.
* Conversion / selectivity evaluated by GC-MS.

Scale-up Study

A scale-up reaction from 10 mmol to 200 mmol substrate was studied for the borylation reaction of 4-bromoanisole over 2 mol % SiliaCat DPP-Pd.

The study reveals that there is no induction period. More than 70 % of 4-bromoanisole was converted to the borylation product within the first 30 min of reaction and nearly all (*98 - 99 %*) substrate was converted in 90 min, except for the reaction with 10 mmol substrate in which the complete conversion required approximately 3 h.

Scale-up Study

Substrate [*mmol*] / [*equiv*]	t [*h*]	Conv. (*Select.*) [%]	Yield [%]
10 / 1	0.5	77	95
	2	92	
	3	100 (97)	
20 / 1	0.5	77	97
	1.5	98	
	2	100 (98)	
40 / 1	0.5	77	97.2
	1.5	99	
	2	100 (98)	
40 / 1	0.5	78	97.5
	1.5	98	
	2	100 (98)	
200 / 1	0.5	79	97
	1.5	99	
	2	100 (98)	

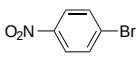
Reaction Method Variation

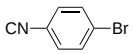
During our investigation, we found out that the substrate's nature has a direct influence on the performance of the borylation. Two methods were developed, one for substrates bearing electron-withdrawing groups and another for substrates containing electron-donating groups and heteroatoms.

Substrate Scope

To explore the scope of the borylation using Silia*Cat* DPP-Pd, we extended its application to various aryl chlorides, bromides and iodides carrying electron-withdrawing or electron-donating groups, and to heteroatom substrates such as pyridine, indole and quinoline. In general, borylation proceeded in good to excellent yields, achieving the desired boronic ester in 3 h. Few examples of conversion and selectivity evaluated by GC-MS are presented below (*refer to the related publication for all results*).

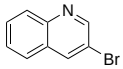
Substrate Scope Conversion and Selectivity Results of Coupling Reaction with of B_2Pin_2 (*conversion / selectivity in %*)

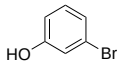

100 / 97

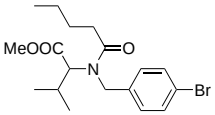

100 / 99

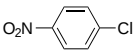

99 / 87

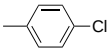

100 / 98

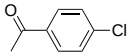

100 / 88

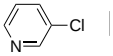

100 / 98

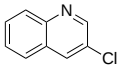

100 / 97

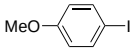

100 / 75

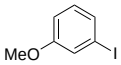

100 / 97


100 / 98


98 / 96

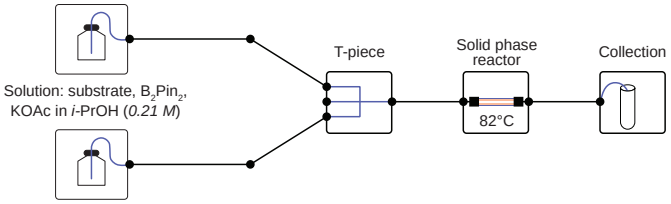

100 / 70


82 / 98


100 / 98

Borylation in Flow Chemistry Scope

The borylation coupling can also be done in flow chemistry. The figure to the right presents the setup used to allow fast and reproducible mixing of liquid reactants in the presence of the solid catalyst. Only one solution was prepared mixing the substrate, bis(pinacolato)diboron and base (*KOAc*) in *i*-PrOH solvent. The solid-phase reactor (*2.4 or 5.1 mL*) was thus charged with respectively 0.80 g and 1.76 g of Silia*Cat* DPP-Pd.



Borylation in Flow Chemistry using Silia*Cat* DPP-Pd

Substrate	Silia*Cat* DPP-Pd	*i*-PrOH (*M*)*	Conditions		Conv. (%)	Select. (%)
			Flow (*mL/min*)	RT (*min*)		
4-bromo-benzonitrile	1 mol %	0.50	Batch	60	100	99
	0.8 g (R_1)	0.25	0.50	2.05	100	95
4-bromo-anisole	2 mol %	0.75	Batch	180	100	99
	1.76 g (R_2)	0.21	0.25	8.67	92	95
2-bromo-toluene	2 mol %	0.75	Batch	120	100	98
	1.76 g (R_2)	0.21	0.25	8.67	97	98

* Molar concentration with respect to the substrate

The optimal reaction conditions developed in the batch reaction over Silia*Cat* DPP-Pd for the borylation reaction of 4-bromobenzonitrile, 4-bromoanisole and 2-bromotoluene were tested under flow in the modular Asia 220 flow chemistry system commercialized by Syrris using a more diluted solution to ensure a homogeneous reaction mixture.

For all experiments, faster kinetics were observed in flow with excellents conversion and selectivities.

Conclusion for the Borylation Reaction

The heterogeneously catalyzed direct synthesis of boronic esters can now be performed with a wide range of aryl chlorides, bromides and iodides, and bis(pinacolato)diboron as the borylating agent over Silia*Cat* DPP-Pd. The use of anhydrous non-toxic *i*-PrOH as a reaction solvent avoids homocoupling and increases the selectivity.

Excellent yields and selectivities were achieved with very low leaching of Pd during catalysis. All the reagents utilized are stable in air and can be easily scaled up. Hence, the process does not require the use of a glovebox or inert conditions, with relevant practical advantages over existing methods that often require the exclusion of air and humidity from the reaction system.

Related Publications for Borylation Reactions

Chem. Cat. Chem., **2014**, *6*, 1340-1348
Org. Proc. Res. Dev., **2014**, *18*, 1556-1559
J. Org. Chem., **2014**, *10*, 897-901

Typical Experimental Procedure: Borylation over SiliaCat DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*).
Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, bis(pinacolato)diboron and the base are added to the reaction solvent.
- After 5 minutes stirring, the aryl halide is added to the resulting mixture.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.
  For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

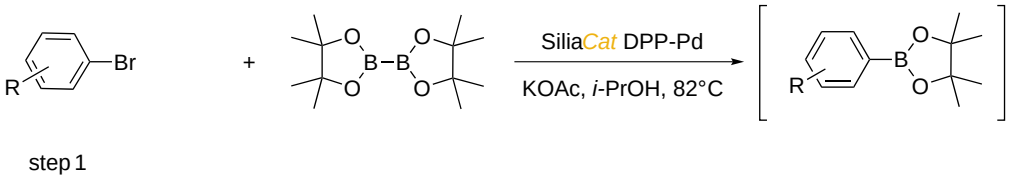
Miyaura Borylation Reactions over Silia*Cat* DPP-Pd			
Substrates	**Aryl-Iodide (*1 equiv*)**	**Aryl-Bromide (*1 equiv*)**	**Aryl-Chloride (*1 equiv*)**
Bis(pinacolato)diboron	1.2 equiv		1.5 equiv
Base KOAc	2.2 equiv		3.0 equiv
Silia*Cat* Loading	≤ 2.0 mol % Pd		
Best Solvents (*anhydrous*)	*i*-PrOH (*0.75 M*)*		*i*-PrOH (*1.25 M*)*
	[*alternate solvents: 2-BuOH, DMF, EtOH (anhydrous solvents)*]		
Temperature	80 - 82°C		
Reaction Time	0.5 - 3.0 h		3.0 - 20 h
Typical Scale	• Under Magnetic Stirring for Screening: 10 mmol scale of aryl halide in 30 mL solvent (*for Ar-Br and Ar-Cl*) or in 20 mL solvent (*for Ar-I*) • Under Mechanical Stirring for Reusability: 20 mmol scale of aryl halide in 60 mL solvent (*for Ar-Br and Ar-Cl*) or in 40 mL solvent (*for Ar-I*).		

* Molar concentration in rapport to the substrate

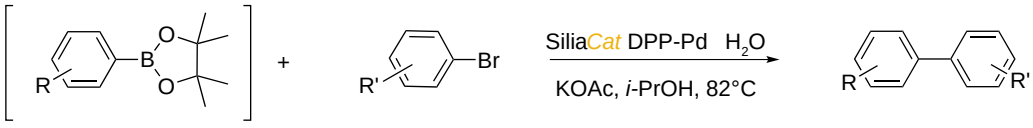
One-Pot Borylation and Suzuki-Miyaura Coupling Reactions of Aryl Halide

Unsymmetrically coupled biaryls are synthesized in high yield starting from different aryl bromides and bis(pinacolato) diboron by carrying out the Miyaura borylation reaction followed by Suzuki-Miyaura reaction in the same reaction pot over 1 - 2 mol % Silia*Cat* DPP-Pd. This catalyst is air-stable and the method does not require the use of inert conditions. The use of non-toxic isopropanol or 2-butanol as reaction solvent further adds to the environmental benefits of this new green synthetic methodology. We present here a brief overview of all results presented in the related publication.

The Silia*Cat* DPP-Pd catalyst mediates the borylation and the subsequent Suzuki-Miyaura reaction in an elegant one-pot sequential synthesis. Hence, an aryl bromide is first converted into the corresponding boronic acid pinacol ester (*step 1*). A different aryl bromide is then added along with aqueous base (*step 2*).



step 1

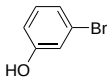
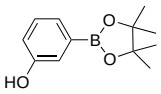
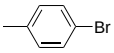
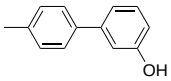
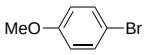
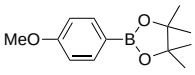
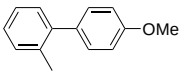
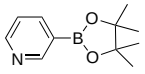
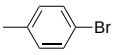
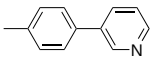


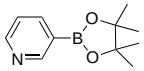
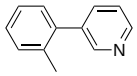
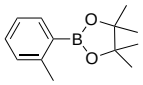
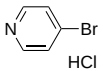
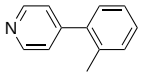
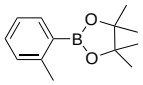
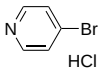
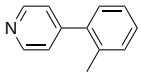
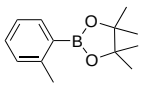
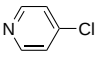
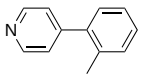
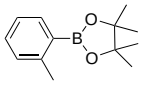
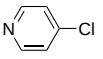
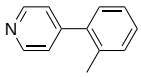
step 2

One-Pot Reaction Scope

Some experiments were tried to demonstrate the versatility of the method. The reaction is carried out in *i*-PrOH or in 2-BuOH. No work-up is performed after the borylation in the first step, nor is any catalyst added prior to conducting the second step of the sequence, the Suzuki-Miyaura reaction. Results shows that different unsymmetrically coupled compounds were obtained in good to excellent yields by coupling numerous different aryl bromides with different aryl halides, including heteroatom-containing aryls.

One-Pot Silia*Cat* DPP-Pd-catalysed Borylation and Suzuki-Miyaura Coupling Reactions

Entry	Substrate	Catalyst (*mol %*)	Base (*equiv*)	Solvent (*M*)	Product	t (*h*)	Conv / Selec (*Yield*) (%)
1		Silia*Cat* DPP-Pd 2	KOAc 2.2	*i*-PrOH (*0.75*)		2	100 / 99
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	85
2		Silia*Cat* DPP-Pd 2	KOAc 2.2	*i*-PrOH (*0.75*)		3	99 / 98
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	92 / 97 (88)
3		Silia*Cat* DPP-Pd 2	KOAc 2.2	*i*-PrOH (*0.75*)		2 3	89 100 / 98
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	83

One-Pot Silia*Cat* DPP-Pd-catalysed Borylation[a] and Suzuki-Miyaura Coupling[b] Reactions (*con't*)							
Entry	**Substrate**	**Silia*Cat* DPP-Pd (*mol %*)**	**Base (*equiv*)**	**Solvent (*M*)[c]**	**Product**	**t (*h*)**	**Conv / Selec (*Yield*)[d] (%)**
4		2	KOAc 2.2	*i*-PrOH (*0.75*)		3	100 / 98
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	82
5		2	KOAc 2.2	*i*-PrOH (*0.75*)		1 2	90 100 / 99
		-	K_2CO_3 2.3	+ 8 mL H_2O		1 3	99 / 95 (89)
6[e]		1	KOAc 2.2	2-BuOH (*1.00*)		1 2	98 100 / 99
		-	K_2CO_3 2.3	+ 8 mL H_2O		1 3	100 / 98 (94)
7[e]		1	KOAc 2.2	2-BuOH (*1.00*)		1 2	98 100 / 99
		-	K_2CO_3 2.3	+ 8 mL H_2O		3 17	86
8[e]		1	KOAc 2.2	2-BuOH (*1.00*)		1 2	98 100 / 99
		1	K_2CO_3 2.3	+ 8 mL H_2O		1 3	95

Experimental conditions. [a]Step 1: Substrate 1 (*10 mmol, 1 equiv*), B_2Pin_2 (*11 mmol, 1.1 equiv*), KOAc (*22 mmol, 2.2 equiv*), 28 mL anhydrous *i*-PrOH, 2 mol % Silia*Cat* DPP-Pd (*0.25 mmol/g palladium loading*), at 82°C. [b]Step 2: Substrate 2 (*12 mmol, 1.2 equiv relative to substrate 1*), K_2CO_3 (*23 mmol, 2.3 equiv relative to substrate 1*), 8 mL distilled H_2O (*i-PrOH / H_2O, 3.5:1, v/v*). [c]Molar concentration with respect to the substrate and to B_2Pin_2. [d]Conversion / selectivity in cross-coupling product evaluated by GC-MS. Yield of the isolated product is given in parentheses. [e]The borylation reaction is carried out at 98°C in 21 mL anhydrous 2-BuOH (*1.0 M molar concentration with respect to the reagents*.)

Conclusion for One-Pot Borylation and Suzuki Coupling

Unsymmetrically coupled biaryls can be synthesized in high yields starting from different aryl bromides and bis(pinacolato) diboron by carrying out the Miyaura borylation reaction followed by the Suzuki-Miyaura reaction over 1 - 2 mol % catalytic amount of Silia*Cat* DPP-Pd in the same reaction pot. There is no need to isolate the intermediate boronic ester, while the air stable sol-gel entrapped palladium catalyst does not require the use of inert conditions.

Finally, the use of isopropanol or 2-butanol as reaction solvents further points out the environmental benefits of the method. As the fine chemicals and pharmaceutical industries are eventually adopting green chemistry synthetic methodologies, this method provides both industries with a clean route to valued compounds that are widely used in many industrial sectors.

Related Publication for Borylation Reactions

Beilstein J. Org. Chem., **2014**, *10*, 897-901

Typical Experimental Procedure: One-Pot Miyaura Borylation / Suzuki Coupling

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required.

Step1: Miyaura Borylation Reaction

- Using the appropriate apparatus recommended for the screening or the reusability reactions, the bis(pinacolato)diboron and the base are added to the reaction solvent.
- After 5 minutes stirring, the aryl halide (*substrate 1*) is added to the resulting mixture and is then warmed up to the desired temperature after which Silia*Cat* is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*). No work-up is performed after the borylation in the first step.

Step 2. Suzuki-Miyaura Coupling Reaction

- After maximum conversion of substrate 1 (*as determined by TLC or GC/MS analysis*), substrate 2 (*aryl bromide or aryl chloride*) and an aqueous K_2CO_3 solutions are added to the reaction mixture.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion of boronic acid obtained in step 1 is reached (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- Silia*Cat* (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- Silia*Cat* is dried under air at room temperature and can be stored in a closed vessel prior to reuse in these conditions.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in ethyl acetate (*EtOAc*) or diethyl ether (Et_2O).
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

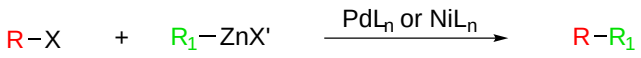
Please see "*Optimization Steps*" presented at page 37.

Step 1: Miyaura Borylation Reaction using Silia*Cat* DPP-Pd		
Substrates 1	**Aryl-Bromide (*1 equiv*)**	**Aryl-Chloride (*1 equiv*)**
Bis(pinacolato)diboron	1.1 equiv	
Base: KOAc	2.2 equiv	
Silia*Cat* Loading	≤ 2.0 mol % Pd	
Best Solvents (*anhydrous*)	*i*-PrOH (*0.75 M*)	*i*-PrOH (*0.75 M*) or 2-BuOH (*1.00 M*)
	Molar concentration with respect to the substrate and the bis(pinacolato)diboron	
Temperature	80 - 82°C	
Reaction Time	0.5 - 3 h	3 - 20 h

Step 2: Suzuki-Miyaura Coupling using Silia*Cat* DPP-Pd		
Substrates 2	**Aryl Bromide (*1.2 equiv*)**	**Aryl Chloride (*1.2 equiv*)**
Base K_2CO_3	2.3 equiv	
Co-solvent	H_2O (*i-PrOH / H_2O, 3.5:1, v/v*)	H_2O (*2-BuOH / H_2O, 2.6:1, v/v*)
Temperature	80 - 80°C	96 - 98°C
Reaction Time	2 - 4 h	2 - 17 h
Typical Scale	• Under Magnetic Stirring for Screening: 10 mmol scale of aryl halide in 30 mL of *i*-PrOH or in 20 mL of 2-BuOH. • Under Mechanical Stirring for Reusability: 20 mmol scale of aryl halide in 60 mL of *i*-PrOH or in 40 mL of 2-BuOH.	

Negishi Coupling Reaction Using Silia*Cat* DPP-Pd

The Negishi C-C coupling is a widely used reaction that couples organic halides, triflates or acetyloxy groups with organozinc using either a palladium or a nickel catalyst. This coupling is gaining in popularity and is often used to synthesize acyclic terpenoid systems. However the reaction needs to be performed under inert and anhydrous conditions due to the sensitivity of the organozincs.



This section presents results in flow chemistry using Silia*Cat* DPP-Pd as catalyst for the Negishi coupling.

Case Study: Silia*Cat* DPP-Pd in a Mild Alkyl-Aryl Negishi Cross-Coupling in Flow Chemistry

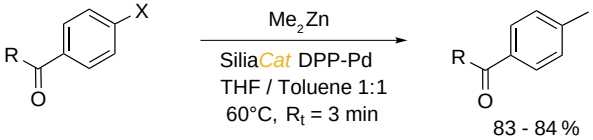
Authors: Alcázar (*Janssen Research and Development*) *et al.*
Publication: *Journal of Flow Chemistry*, **2014**, *4*, 22-25

Overview

After obtaining excellent results for a mild Suzuki-Miyaura coupling catalyzed by Silia*Cat* DPP-Pd (*p. 34*), Alcázar *et al*. later reported using the same catalyst for a novel alkyl-aryl Negishi cross-coupling in flow, in very mild and clean conditions.

The group reports that *"after screening a wide variety of reaction conditions in batch using microwave irradiation,* Silia*Cat* *DPP-Pd was identified as the most suitable catalyst for the coupling of a model system consisting of 1-bromo-4-nitrobenzene and dimethylzinc"*.

Scale-up runs:



Conclusion

The reaction was achieved in very mild conditions and quickly. Good to excellent yields were obtained in most cases: esters, ketones, aldehydes, heterocyclic substrates and compounds bearing ortho substituents were compatible in the process, as well as aryl bromides, iodides and activated chlorides. Triflates and nonaflates, on the other hand, could not be coupled efficiently.

The same catalyst cartridge could be re-used for more than 20 consecutive reactions without any decrease in activity and minimal leaching, even on scale-up runs (*27 ppb of Pd*).

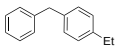
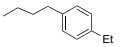
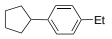
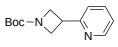
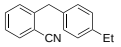
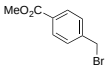
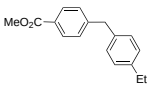
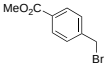
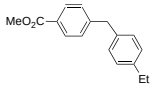
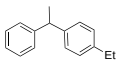
Case Study: Silia*Cat* DPP-Pd in the Synthesis of Organozinc Halides Coupled to Negishi Reactions

Authors: Alcázar (*Janssen Research and Development*) *et al*.
Publication: *Advanced Synthesis & Catalysis,* **2014**, *356,* 3737-3741

Overview

Negishi coupling is one of the very useful carbon-carbon bond forming coupling reaction, but a little less known than other types of coupling due to the less available organozinc species. Alcázar (*Janssen-Cilag*), McQuade (*Florida State University*) and coworkers reported an effective and reproducible synthesis of organozinc halides with excellent yields, using an activated packed-bed of metallic zinc. Such organozinc species could further be used downstream in subsequent Negishi couplings, catalysed with Silia*Cat* DPP-Pd.

Negishi Coupling

Entry	R-X	Aryl-X	Product	Yield *(%)*
1[a]				81
2[b]				74
3[c]				83
4[d]				71
5[a]				81
6[a]				79
7[b]				82
8[b]				84
9[a]				86

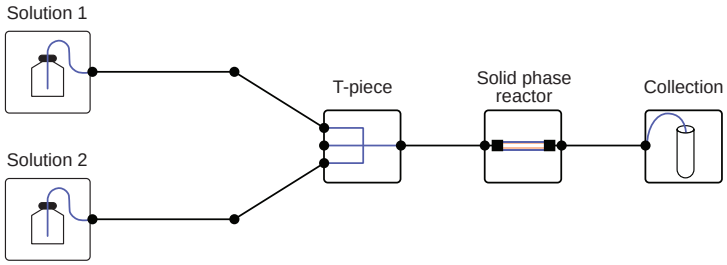
[a] Zn column, r.t.; Silia*Cat* DPP-Pd column 60°C., [b] Zn column, 60°C; Silia*Cat* DPP-Pd 60°C.
[c] Zn column, 60°C and LiCl (*1 equiv*) as additive; Silia*Cat* DPP-Pd column, 80°C.
[d] Zn column, 110°C and LiCl (*1 equiv*) as additive; Silia*Cat* DPP-Pd column, 60°C. [e] Zn column, r.t.; Silia*Cat* DPP-Pd column, 80°C.

Conclusion

It was demonstrated that a large library of organozinc halides could be produced from shelf-stable halides and used *in situ* in a continuous packed-bed approach. Moreover the team reports that "*the two stage zinc insertion / Negishi reaction functions at the high end laboratory scale with ease suggesting that the approach is stable and robust enough to support much larger scale chemistry*".

Typical Experimental Procedure: Negishi Couplings in Flow Using Silia*Cat* DPP-Pd

- Typical coupling reactions are performed in an appropriate solvent (*HPLC grade*) at the recommended temperature (*see table below*). Anhydrous solvents and inert conditions are required.



- Typical Flow Setup:
- Solution Preparation:
  - *Solution 1*: aryl halide (*1 equiv*) in dry THF (*0.20 M*)
  - *Solution 2*: organozinc reagent (*1.3 equiv*) in dry toluene (*0.30 M*)
- The two solutions are pumped using the flow system.
- The solutions, mixed in a T-piece device, are driven through a preheated glass column reactor with an adjustable end (*0.785 cm ID × 6.5 cm length*) packed manually with Silia*Cat* DPP-Pd (*1 g*).
- The conversion of the aryl halide is monitored at the reactor outlet using GC-MS.

Work-up

Isolation of the coupling product

- The outlet solution is concentrated in vacuo and the residue is redissolved in ethyl acetate (*EtOAc*) or diethyl ether (Et_2O)
- The organic layer is then washed twice with water and once with brine.
- The organic layer is separated, dried using anhydrous magnesium sulfate, filtered and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

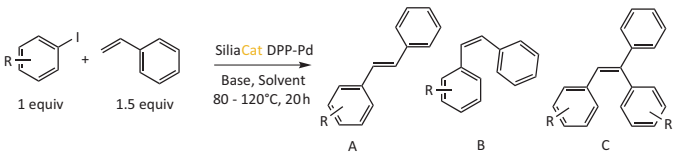
Negishi Coupling in Flow using Silia*Cat* DPP-Pd	
Substrates	***Solution 1*: Halide & Pseudohalide solution, 0.25 M in anhydrous THF (*1 equiv*)**
R_1R_2Zn	*Solution 2*: Organozinc solution, 0.30 M in anhydrous toluene (*1.3 equiv*)
Silia*Cat* Catalyst (*column reactor*)	Preheated glass column reactor with an adjustable end (*0.785 cm ID x 6.5 cm length*) charged with 1 g supported catalyst.
Temperature	60°C
Residence Time	3 min
Flow Rate	*Solution 1*: 0.20 mL/min *Solution 2*: 0.30 mL/min

Heck Coupling Using SiliaCat DPP-Pd

The Heck reaction, also known as the Mizoroki-Heck reaction, is the coupling of a halide with an alkene in the presence of a base and a palladium catalyst. This coupling allows a substitution reaction on alkenes and is of great importance in pharmaceutical research. We determined that the best catalyst for this reaction is SiliaCat DPP-Pd. It showed good reactivity for aryl iodides, bromides and chlorides.

Base and Solvent Effects

The Heck coupling between iodobenzene and styrene was used to evaluate the influence of solvent and base. The best combinations are KOAc / DMF, Et_3N / MeCN and nPropyl / neat. Using these systems, high yields and great selectivity in favor of product A were obtained.



Base and Solvent Effects (*SiliaCat DPP-Pd*)

SiliaCat (*mol %*)	Base	Solvent (*0.4 M*)*	Time (*h*)	Conversion A / B / C (%)
0.5	KOAc	DMF	24	100 (90 / 9.5 / 0.5)
	Na_2CO_3		24	67 (62 / 47 / 0)
0.1	Et_3N	MeCN	24	93 (77 / 6 / 11)
		H_2O	24	75 (70 / 5 / 0)
	nPropyl	(*neat*)	20	100 (95 / 5 / 0)

* Solvent substrate concentration

Catalytic Performance and Comparison vs Homogeneous Catalyst

SiliaCat DPP-Pd is a very efficient catalyst for the Heck coupling and allows greater selectivity over a homogeneous Pd catalyst (*TPP is required*). In addition to affording a higher yield of the desired product, the catalyst left minimal residual Pd, TPP or TPPO in solution that would have otherwise required the use of a metal scavenger, chromatography or trituration to remove.

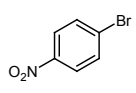
Catalytic Performance and Comparaison vs Homogeneous

Substrate R	Substrate X	SiliaCat DPP-Pd (*mol %*)	Base	Solvent (*0.4 M*)*	Conversion A / B / C (%)	Phosphine Leaching (*ppm*)
4-CN	Br	0.25	NaOAc	DMF	100 (95 / 5 / -)	-
4-NO_2					99 (97 / 2 / -)	-
2-CH_3			Et_3N	MeCN	71 (67 / 5 / -)	-
4-OMe	I				75 (60 / 15 / -)	-
H	I	0.1			100 (98 / 2 / -)	0
H	I	1.0 $Pd(OAc)_2$ PPh_3	Et_3N	MeCN	100 (70 / 22 / 8)	6,030

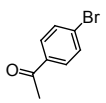
* Solvent substrate concentration

Substrate Scope and Microwave Compatibility

SiliaCat DPP-Pd is an efficient catalyst in the Heck coupling with different substrates. In all cases, conversion and selectivity were excellent. Microwave technology allows faster kinetics with good yields.



Substrate #1



Substrate #2

Substrate Scope and Microwave Compatibility

Substrate	Mode	mol %	Time	Temp. (°C)	Conv. / Sel. (%)
#1	Batch	0.5	24 h	120	100 / 97
	Microwave	0.2	10 m	125	93 / 85
#2	Batch	0.2	24 h	135	100 / 98
	Microwave	0.2 0.5[1]	10 m 30 m[1]	125 150[1]	92 / 81 99 / 93[1]

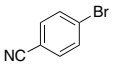
[1] Et_3N in water

Comparison of Various Heterogeneous Pd-Catalysts

The effectiveness of Silia*Cat* DPP-Pd for the Heck coupling were investigated and compared with other catalysts (*heterogeneous and homogeneous*) available on the market often used for this coupling.
It is very important to note that for all reactions, all catalysts were used in the manufacturer's optimized reactions and not just SiliCycle's in order to be able to make relevant conclusions. Experiments were performed with two different aryl halides and alkenes.

Experimental conditions

- Protocol with Silia*Cat* DPP-Pd was drawn from *Topics in Catalysis*, **2010**, *53*, 1059-1062
  [*0.1 mol % Silia*Cat* DPP-Pd; Et_3N; H_20; 100°C; 24 h*]
- Protocol with PhosphonicS was drawn from *Journal of Molecular Catalysis A: Chemical*, **2007**, *273*, 298-302
  [*5 mol % Si-Palladium acetate ethylthioglycolate; K_2CO_3; NMP; 110°C; 24 h*]
- Protocol for Johnson-Matthey Pd-Smopex-111 was drawn from *Org. Proc. Res. Dev.*, **2007**, *11*, 769-772
  [*2.5 weight % Pd-Smopex-111; NMP; 118°C; 20 - 24 h*]. Synthetized from Smopex-111 and $Pd(OAc)_2$.
- Typical protocol with the homogeneous catalyst: 1 mol % $Pd(OAc)_2$, PPh_3; TMEDA, 125°C; 24 h.

Heck Coupling Conversion Comparison (*in %*)					
Aryl Halide	Vinyl	Silia*Cat* DPP-Pd	Pd Smopex-111	Phosphonics SCRPd	$Pd(OAc)_2$
		**98**	23	63	0
		**76**	0	0	0

Conclusion

Experiments showed that Silia*Cat* DPP-Pd was the most effective catalyst. PhosphonicS' catalyst showed good results, but 10 times more w/w, 20 times more mol % Pd were required.

Conclusion for Heck Coupling

Various aryl iodides and aryl bromides were tested in the Heck coupling using the Silia*Cat* DPP-Pd in batch mode and under microwave irradiation. Obtained results show good conversions for aryl iodide and bromide substrates with different electron-withdrawing groups and electron-donating groups. The use of Silia*Cat* DPP-Pd for the Heck coupling allows clean final product with minimal purification and no contamination with palladium, TPP or TPPO.

Related Publication for Heck Coupling

Org. Proc. Res. Dev., **2012**, *16*, 117-122

Typical Experimental Procedure: Heck Couplings over Silia*Cat* DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse. For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

Heck Coupling Reactions over Silia*Cat* DPP-Pd		
Substrates	**Aryl-Iodide (*1 equiv*)**	**Aryl-Bromide (*1 equiv*)**
Olefin	1.5 equiv	
Base	1.5 equiv [Et_3N or NaOAc]	1.5 equiv [NaOAc]
Silia*Cat* Loading	≤ 0.5 mol % Pd	
Best Solvents & Temperature	MeCN (*80°C*) or DMF (*120°C*)	DMF (*120°C*)
Reaction Time	20 - 24 h	
Typical Scale	• Under Magnetic Stirring for Screening: 20 mmol scale of aryl halide in 15 mL MeCN or in 20 mL DMF. • Under Mechanical Stirring for Reusability: 40 mmol scale of aryl halide in 30 mL MeCN or in 40 mL DMF.	

Sonogashira Coupling Using SiliaCat DPP-Pd & Pd⁰

The Sonogashira coupling reaction of aryl halides and terminal acetylenes is an effective method for the formation of substituted acetylenes. This reaction is frequently utilized as a key step in natural product chemistry and for the synthesis of acetylene compounds, which have several applications.

Catalyst Concentration and Solvent Effects

Sonogashira coupling between iodonitrobenzene and phenylacetylene was achieved easily and without the need for co-catalysts to activate the alkyne, making the use of SiliaCat an efficient method for the formation of substituted acetylenes. All catalysts screened presented excellent efficiency, even in low amounts.

Catalyst Concentration and Solvent Effects

SiliaCat DPP-Pd

mol (%)	Solvent (*M*)*	Time	Conv. (%)
0.5	EtOH / H_2O (*0.07*)	30 min	100
	MeOH / H_2O (*0.07*)	5 min	100
0.1	EtOH / H_2O (*0.07*)	1 h	100
	MeOH / H_2O (*0.07*)	15 min	100
0.01	EtOH / H_2O (*0.13*)	3 h	100
0.002	EtOH / H_2O (*0.13*)	8 h	100

Catalyst Concentration and Solvent Effects

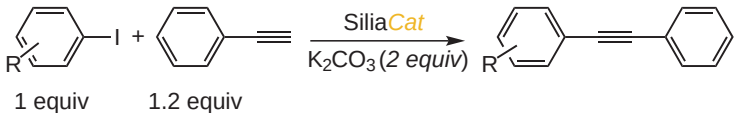
SiliaCat Pd⁰

mol (%)	Solvent (*M*)*	Time	Conv. (%)
0.1	EtOH (*0.1*)	2 h	100
	EtOH (*0.05*)	30 min	100

* Solvent substrate concentration

Iodo-Substrate Scope and Microwave Compatibility

Couplings with iodoaryls and phenylacetylene were also investigated. The table below shows that SiliaCat is an efficient tool for the formation of substituted acetylenes.



1 equiv 1.2 equiv

Iodo-Substrate Scope and Microwave Compatibility

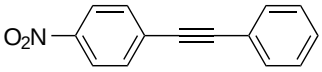
R	Mode	SiliaCat DPP-Pd mol (%)	SiliaCat DPP-Pd Conditions	SiliaCat DPP-Pd Conv. / Sel. (%)	SiliaCat Pd⁰ mol (%)	SiliaCat Pd⁰ Conditions	SiliaCat Pd⁰ Conv. / Sel. (%)
4-NO_2	Batch	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100
	MW	0.6	MeOH / H_2O (*0.2 M*) 100°C, 2 min	100 / -	0.1	MeOH (*0.1 M*) 75°C, 5 min	100 / -
4-OMe	Batch	1	EtOH (*0.08 M*) 77°C, 4 h	99 / 98	1	EtOH (*0.08 M*) 77°C, 4 h	99 / 98
4-CH_3	Batch	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100
	MW	0.5	MeOH / H_2O (*0.2 M*) 100°C, 2 min	90 / -	0.1	MeOH (*0.2 M*) 75°C, 5 min	100 / -

Bromo-Substrate Scope and Microwave Compatibility

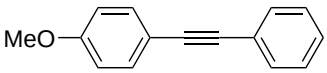
SiliaCat DPP-Pd and Pd^0 are also efficient catalysts for use with bromo substrates. A few examples of the Sonogashira coupling between various bromoaryls substrates (*1 equiv*) and phenylacetylene (*1.25 equiv*) using K_2CO_3 (*2 equiv*) in MeOH (*0.2 M*) are shown below.

Conversions obtained with 1 mol % of SiliaCat DPP-Pd and / or Pd^0 under microwave irradiation are presented below. Classical heating is also possible, but kinetics are significantly lower (*a few hours compared to 15 minutes*).

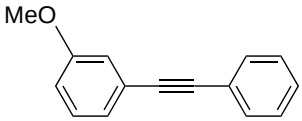
From Aryl Iodide Substrate Scope Conversion Results



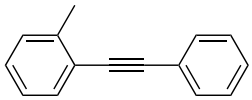
DPP-Pd: 99 %
Pd^0: 99 %



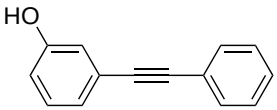
DPP-Pd: 98 %
Pd^0: 98 %



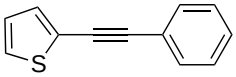
DPP-Pd: 99 %
Pd^0: 97 %



DPP-Pd: 98 %
Pd^0: 90 %

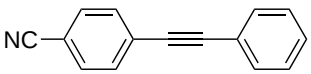


DPP-Pd: 89 %
Pd^0: 80 %

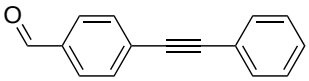


DPP-Pd: 82 %
Pd^0: 74 %

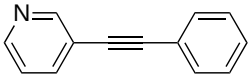
From Aryl Bromide Substrate Scope Conversion Results



DPP-Pd: 98 %
Pd^0: 98 %



DPP-Pd: 98 %
Pd^0: 98 %



DPP-Pd: 86 %
Pd^0: 82 %

Conclusion for Sonogashira Coupling

Sonogashira cross couplings can be smoothly carried out over a small amount (*0.5 - 1 mol %*) of SiliaCat DPP-Pd or Pd^0 catalyst under ligand-free and copper-free conditions. The scope of the method does not include aryl chlorides yet.

Related Publications for Sonogashira Coupling

Catal. Sci. Technol., **2011**, *1*, 736-739
Org. Proc. Res. Dev., **2012**, *16*, 117-122
ACS Sustainable Chem. Eng., **2013**, *1*, 57-61

Typical Experimental Procedure: Sonogashira Couplings over Silia*Cat*

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd or Pd^0 is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse. For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

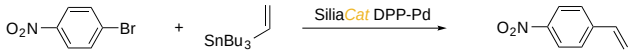
Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

Sonogashira Coupling Reactions over Silia*Cat* Catalysts		
Products	**Aryl Iodide**	**Aryl Bromide**
Alkyne	1.2 equiv	1.3 equiv
Base	K_2CO_3 2.0 equiv	KOAc 2.0 equiv
Silia*Cat* Catalyst	Silia*Cat* DPP-Pd or Pd^0 (*CuI free*)	
Silia*Cat* Loading	≤ 1.0 mol % (*DPP-Pd*) ≤ 0.5 mol % (*Pd^0*)	≤ 2.0 mol %
Best Solvent (*HPLC Grade*) & Temperature	MeOH (*63°C*) or EtOH (*77°C*)	DMF or DMAc (*80°C*)
Reaction Time	0.5 - 4.0 h	2.0 - 4.0 h
Typical Scale	• Under Magnetic Stirring for Screening: 6 mmol scale of aryl iodide in 60 mL MeOH or EtOH. • Under Mechanical Stirring for Resusability: 20 mmol scale of aryl bromide in 40 mL solvent.	

Stille Coupling Using SiliaCat DPP-Pd

The Stille coupling is a versatile reaction for C-C bond formation. It is a coupling between a halide and an organotin compound. This reaction is widely used in synthesis, but a major drawback is the toxicity of the tin compounds involved. In Stille couplings, a Pd^0 or Pd^{II} catalyst is required and it must be compatible with a wide variety of functional groups (*very few limitation on the R-group*). SiliCycle has developed catalysts that are highly efficient for Stille couplings, as shown below.



Catalyst Concentration and Solvent Effects

In this work we report the heterogeneous SiliaCat DPP-Pd Stille coupling reaction of 4-bromonitrobenzene with tributylvinyltin in dioxane or in toluene.

The results presented in the table show the importance of the solvent. Al low catalyst concentration (*0.25 mol % of SiliaCat DPP-Pd in toluene*) the reaction was complete in 17 h.

However, under the same conditions but in dioxane as solvent, only 50 % conversion was obtained in 17 h and 74 % in 22 h. To improve the conversion in dioxane the amount of catalyst was increased from 0.25 mol % to 2 mol % of SiliaCat DPP-Pd with complete conversion in 17 h.

As a general rule, if the solvent and concentration of the substrate are kept constant, increasing the amount of catalyst, thus increasing the number of catalytic sites, will speed up the kinetics of the reaction.

Catalyst Concentration and Solvent Effects

SiliaCat DPP-Pd (*mol %*)	Solvent (*M*)*	Time (*h*)	Conversion (%)
0.25	Toluene (*0.1 M*)	17	99
	Dioxane (*0.1 M*)	17	50
		22	74
0.5		17	80
		22	100
2.0		17	99

SiliaCat DPP-Pd Reusability and Leaching

The evaluation of reusability and leaching was done using Stille coupling reaction of 4-bromonitrobenzene with tributylvinyltin in dioxane (*0.1 M*) over 2 mol % Pd, for 17 h. The minimal leaching and the robustness of the organoceramic matrix are important factors that allow SiliaCat DPP-Pd to be reused several times. After four runs, 100 % conversion is still achieved.

Scope Substrates and Additive CsF Influence

Reactions were performed at reflux until the GC/MS analysis showed maximum conversion. Anhydrous conditions are not required.

Catalytic Performance and Additive CsF Influence

Substrate (*R*)	Substrate (*X*)	SiliaCat DPP-Pd (*mol %*)	Additive (*equiv*)	Solvent (*0.1 M*)	Time (*h*)	Conversion (%)
4-CN	Br	2	-	Dioxane	18	87
4-F		10	-		24	99
			CsF (*2*)	Toluene		100
H			-			100
4-CH_3			CsF (*2*)	Dioxane		100
4-OCH_3						100
H	I			Toluene		100
4-NO_2		2	-	Dioxane	18	88

Note: R'$SnBu_3$ was vinyl (*1.1 equiv*)

SiliaCat DPP-Pd vs Competitive Catalysts

Always using the same reaction as for the reusability and leaching, comparative analysis with other Pd catalysts available on the market demonstrates SiliaCat DPP-Pd to be comparable or better in standard Stille conditions.

SiliaCat DPP-Pd vs Competitive Catalysts (*results in %*)					
SiliaCat DPP-Pd	Escat 1351	EnCat 30	Royer Catalyst	$Pd(PPh_3)_4$	$Pd(OAc)_2$
99	44	95	90	72	20

Case Study: Stille Reaction using the SiliaCat DPP-Pd in the Synthesis of a Thiophene-Phthalimide-Based Molecular Semiconductor under Microwave-Irradiation Conditions

Authors: Welch (*Dalhousie University*) *et al*.
Publication: *RSC Adv.*, **2015**, *5*, 26097-26106

Welch's group from Dalhousie University have studied the utility of a heterogeneous Pd catalyst for the synthesis of a molecular semiconductor, via various cross-coupling reactions (*Stille, Suzuki and direct heteroarylation*).

Stille Reaction

The target molecule, SM1 (*5,50(2,20-bithiophene-5,50 -diyl)- bis(2-hexylphthalimide*)), was synthetized under microwave irradiation via Stille reaction.

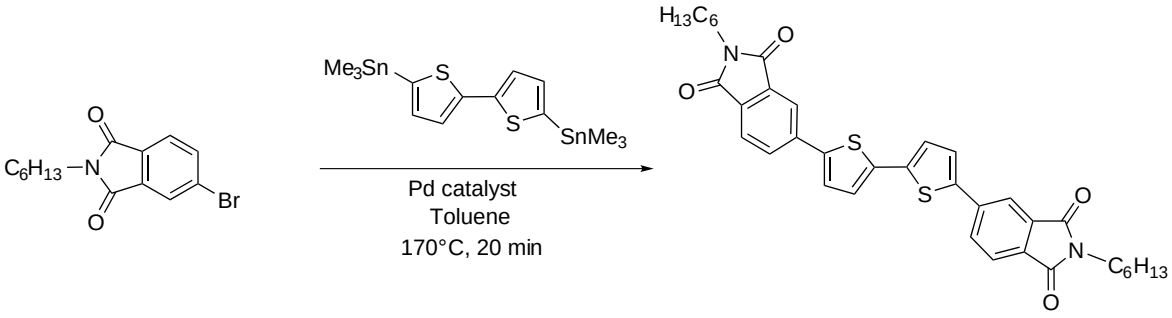
Three Pd-based catalysts were used for their initial screening:

1) $Pd(PPh_3)_4$
2) $Pd(PPh_3)_2Cl_2$
3) SiliaCat DPP-Pd

Welch and coworkers report that, while starting reagents were converted to SM1 with all three catalysts, SiliaCat DPP-Pd gave high yields, and SM1 was the major product albeit small baseline impurities (*H^1 NMR analysis*).

Conclusions

- *"Stille reaction protocols have highlighted the excellent performance of SiliaCat DPP-Pd in comparison to homogeneous catalyst alternatives and demonstrated effective conversion of starting material to product with catalyst loadings down to 0.1 mol %. SiliaCat DPP-Pd proved to be tolerant to both lab grade reagents and the capacity for two-fold recyclability without any significant impact on the material product and the respective yield".*
- *"The robust and efficient performance of SiliaCat DPP-Pd coupled with its capacity to be used and stored under ambient conditions should be extremely useful for both routine and selected synthesis of organic semiconductors relevant to the field of organic electronics, in particular photovoltaics and thin-film transistors".*

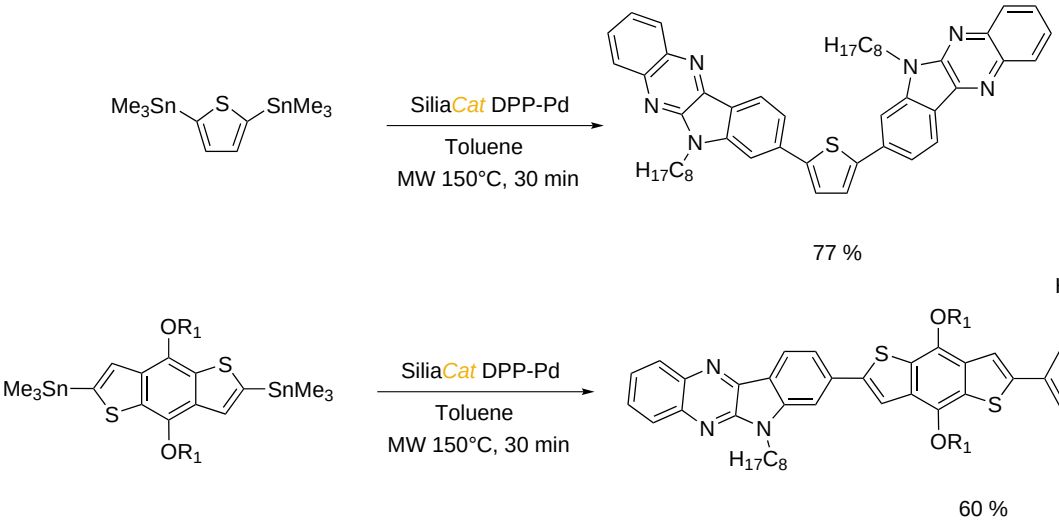


Case Study: Stille Coupling Using the Silia*Cat* DPP-Pd for the Synthesis of Indoloquinoxaline for Organic Electronics

Authors: Welch (*Dalhousie University*) *et al*.
Publication: *Dyes and Pigments*, **2015**, *123,* 139-146

Welch's group from Dalhousie University studied the utility of Silia*Cat* DPP-Pd in the synthesis of Indoloquinoxaline, a terminal building block for the construction of π-conjugated small molecules relevant to organic electronics. Indeed, indoloquinoxaline is a π-conjugated system that combines both electron withdrawing and donating nitrogen atoms.

Carbon-carbon bond forming reactions were done via a Stille coupling under microwave, using Silia*Cat* DPP-Pd.



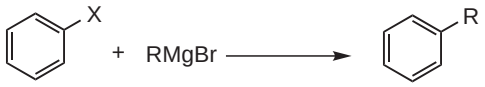
Conclusion for Stille Coupling

The Silia*Cat* DPP-Pd is a great alternative to homogenous catalysts for the Stille coupling. It can be used in various type of applications such as the synthesis of active intermediates and also in electronics. The catalyst is reusable and yields coupling products with minimal leaching.

Note: Typical experimental procedure for the Stille Coupling can be found at page 57.

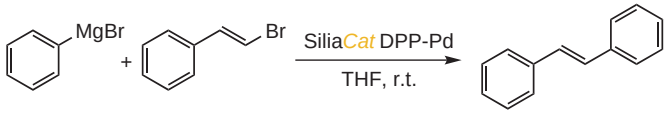
Kumada Coupling Using Silia*Cat* DPP-Pd

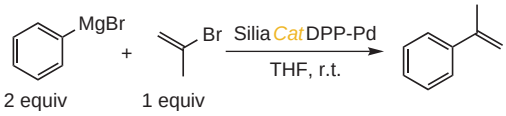
The Kumada coupling is the direct cross-coupling between an alkyl or an aryl Grignard and a halocarbon. It can be catalyzed by a Pd or a Ni catalyst.



Catalyst Concentration Effect

At a constant concentration of substrate, an increase of the amount of Silia*Cat* DPP-Pd from 0.1 (*or 0.2*) to 1.0 will increase the kinetics (*completed in only 15 minutes*). By increasing the concentration of the catalyst, thus thereby increasing the number of active sites, conversion of the substrate will be favored.





Catalyst Concentration Effect

Silia*Cat* DPP-Pd (*mol %*)	Solvent (*M*)	Time (*min*)	Conversion (%)
1.0	THF (*0.07 M*)	15	96
0.5	THF (*0.07 M*)	15	95
0.2	THF (*0.08 M*)	120	94

Catalyst Concentration Effect

Silia*Cat* DPP-Pd (*mol %*)	Solvent (*M*)	Time (*min*)	Conversion (%)
1.0	THF (*0.08 M*)	15	98
0.5		90	96
0.2		240	98

Catalyst Reusability and Leaching

Minimal leaching and robustness of the organoceramic matrix are important factors that allow it to be reused.

Silia*Cat* Reusability and Leaching

Reusability	Conversion (%)	Leaching (*ppm*)	
		Pd	Si
1st	98	0.20	1.5
2nd	95	0.20	2.3
3rd	94	0.50	1.7

Catalytic Activity

Silia*Cat* DPP-Pd showed good reactivity for aryl iodides and bromides. Inert conditions are required for Kumada couplings due to the presence of Grignard reagent. Reactions were done in THF (*0.05 - 0.08 M*).

Catalytic Activity

Substrate (*R*) / Halide (*X*)	R-MgBr (*2 equiv*)	Time (*h*)	Conversion (%)	Substrate (*R*) / Halide (*X*)	R-MgBr (*2 equiv*)	Time (*h*)	Conversion (%)
4-OCH_3 / Br	Ph-MgBr	18	98	4-F / Br	Ph-MgBr	24	94
	i-Bu-MgBr		95	H / I			99
4-CH_3 / Br	Ph-MgBr		96	4-OCH_3 / I			94
	i-Bu-MgBr		98	4-CH_3 / I			95

Conclusion of the Kumada Coupling

Silia*Cat* DPP-Pd can be succesfully used for the Kumada coupling for various substrates and shows good reactivity.

Typical Experimental Procedure: Stille & Kumada Couplings over Silia*Cat* DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse. For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

Stille Coupling Reactions over Silia*Cat* DPP-Pd		
Substrates	**Aryl-Iodide (*1 equiv*)**	**Aryl-Bromide (*1 equiv*)**
$R'SnBu_3$	1.1 equiv	
Additive (*CsF*)	2.0 equiv (*if needed for higher conversion*)	
Silia*Cat* Loading	≤ 2.0 mol % Pd	≤ 10 mol % Pd
Best Solvent & Temperature	Dioxane (*100°C*) or Toluene (*100°C*)	
Reaction Time	18 - 24 h	
Typical Scale	• Under Magnetic Stirring for Screening: 3 mmol scale of aryl halide in 30 mL solvent. • Under Mechanical Stirring for Reusability: 5 mmol scale of aryl halide in 50 mL solvent.	

Kumada Coupling Reactions over Silia*Cat* DPP-Pd		
Substrates	**Aryl-Iodide (*1 equiv*)**	**Aryl-Bromide (*1 equiv*)**
R'MgBr	2.0 equiv Ph MgBr, *i*-BuMgBr, *i*-PrMgBr	
Silia*Cat* Loading	≤ 2.0 mol %	≤ 10 mol %
Best Solvent & Temperature	THF (*60°C*)	
Reaction Time	18 - 24 h	
Typical Scale	• Under Magnetic Stirring for Screening: 3 mmol scale of aryl halide in 35 - 60 mL anhydrous solvent under inert conditions. • Under Mechanical Stirring for Reusability: 3 mmol scale of aryl halide in 35 - 60 mL anhydrous solvent under inert conditions.	

Hydrogenation of Nitroarenes Using SiliaCat Pd⁰ & Pt⁰

Functionalized anilines are important intermediates in various industries such as pharmaceuticals, polymers and dyes. Simple aromatic amines are generally obtained by catalytic hydrogenation of nitroarene compounds with various heterogeneous commercial catalysts (*supported nickel, copper, cobalt*) including Pd/C and Pt/C. Yet, the selective reduction of a nitro group with H_2 when other reducible groups are present in the same molecule is generally not feasible with these catalytic materials and requires the use of advanced heterogeneous catalysts. SiliaCat Pd⁰ and Pt⁰ exhibit chemoselective catalytic activity for the hydrogenation reaction of a series of substituted nitro compounds under remarkably mild conditions, namely at room temperature in methanol under a H_2 filled balloon (*1 atm*), using 0.5 mol % catalyst amount.

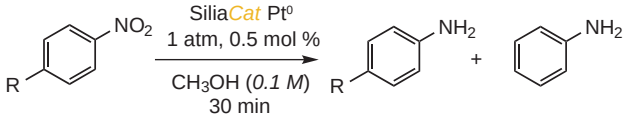
SiliaCat Pd⁰ is an excellent catalyst choice for the hydrogenation of nitroarene in presence of "moderately" reducible functional groups. However, when more challenging substrates containing sensitive functionalities (*such as double or triple bonds, carbonyls*) or with halo-nitroarenes, the use of SiliaCat Pt⁰ is recommended.

Note: detailed experimental procedure can be found at page 66.

SiliaCat Reusability

The reusability tests of SiliaCat Pd⁰ & Pt⁰ were studied using 4-chloronitrobenzene as substrate. Reusing both catalysts in 7 consecutive cycles did not result in any loss of catalytic activity. Complete substrate conversion was obtained even after the seventh cycle, with 99 % selectivity.

For the SiliaCat Pt⁰, the selectivity of the reaction even improves with each subsequent cycle going from 84 % in the first run up to 99 % in run 7. The positive-feedback phenomenon of effective selectivity in consecutive reaction cycles is probably attributed to the silica matrix alkylation.



SiliaCat Reusability in (%)

Reusability	SiliaCat Pd⁰ Conv. (*Selectivity*)	SiliaCat Pt⁰ Conv. (*Selectivity*)
1	100 (99.7)	100 (84.1)
2	100 (99.6)	100 (89.7)
3	100 (99.6)	100 (90.5)
4	100 (99.2)	100 (92.6)
5	100 (99.7)	100 (98.8)
6	100 (99.6)	100 (99.5)
7	100 (99.3)	100 (99.3)

SiliaCat Pt⁰ vs Competitive Catalysts

Other commercially available Pt heterogeneous catalysts [*Pt/C, Pt/SiO_2 and Reaxa Pt(0)EnCat40*] were tested in the selective reduction of 4-chloro-nitrobenzene. In comparison to other Pt(0) heterogeneous catalysts, the SiliaCat Pt⁰ catalyst proved to be much more reactive, with complete conversion after 0.5 h with just 0.5 mol %. Furthermore, selectivity was significantly higher with only 4 % aniline formed as by-product. No secondary product was observed in solution.

SiliaCat Pt⁰ vs Competitive Catalysts

Catalyst	SiliaCat Pt⁰			Pt/C			Pt/SiO_2			Reaxa Pt(0)EnCat40 dry		
Mol (%)	5	1	0.5	5	1	0.5	5	1	0.5	5	1	0.5
Time (*h*)	0.5	0.5	0.5	1	1	1	1	2	2	0.5	2	2
Product (%)	96	92	88	82	65	43	84	88	48	87	90	86
Aniline (%)	4	8	12	14	4	0	13	10	2	13	10	13

Exp. conditions: 2 mmol substrate in 20 mL MeOH under hydrogen balloon at room temperature.

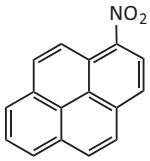
Substrate Scope and Selectivity

The hydrogenation of different nitro compounds containing various functionalities, was attempted to demonstrate the selectivity of SiliaCat catalysts in a wide range of reactions. The reaction was tested under hydrogen balloon, at room temperature conditions in methanol (*0.05 - 0.1 M*) using 0.5 - 1 mol % SiliaCat catalysts. Conversion and selectivity are presented below for various substrates. Please see the related publication for all details as well as other examples.

Substrate Scope and Selectivity Results

Substrate #	SiliaCat Pd⁰			SiliaCat Pt⁰		
	Time (*h*)	Conversion (%)	Selectivity (%)	Time (*h*)	Conversion (%)	Selectivity (%)
1	1	100	100	1	100	98
2		100	100		98	100
3		100	98		100	100
4		100	100	2	100	98
5		100	92	1	100	100
6		100	100		100	100
7		100	100		100	100
8		100	100		100	100
9	2	100	65	0.5	100	93
10	1	100	97	1	100	91
11		100	10		100	80
12	4	100	0		100	80

Substrate Structures



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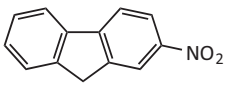

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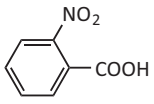

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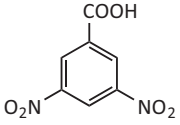

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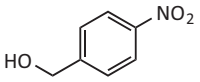

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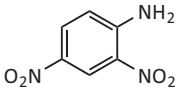

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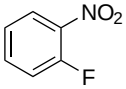

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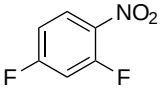

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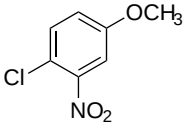

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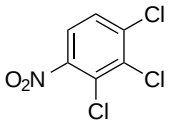

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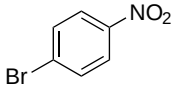

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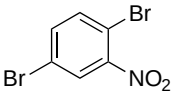
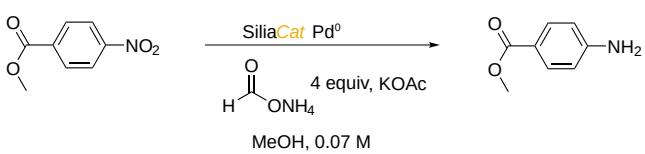


12

Selective Hydrogenation in Flow using Ammonium Formate

The use of ammonium formate as a hydrogen source was investigated in flow chemistry and compared with batch mode using SiliaCat Pd⁰. Compared to the same process performed under batch conditions, the operation under continuous flow affords fully selective conversion in only 14 minutes, versus 60 minutes required for maximum 95 % selectivity in batch reactions.

Note: reactions were done at room temperature.



Hydrogenation using Ammonium Formate

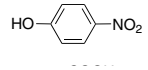
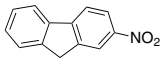
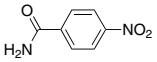
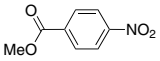
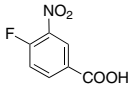
Mode	Time (*min*)	Conversion (%)	Selectivity (%)
Batch	60	95	100
Flow	14	100	100

Comparison of Various Heterogeneous Pd-Catalysts

The effectiveness of Silia*Cat* Pd^0 for the hydrogenation of nitroarenes was investigated and compared with other heterogeneous catalysts available on the market. **It is very important to note that for all reaction conditions, all catalysts were used in the manufacturer's optimized reaction conditions and not just SiliCycle's** in order to be able to make relevant conclusions. Reactivity of Silia*Cat* Pd^0 was compared with Reaxa EnCat Pt^0 catalyst as well as with palladium on carbon Pd/C (*conventional hydrogenation method*) for six different compounds.

Experimental conditions

- For Silia*Cat* Pd^0: 1 mol % Silia*Cat* Pd^0; MeOH; H_2 (*1 atm*); 30 min
- For Reaxa EnCat Pt^0: 5 mol % Pt^0 EnCat; MeOH; H_2 (*1 atm*); 30 min
- For Pd/C: 1 mol % Pd/C; MeOH; H_2 (*1 atm*); 30 min

Hydrogenation Conversion Comparison (*in %*)			
Nitroaryl	Silia*Cat* Pd^0	Reaxa EnCat Pt^0	Pd/C (*5 %*)
	**100**	15	**99**
	**98**	0	**100**
	**100**	45	**100**
	**100**	12	**100**
	**100**	22	**100**
	**100**	46	**100**

Conclusion

In all cases, Silia*Cat* Pd^0 and Pd/C were comparable, but handling is simpler with Silia*Cat*, making this catalyst a **safer** replacement for Pd/C. For all reactions, the EnCat results were significantly lower compared to the other catalysts.

Conclusion of Selective Hydrogenation of Nitroarenes

The selective hydrogenation of different nitro compounds in the presence of various functionalities, including reducible carbonyl, amide, ester, amine and halide groups was achieved with Silia*Cat* Pd^0 or Pt^0 catalyst in methanol at room temperature and under 1 atm H_2 pressure.

Related Publications for Hydrogenation of Nitroarenes

Adv. Synth. Catal., **2011**, *353*, 1306-1316
Catal. Sci. Technol., **2011**, *1*, 1616-1623
Nanoscale, **2014**, *6*, 6293-6300

Hydrogenation of Alkenes and Alkynes Using Silia*Cat* Pd^0

Catalytic hydrogenation of unsaturated C-C bonds can be achieved using either homogeneous or heterogeneous catalysts. However, with many catalysts, purification of the desired alkene is really hard due to lack of selectivity. Silia*Cat* Pd^0 can be used to mediate at room temperature the selective hydrogenation of a wide variety of alkenes under 1 atm of H_2 using 0.1 mol % of catalyst amount. Various solvents can be used (*methanol, ethanol, THF or MeOH / THF*) at 0.25 M concentration in respect to the substrate. The catalyst is reusable with negligeable leaching of palladium, providing the chemical industry with a suitable replacement for less selective metal-based catalysts.

Silia*Cat* Pd^0 Reusability and Leaching

The reusability of Silia*Cat* Pd^0 was explored in the hydrogenation of *trans*-cinnamic acid. Reusing the catalyst in five consecutive cycles did not show any loss in catalytic activity with minimal leaching of Pd and Si (*assessed by ICP-OES*). Complete substrate conversion was obtained even after the fifth cycle, with 99 % selectivity.

Silia*Cat* Pd^0 Reusability and Leaching

Run	Conversion (%)	Selectivity (%)	Leaching (*ppm*) Pd	Si
1	100	100	0.09	0.06
2	100	100	0.09	0.03
3	100	100	0.12	0.02
4	100	99	0.09	0.03
5	100	99	0.08	0.02

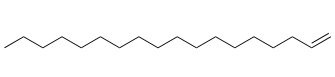
Substrate Scope and Selectivity

The hydrogenation of various alkenes was done to demonstrate the versatility of this catalyst. The material was tested under 1 atm of H_2, at room temperature conditions in different solvents at 0.25 M using 0.1 mol % Silia*Cat* Pd^0. Conversion and selectivity are presented below for various substrates. Please see the related publication for all details as well as other examples.

Substrate Scope and Selectivity Results

Substrate	Time (*h*)	Conversion (%)	Selectivity (%)	Substrate	Time (*h*)	Conversion (%)	Selectivity (%)
1	0.5	100	99	5	0.5	100	97
2	1	100	99	6	2	100	100
3	1	100	99.5	7	0.5	100	100
4	2	100	100	8*	2	100	99

Substrate Structures



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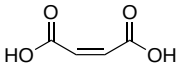

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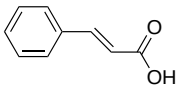

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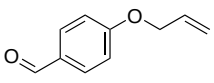

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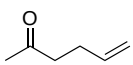

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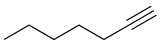

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* The hydrogenation is not selective and forms the corresponding alkane.

Related Publication for Hydrogenation of Alkenes & Alkynes

Org. Proc. Res. Dev., **2012**, *16*, 1230-1234

Selective Hydrogenation of Vegetable Oils over SiliaCat Pd^0

SiliaCat Pd^0 is an efficient heterogeneous catalyst for the hydrogenation of a wide variety of vegetable oils under 1 atm of H_2 in methanol over 0.1 mol % of catalyst. A low concentration of catalyst is enough to promote full hydrogenation of fatty acids, fatty acid methyl esters and vegetable oils with no isomerisation and negligible leaching of palladium. The catalyst is fully reusable, opening the route to replacement of Ni-based catalyst in the oleochemicals industry.

SiliaCat Pd^0 Reusability and Leaching

SiliaCat Pd^0 can be reused several time without any loss in the reactivity and minimal leaching of Pd and Si. Complete data is provided inside the related publication.

Substrate Scope

To further investigate the catalyst selectivity, hydrogenation of different fatty acids containing different numbers of double bonds were attempted to form the corresponding saturated product. Reactions were conducted in methanol 0.25 M over 0.1 - 0.2 mol % SiliaCat Pd^0.

Substrate Scope and Leaching Results

Substrate	Catalyst (*mol %*)	Time (*h*)	Conversion (%)	Yield (%)	Leaching (*ppm*) Pd	Si
Oleic acid (*cis C18:1*)	0.1	3	100	99.5	0.25	0.10
Linoleic acid (*cis C18:2*)		4	100	97.5	0.25	0.19
α-linolenic acid (*cis C18:3*)		5	100	99.4	0.29	0.07
Eicosapentaenoic acid ethyl esther (*cis C20:5*)	0.2	3	100	N/A	0.13	0.18
Erucic acid (*cis C22:1*)			100	N/A	-	-

To explore the scope of the method, different vegetable oils were then hydrogenated in THF / MeOH (*0.5 M*) over 0.1 mol % SiliaCat Pd^0. In general, complete substrate conversion of the vegetable oil to saturated product was obtained after 3 h.

Substrate Scope and Leaching Results of Vegetable Oils

Substrate	Time (*h*)	Conversion (%)	Leaching (*ppm*) Pd	Si
Sunflower oil (*linoleic acid 64.5 %, oleic acid 25.5 % and other 10 %*)	3	99	0.3	0.19
	2	99	0.08	0.19
Corn oil (*linoleic acid 54 %, oleic acid 27 % and other 19 %*)	3	98	0.17	0.19
Soybean oil (*linoleic acid 50 %, oleic acid 27 %, linolenic acid 9 % and other 14 %*)		99	0.52	0.42
Canola oil (*linoleic acid 22 %, oleic acid 58 %, linolenic acid 9 % and other 11 %*)		99	0.36	0.16
Olive oil (*linoleic acid 8 %, oleic acid 72 % and other 20 %*)	2	99	0.32	0.19

Conclusion of Hydrogenation of Vegetable Oils

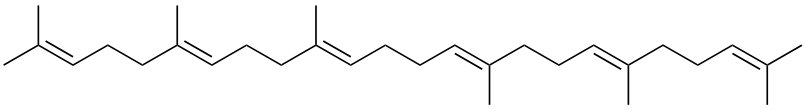
In conclusion, only 0.1 mol % of SiliaCat Pd^0 selectively mediates the full conversion to saturated vegetable oils at room temperature under 1 atm of H_2. The catalyst is also reusable, offers minimal leaching and provides pure product (*no purification usually required*).

Related Publication for Hydrogenation of Vegetable Oils

Org. Proc. Res. Dev., **2012**, 16, 1307-1311

Hydrogenation of Squalene to Squalane Using Silia*Cat* Pd^0

The complete hydrogenation of highly unsaturated all-trans linear squalene into valuable fully saturated squalane is achieved smoothly under mild conditions over the sol-gel entrapped Pd catalyst Silia*Cat* Pd^0. The catalysis is truly heterogeneous, and the catalyst is stable and reusable, which opens the route to an easier and less expensive hydrogenation of squalene. A brief overview of our results are presented here. Please refer to the related publication for all the details.



Squalene

Solvent Effect

We first performed a series of experiments using a commercial squalene sample (*98 wt % purity*) aimed to identify the best solvent for the catalytic hydrogenation of squalene over the Silia*Cat* Pd^0 catalyst under 1 atm of H_2 at temperatures between 22 and 50°C.

The best conditions identified were, 0.5 mol % Silia*Cat* Pd^0 in ethanol 0.50 M with respect to squalene under 1 atm H_2 at 50°C.

Solvent Effect

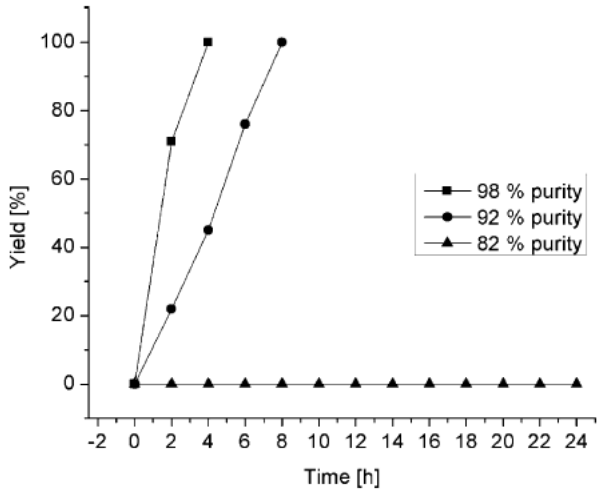
Solvent (*Conc. [M]*)	Tempature (°C)	Time (*h*)	Conversion (*isolated yield %*)
EtOH (*0.25*)	22	6	100 (-)
	30	6	100 (98.4)
	50	5	100 (99.2)
EtOH (*0.33*)	30	6	100 (99.2)
	50	4	100 (99.5)
EtOH (*0.50*)	50	4	100 (99*)
MeTHF / EtOH 1:1 (*0.50*)	50	4	100 (75*)
	50	6	100 (98*)

* Yield evaluated by GC-MS analysis.

Squalene Purity Effect

The purity of the squalene used has a direct influence on the success of the hydrogenation. Using the optimal condition determined in the previous section, three grades of squalene were evaluated. The higher the purity, the easier is the hydrogenation reaction.

Using squalene with purity above 90 % allows complete conversion in a very short period of time. However, less pure squalene (*82 wt % purity*) did not provide any reaction using these conditions. Another set of conditions were developed for this grade of squalene without solvent using 0.3 mol % Silia*Cat* Pd^0 under 3 atm H_2 at 100°C for 24 hours (*100 % conversion, 85 % yield*).



Conclusion for Hydrogenation of Squalene to Squalane

This reaction is still under development but Silia*Cat* Pd^0 can be succesfully used for the hydrogenation of squalene and can be reused several time without loss in the reactivity. Reaction can also be done without any solvent and on various purity grades of squalene. Please refer to our website for all the datas.

Related Publication for Hydrogenation of Squalene

Chem. Cat. Chem., **2015**, *7*, 2071-2076

Selective Debenzylation Using SiliaCat Pd⁰

The selective debenzylation of aryl benzyl ethers, benzyl esters and benzyl amines, while leaving other sensitive groups intact, can be carried out in high yield under mild conditions (*namely at room temperature under 1 atm H_2, using 0.5 mol % SiliaCat Pd⁰*).

Selective and smooth deprotection is critical. The commonly used method makes use of catalytic hydrogenolysis to cleave benzylic groups with H_2 under pressure and in the presence of a heterogeneous catalyst such as Pd/C or Raney Ni. However, very often the deprotection reaction conditions are not compatible with other functional groups, such as nitro, unsaturated bonds and halogen groups. SiliaCat catalysts offer a number of additional advantages over traditional Pd/C. They are non pyrophoric and have a higher density and lower catalytic consumption (*< 1 mol % vs 5 - 10 % for Pd/C*) due to fast kinetics and high turnover.

Solvent & Catalyst Concentration Effects

Solvent choice is critical for any debenzylation reaction. Therefore, in order to optimize the reaction conditions, 1-(benzyloxy)-4-methoxybenzene was used as our substrate of choice. A series of commonly employed solvents were screened under 1 atm of H_2 at room temperature using 2 mol % of catalyst at different solvent concentrations. The best results were achieved with methanol and ethanol.

The molar concentration of the solvent is crucial for this reaction. The best results were achieved by using a methanol concentration of 0.07 M and 0.5 - 1 mol % SiliaCat Pd⁰, with complete conversion obtained after 1 - 2 hours. (*refer to related publication for all the details*).

Solvent Effect

Solvent	Substrate Conc. (*M*)	Time (*h*)	Conversion (%)
EtOH	0.1 / 0.07	16 / 4	17 / 100
MeOH		16 / 0.5	15 / 100
THF	0.07	20	15
EtOAc			20
Hexane			21

SiliaCat Pd⁰ Reusability and Leaching

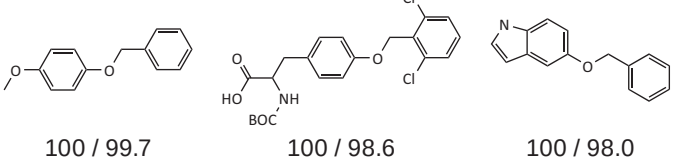
Catalyst stability and reusability are crucial features of any catalyst seeking commercial applications. SiliaCat Pd⁰ was thus reused six consecutive times in the O-debenzylation reaction of 1-(benzyloxy)-4-methoxybenzene under the standard mild conditions developed in our laboratory. The activity remained approximately constant, and expanding the reaction time by 50 % was sufficient to keep conversion constant.

SiliaCat Pd⁰ Reusability and Leaching

Reusability	Time (*h*)	Conversion (%)	Leaching (*ppm*)	
			Pd	Si
1st	1	100	0.7	2.5
2nd		100	0.3	1.3
3rd	1.5	100	0.3	2.3
4th		100	0.2	1.4
5th		99	0.2	0.8
6th		100	0.1	0.5

Substrate Scope and Selectivity

SiliaCat Pd⁰ is an efficient catalyst for the selective debenzylation of different aryl benzyl ethers, benzyl amino-acids and benzylprotected sugars leaving other sensitive groups intact. Refer to our publication in *ChemCatChem,* **2011**, *3*, 1-5 for more examples. Conversion and yields (*in %*) of some key examples using 1 mol % of catalyst are presented here.



100 / 99.7 (*1 h*) | 100 / 98.6 (*1 h*) | 100 / 98.0 (*20 h*)

SiliaCat Pd⁰ vs a Competitive Catalyst

Using the same reaction as the one used to demonstrate the reusability of SiliaCat Pd⁰ in the O-debenzylation reaction, we also tested the commercial catalyst Pd⁰ EnCat, a polyurea-entrapped catalyst.

SiliaCat shows better performance over the EnCat catalyst.

SiliaCat Pd⁰ vs a Competitive Catalyst

Catalyst (*mol %*)	Time (*h*)	Conversion (%)	Selectivity (%)
SiliaCat Pd⁰ (*0.5*)	1 / 2	95 / 100	- / 100
SiliaCat Pd⁰ (*1.0*)	0.5 / 1	75 / 100	- / 100
Pd⁰ EnCat (*10*)	16	100	100

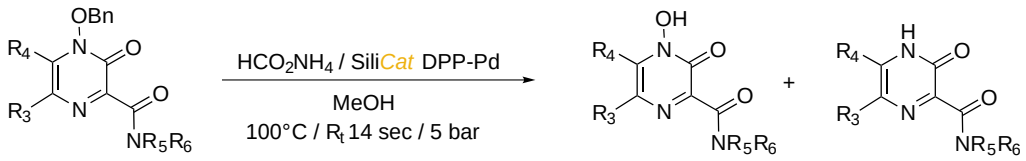
Case Study: Selective *O*-Debenzylation Using SiliaCat DPP-Pd in Flow Chemistry

Authors: De Borggraeve (*University of Leuven*) *et al*.
Publication: *Journal of Flow Chemistry*, **2015**, *5*, 6-10

De Borggraeve's research group has developed a new synthesis of *N*-hydroxypyrazin-2(*1H*)-ones via the selective O-debenzylation of 1-benzyloxypyrazin-2(*1H*)-ones using flow chemistry. An appropriate catalyst was needed for the debenzylation and SiliaCat DPP-Pd showed excellent results.

The optimization reaction was done using the model system 1-benzyloxy-*N,N*-diethyl-5,6-dimenthylpyrazin-2(1*H*)-one-3-carboxamide. The reaction showed acceptable conversion at 60 °C and was complete at 80 - 100°C at a residence time of 14 sec without losing selectivity for the formation of the desired prodcut (*N-OH form : N-H form = 97 - 98 % : 1 - 2 %)*

Based on these promising results, a large library of aspergillic acid-like hydroxamic acids was produced under the experimental conditions for debenzylation that were considered to be optimal. The obtained yields were good to very good, and the selectivities good to excellent.



1 **2** **3**

Yield: 72 - 96 %

Conclusion of Selective Debenzylation

SiliaCat Pd⁰ is suitable for the selective debenzylation of numerous substrates under mild conditions with only 1 - 2 mol % catalyst amount. Benzyl-protected sugars, amino acids, ethers and esters are smoothly debenzylated under 1 atm of H_2 at room temperature.

Related Publication for Selective Debenzylation

Chem. Cat. Chem., **2011**, *3*, 1146-1150

Typical Experimental Procedure: Hydrogenation Using Silia*Cat* Pd^0 & Pt^0

Note: For each hydrogenation reaction, please refer to the related table presented next page for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). The hydrogenation reaction being an exothermic reaction, an exotherm may be observed as the reaction progresses.Reusability tests are done using a high pressure reactor.

Palladium on carbon (*Pd/C*) frequently ignites when it first comes in contact with methanol (*and to a lesser extent, any flammable organic solvent*) and as such represents a significant safety risk. Even if Silia*Cat* is a safer alternative, these procedures are recommended whenever this catalyst is used in conjunction with hydrogen gas.

Hydrogenation using a balloon

1. Weigh out Silia*Cat* and transfer into a round bottom flask equipped with a condenser and a stirring bar.
   Note*: we suggest using a two-neck flask*.
2. Add solvent and the reaction substrate.
3. Attach a balloon of hydrogen to the condenser with an adapter that allows the balloon to be closed off from the reaction flask.
4. While stirring, the reaction mixture is purged by cycling an inert gas (*nitrogen or argon*) and vacuo twice.
5. The reaction mixture is degassed twice with hydrogen for one minute by opening the balloon adapter.
6. The reactor is now ready for the hydrogenation reaction.

Hydrogenation using a high pressure reactor (*bomb reactor*)

1. Weigh out Silia*Cat* and transfer into the appropriate bomb reactor.
2. Add solvent and the reaction substrate and seal the reactor.
3. While stirring, the reaction mixture is purged by cycling an inert gas (*nitrogen or argon*) and vacuo twice.
4. Fill the reactor with hydrogen up to the desired pressure using the gauge.
5. Seal the reactor by closing off the hydrogen source and disconnect the reactor from the regulator.
6. You can now run your hydrogenation reaction.

Work-up Procedures: When the hydrogenation is finished, please use the following procedure for the work-up.

Destructive work-up (*if you do not want to use Silia*Cat* for another reaction*)

1. Remove the hydrogen balloon from the flask (*for balloon reactions*) or slowly allow the reactor to return to atmospheric pressure.
2. Purge reaction vessel twice with an inert gas (*nitrogen or argon*).
3. The reaction mixture can also be purged through bubbling of nitrogen or argon for 10 - 15 minutes for added safety.
4. Under a moderate vacuum, filter the reaction mixture through a Büchner funnel using a glass fiber filter (*grade 691*).
5. Rinse the flask with your preferred solvent (*we suggest using an aprotic solvent like ethyl acetate (EtOAc) or tetrahydrofuran (THF) for safety reasons*).
6. Using the same solvent as step 5, wash Silia*Cat* on the Buchner to make sure any product of interest is not adsorbed on the catalyst.
7. Disconnect the Büchner funnel from the receiving flask and then add several mL of water to the filter.
8. Discard the wet Silia*Cat* and filtering aid in a dedicated waste jar that contains water.

Nondestructive work-up (*if you want to reuse Silia*Cat* for another reaction*)

Note*: reusability study for large scale in progress.*

1. Follow steps 1 - 4 from the procedure above (*"Destructive work-up"*).
2. Under vacuum, rinse the Silia*Cat* on the Buchner with an aprotic solvent (*EtOAc or THF*) using 4-fold the amount of catalyst used. **DO NOT DRY COMPLETELY THE CATALYST.**
3. Transfer the humid Silia*Cat* in a round flask and dry the solid under argon during several hours (*overnight*).
4. Store the catalyst under normal conditions, in a closed vessel prior to reuse. For prolonged storage, keep under argon at 8°C.

Caution! The catalyst can be isolated by filtration under vacuum but it should not be dried under vacuum in presence of air / methanol.

If for any reason the catalyst is dried completely under vacuo, the adsorbed hydrogen can slowly react (*after a few minutes of drying*) with oxygen to create an exothermic reaction (*> 320°C*). If the catalyst is dried completely, close the vacuum and wash with water.

Functionalized Nitroarene Hydrogenation Reactions using Silia*Cat* Catalysts		
Substrate	**Nitroarenes & Nitro-functionalized Aryl Halides**	
Silia*Cat* Catalyst	Silia*Cat* Pd^0	Silia*Cat* Pt^0
Silia*Cat* Loading	≤ 1.0 mol % Pd or Pt	
Best Solvents	MeOH, THF, MeTHF, EtOH	MeOH, THF, MeTHF, EtOAc, EtOH, hexane
Temperature	20 - 22°C	
H_2 Pressure	1 atm	
Reaction Time	0.5 - 4 h	
Typical Scale	• Under Magnetic Stirring for Screening: 2 mmol scale of functionalized nitroarene in 20 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 20 mmol scale of functionalized nitroarene in 200 mL solvent (*HPLC grade*).	

Alkene Hydrogenation Reactions Using Silia*Cat* Pd^0	
Substrate	**Non-functionnalized and functionnalized Alkenes**
Silia*Cat* Loading	≤ 0.5 mol % Pd
Best Solvents	MeOH or EtOH [THF, MeTHF, MeOH / THF(*1:1, v/v*)]
Temperature	20 - 22°C
H_2 Pressure	1 atm
Reaction Time	0.5 - 4 h
Typical Scale	• Under Magnetic Stirring for Screening: 6 mmol scale of alkene in 25 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 50 mmol scale of alkene in 200 mL solvent (*HPLC grade*).

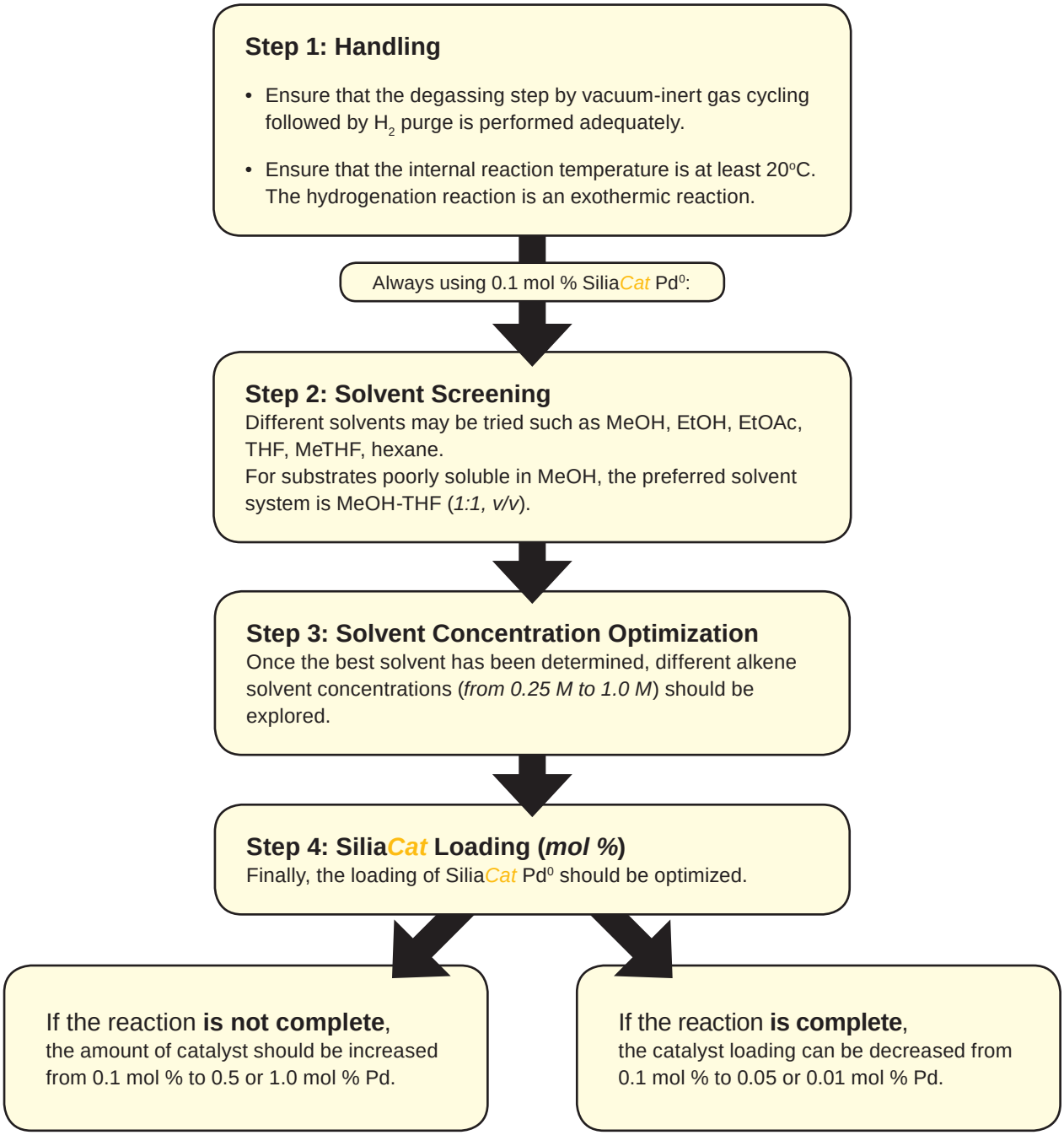
Vegetable Oil Hydrogenation Reactions Using Silia*Cat* Pd^0	
Substrate	**Vegetable Oils**
Silia*Cat* Loading	≤ 0.5 mol % Pd
Best Solvents	MeOH (*0.25 M or 0.5 M*) THF, MeTHF, EtOAc, EtOH, THF / MeOH (*5:1, v/v*)
Temperature	20 - 40°C
H_2 Pressure	1 atm
Reaction Time	0.5 - 6 h
Typical Scale	• Under Magnetic Stirring for Screening: 15 mmol scale of fatty acid (*or vegetable oil*) in 60 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 50 mmol scale of fatty acid (*or vegetable oil*) in 200 mL solvent (*HPLC grade*).

Squalene Hydrogenation Using Silia*Cat* Pd^0		
Substrate	**Squalene**	
Silia*Cat* Loading	≤ 1.0 mol % Pd	
Best Solvents	EtOH	EtOH or neat
Temperature	50°C	50 - 70°C
H_2 Pressure	1 atm	1 - 3 atm
Reaction Time	4 - 8 h	2 - 24 h
Typical Scale	• Under Magnetic Stirring for Screening: 10 mmol scale of squalene in 30 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 50 mmol scale of ene in 150 mL solvent (*HPLC grade*).	

Debenzylation Reactions Using Silia*Cat* Pd^0	
Substrate	**Benzyl Protected Group**
Silia*Cat* Loading	≤ 2.0 mol % Pd
Best Solvents	EtOH [MeOH, THF, MeTHF, EtOAc, Hexane]
Temperature	20 - 22°C
H_2 Pressure	1 atm
Reaction Time	0.5 - 24 h
Typical Scale	• Under Magnetic Stirring for Screening: 4 mmol scale of benzyl protected group in 40 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 20 mmol scale of benzyl protected group in 200 mL solvent (*HPLC grade*).

Optimization Steps

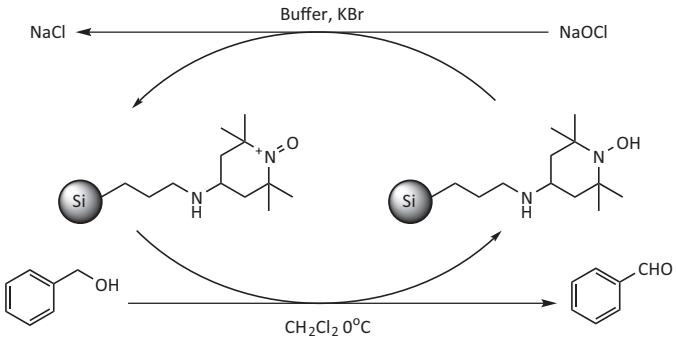
If the reaction fails or if the conversion is incomplete, optimization steps can be undertaken. The alkene hydrogenation example presents the pathway (*order*) you need to follow for each type of hydrogenation.



Oxidation Using Silia*Cat* TEMPO

Aldehydes and ketones, either as starting materials, synthetic intermediates, or final products, are of great interest in synthetic chemistry. Such carbonyl-containing products can lead to carbon-carbon (*i.e. Wittig, Aldol, alkylation*) or carbon-nitrogen bond formation. Over the years, chemists have discovered various oxidizing agents such as pyridinium chlorochromate (*PCC*), MnO_2, Dess-Martin periodinane or Swern oxidation conditions. Although all of these methods lead to the aldehyde (*limited oxidation of the aldehyde to the carboxylic acid*), they have drawbacks such as the hazards and toxicity associated with residual metal contamination.

The development of environmentally friendly methods for the selective catalytic oxidation of alcohols to aldehydes and ketones can have significant impact on modern methods of chemical synthesis. Silia*Cat* TEMPO is the oxidation solution of choice.



Catalytic Performance and Leaching

Silia*Cat* TEMPO was investigated under the Montanari-Anelli conditions. The catalytic cycle involves regeneration of the oxidative species with NaOCl in presence of KBr as co-catalyst to form the anion OBr^-.

Silia*Cat* TEMPO can be used in quantity as low as 0.01 mol % to provide the desired aldehyde in short reaction times. ICP analysis confirms that the catalyst is leach-resistant (*[Si] ≤ 3 ppm*).

Catalytic Performance and Leaching

Silia*Cat* (*mol %*)	Time (*h*)	Conversion (%)	Si Leaching (*ppm*)
0.1	1	95	-
0.01	2	83	3
	3	95	1.6
	4	97	1.5
0.02	2	96	-
	3	100	2

Silia*Cat* TEMPO Reusability

The minimal leaching profile and the robustness of Silia*Cat* TEMPO's organoceramic matrix allow it to be reused several times. Silia*Cat* TEMPO is recycled by post-reaction filtration, DCM washes and air drying.

Silia*Cat* TEMPO Reusability

Reusability	Time (*min*)	Conversion (%)	Reusability	Time (*min*)	Conversion (%)	Reusability	Time (*min*)	Conversion (%)
1st	30	100	Results for run 3 to 7 were similar to 1 - 2			9th	30 / 60	97 / 100
2nd	30	100	8th	30 / 60	95 / 100	10th	30 / 60	90 / 100

Influence of Co-Catalyst and Temperature

SiliCycle investigated wether it was necessary to use a co-catalyst (*KBr*) for the reaction to proceed effectively. As shown in the table, although KBr is not required for the reaction, it does have a significant impact on kinetics. The reaction can still proceed to completion without KBr but requires longer time and / or more Silia*Cat* TEMPO. It was also demonstrated that the reaction can be carried out at room temperature without KBr.

Influence of KBr and Temperature

Silia*Cat* (*mol %*)	KBr (*equiv*)	Temp. (°C)	Time (*min*)	Conversion (%)
0.1	0.1	0	60	95
	0		60	80
			210	100
0.2			105	96
		22	60	76
			90	87

Influence of Solvents, pH and NaOCl

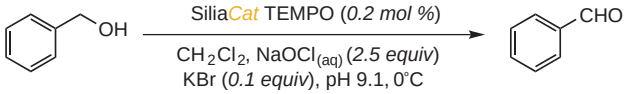
As shown on the right, the reaction can be carried out at pH 9.0 or at pH 7.5 with high conversions. The catalytic conditions are selective towards the aldehyde, rather than the carboxylic acid, even with 10 equiv of NaOCl.
***Note**: the reaction can also be pursued in water or with other organic solvents.*

Influence of Solvent, pH and $NaOCl_{(aq)}$

SiliaCat (*mol %*)	$NaOCl_{(aq)}$ (*equiv*)	Solvent	pH	Time (*min*)	Conversion (%)
0.2	2.50	DCM	9.0	60	98
	10.00			90	98
	1.25		7.5	60 / 90	83 / 86
	2.50				94 / 98

SiliaCat TEMPO vs Homogeneous TEMPOs

Comparative analysis versus homogeneous TEMPOs demonstrates the SiliaCat TEMPO to be comparable or better at neutral pH and significantly superior in basic conditions.



SiliaCat TEMPO vs Homogeneous TEMPOs

pH	SiliaCat TEMPO	4-MeO-TEMPO	4-Oxo-TEMPO
7.5	91	99	45
9.0	98	55 (40)[1]	73

[1] In parenthesis = conversion to carboxylic acid.

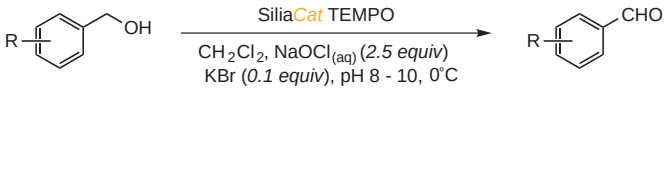
Substrate Scope with SiliaCat TEMPO

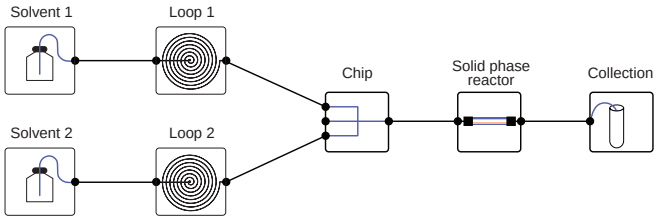
SiliaCat TEMPO is efficient with different substrates under standard condition as presented in the table at right.

It is also suitable for continuous synthesis under flow chemistry using the pathway presented below. SiliaCat TEMPO was placed at 20°C using a 0.7 mL reactor packed with the catalyst and different flow rates (*from 50 to 500 µL/min*). In all experiments, complete conversion was obtained with 100 % selectivity.

Substrate Scope with SiliaCat TEMPO

Substrate (*R*)	Catalyst (*mol %*)	Time (*min*)	Conversion (%)
3-NO_2	0.4	90	100
4-NO_2			98
4-Cl			95
3-phenyl-1-propanol		60	97
1-phenyl-3-propanol		180	95[1]





Conclusion of Oxidation of alcohols

SiliaCat TEMPO is an effective oxidizing catalyst presenting unique advantages such as high activity, robustness, leach-proof properties and selectivity toward the oxidation of alcohols into aldehydes and ketones, both very valuable functional groups in organic chemistry.

Related Publications for Oxidation

Nanoscale, **2014**, *6*, 6293-6300
Topics in Catalysis, **2010**, *53*, 1110-1113
Org. Proc. Res. Dev., **2010**, *14*, 245-251
Chemistry Today, **2009**, *27*, 13-16
Org. Proc. Res. Dev., **2007**, *11*, 766-768

Typical Experimental Procedure: Alcohol Oxidation Using Silia*Cat* TEMPO

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required.

- Typical reactions are conducted using a 500 mL three-necked round-bottom flask equipped with a mechanical stirring system and a digital temperature controller in dichloromethane (*HPLC grade*) at 0°C (*ethyl acetate can also be used*).
- The primary alcohol and *n*-decane (*used as internal standard calibration curve*) are dissolved in dichloromethane (*60 mL*).
- The alcohol-decane solution is then mixed with aqueous KBr solution (*2.55 mL*) and maintained at 0°C in an ice bath.
- The resulting mixture is then treated with Silia*Cat* TEMPO , then by aqueous NaOCl (*60 mL*) buffered at pH 9.0 using $NaHCO_3$.
  Note: *The reaction is exothermic and aqueous NaOCl is added slowly over a 10 min period.*
- The reaction mixture is then vigorously stirred (*1,000 RPM*) at 0°C until maximum conversion is reached (*as determined by GC/FID analysis with n-decane as internal standard*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by GC/FID analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.03 - 1.00 g*) is washed with deionized water (*3 x 10 mL*) and DCM (*3 x 10 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.

Isolation of the oxidation product

- The organic layer is washed 3 times with deionized water (*3 x 100 mL*).
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

If the reaction fails or if the conversion of the primary alcohol is not complete, optimization steps can be undertaken.

- **Step 1: Handling**
  - Check if the reaction temperature is 0°C.
  - Check if the reaction mixture, which must be a two phase system, is vigorously stirred at 1,000 RPM.

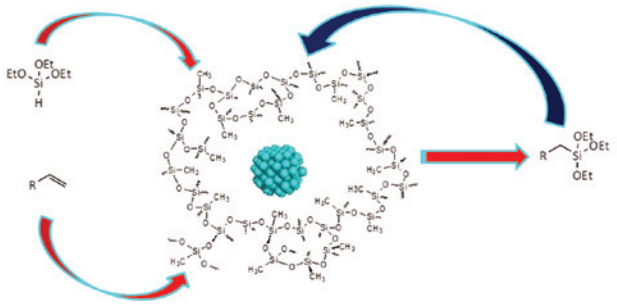
Always using 0.5 mol % Silia*Cat* TEMPO:

- **Step 2: Solvent Screening**
  Different solvents may be tried such as as DCM or EtOAc.
- **Step 3: Solvent Concentration Optimization**
  Once the best solvent has been determined, different solvent concentrations (*from 0.2 M to 1.0 M*) should be explored.

Primary Alcohol Oxidation over Silia*Cat* TEMPO	
Substrates	**60 mL primary alcohol in dichloromethane solution (*0.2 M, 12 mmol alcohol, 1 equiv*)**
n-Decane	0.3 equiv
Additive (*KBr*)	2.55 mL of KBr aqueous solution (*0.5 M, 0.1 equiv*)
NaOCl	60 mL of NaOCl aqueous solution (*2.5 equiv*) (*buffered at pH 9.0 using $NaHCO_3$*)
Silia*Cat* Loading	≤ 1.0 mol %
Best Solvents	Dichloromethane or Ethyl Acetate (*ETOAc*)
Temperature	0°C
Reaction Time	0.5 - 24 h
Typical Scale	Under Mechanical Stirring (*1,000 RPM*) for Reusability: 12 mmol scale of primary alcohols in dichloromethane.

Hydrosilylation Using Silia*Cat* Pt^0

Hydrosilylation reactions are a widely used method to prepare organosilicon products. The reaction consists of the addition of *Si*-H bonds on unsaturated bonds like alkenes, alkynes or ketones, where catalysts are often required (*usually* H_2PtCl_6). Silia*Cat* Pt^0 can be used for hydrosilylation reactions.

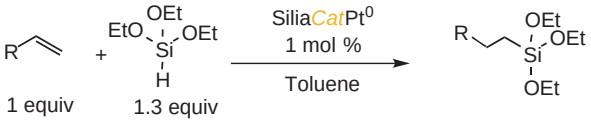


Closing the Organosilicon Synthetic Cycle:
Hydrosilylation of Alkenes over Silia*Cat* Pt^0

Substrate Scope and Selectivity

A number of representative alkenes reacted with triethoxysilane over the solid catalyst under the conditions shown in the table below were tested. Non-functionalized alkenes such as 1-octene or 1-decene are smoothly converted into the corresponding organo-alkoxysilanes at room temperature or faster at 60°C. Usually, raising the reaction temperature slightly enhances the conversion of longer chain alkenes and dramatically improves the selectivity.

The hydrosilylation of linear olefins involves a certain degree of isomerization, namely, either shift of the double bond or even skeletal modification of the starting molecules. Hence, in order to slow down isomerization and obtain a higher reaction rate, reaction is best carried out at 60°C over 1 mol % catalyst amount.



Substrate Scope and Selectivity Results

Substrate	Catalyst (*mol %*)	Substr. Solvent Conc. (*M*)	Temp. (*°C*)	Time (*h*)	Conversion (%)	Selectivity (%)
1-octene	1.0	Toluene (*0.5*)	22 / 60	5	88 / 99	98 / 99
1-decene					100 / 100	97 / 98
1-octadecene					95 / 98	56 / 83
3,3-diethoxyprop-1-ene					94 / 100	93 / 81
4-vinyl-benzamine			60	5 / 24	47 / 80	96 / 96
Styrene	0.5			1	100	68
Acrolein diethyl acetal	0.5 / 1.0			1 / 3	100 / 100	100 / 100
5-hexen-2-one	1.0	DCM (*0.5*)	22	23	100	100

Conclusion of Hydrosilylation

We have discovered that 0.5 - 1 mol % of Silia*Cat* Pt^0 selectively mediates the hydrosilylation of different olefins under inert atmosphere at room temperature or at 60°C, depending on the substrate. Ultra-low leaching of Pt ensures very low levels of metal contamination in crude product.

Related Publications for Hydrosilylation

ACS Sustainable Chem. Eng., **2013**, *1*, 249-253
Eur. J. Org. Chem., **2013**, 6227-6235

Typical Experimental Procedure: Hydrosilylation Reactions Using SiliaCat Pt^0

Note: Please refer to the table below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*).
The reaction is performed in anhydrous toluene under inert conditions.

- Using a dry vessel and a mechanical stirrer, the desired amount of SiliaCat Pt^0 is added and degassed three times by applying vacuum and then purging with an inert gas (*nitrogen or argon*).
- The olefin and triethoxysilane (*previously degassed for 15 minutes with an inert gas*) are dissolved in anhydrous solvent.
- Under mechanical stirring, the mixture is warmed up to the desired temperature.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with toluene (*3 x 15 mL*) and THF (*3 x 15 mL*).
- SiliaCat is dried under air at room temperature and can be stored in a closed vessel prior to reuse in these conditions.

Isolation of the coupling product

- The filtrate is concentrated under vacuum yielding a high purity crude product that typically does not require extensive purification. If needed, the crude product can be purified using flash chromatography or distillation.

Optimization Steps

If the reaction fails or if the conversion of the primary alcohol is not complete, optimization steps can be undertaken.

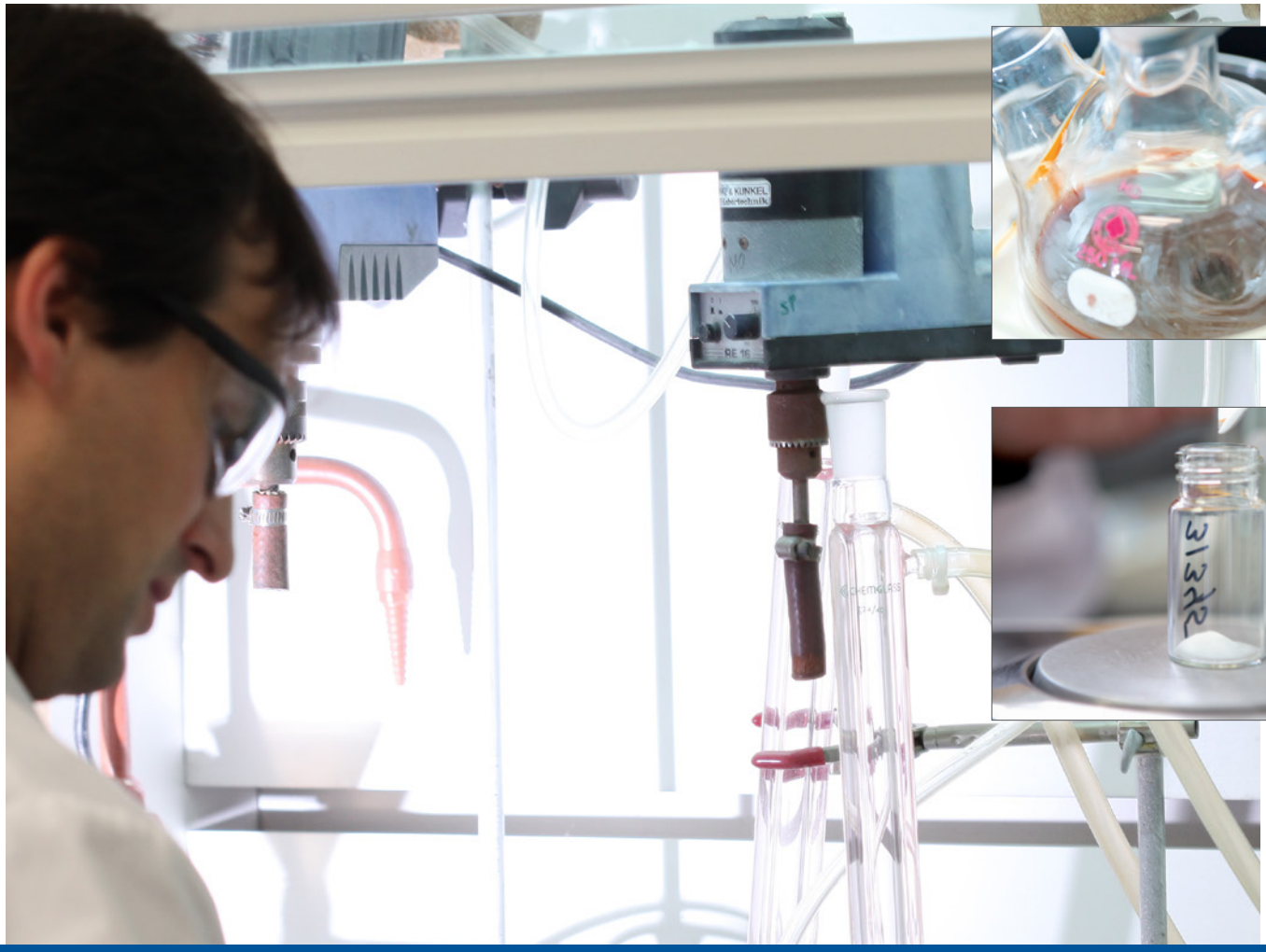
- **Step 1: Handling**
  - Check if the reaction temperature is adequate.
  - Check if the reaction mixture, which must be a two phase system, is vigorously stirred at 700 RPM.

Always using 2.0 mol % SiliaCat Pt^0:

- **Step 2: Solvent Concentration Optimization**
  Always using anhydrous toluene as solvent, different alkene solvent concentrations (*from 0.25 M to 1.0 M*) should be explored.

- **Step 3: SiliaCat Loading (*mol %*)**
  Finally, the loading of SiliaCat Pt^0 should be optimized
  a. If the reaction is not complete, the amount of catalyst should be increased from 2.0 mol % to 2.5 mol % Pt.
  b. If the reaction is complete, the catalyst loading can be decreased from 2.0 mol % to 1 mol % or to 0.05 mol % Pt.

	Hydrosilylation Reactions Using SiliaCat Pt^0
Substrates	**Olefine (*0.5 M in anhydrous toluene*) 1 equiv**
$HSi(OEt)_3$	1.3 equiv
SiliaCat Catalyst	SiliaCat Pt^0 (*0.2 mmol/g Pt loading*)
SiliaCat Loading	≤ 2.0 mol % Pt
Best Solvent	Anhydrous Toluene
Temperature	65 - 90°C
Reaction Time	1 - 24 h
Typical Scale	• Under Mechanical Stirring for Reusability: 20 mmol scale of olefine in 40 mL anhydrous solvent under inert conditions.

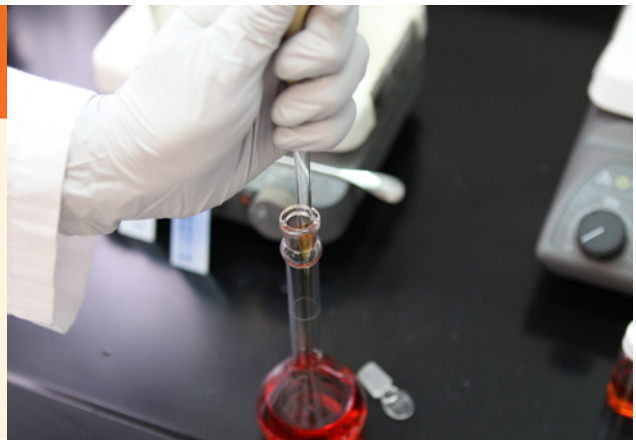


Organic Synthesis

SiliaBond® Reagents & Oxidants

Silica-Based Reagents & Oxidants in Organic Chemistry

Discover How Heterogeneous Reagents & Oxidants Can Optimize your Synthesis



Our heterogeneous supports for chemical synthesis are offered in two different forms:

- **Silia*Bond*** Reagents (*for both catalytic & stoechiometric reactions*)
- **Silia*Bond*** Oxidants

Available Formats: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 10 kg, 25 kg, etc.

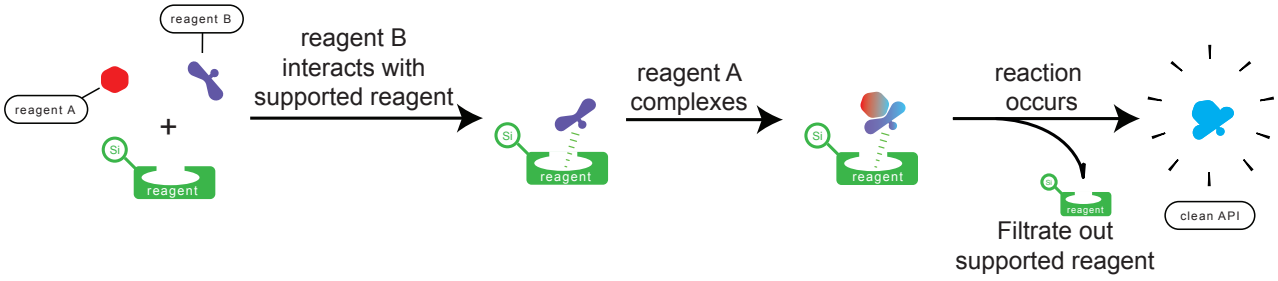
What are Silia*Bond* Heterogeneous Reagents & Oxidants?

Increasingly, the use of heterogeneous reagents in organic synthesis and chemical production is growing in importance. This technology is completely in line with the industries seeking improved sustainability and reduced ecological footprint.

This strong trend is directly derived from the inherent benefits offered by silica-based heterogeneous reagents & oxidants:

- **Extremely easy product / API isolation and purification** (*simple & quick filtration of the heterogeneous support*)
- **Eliminates or strongly reduces the need for laborious purifications**
- **No leaching of silica or catalyst and no cross contamination**
- **Highly suitable for either batch or continuous flow applications**
- Convenient for high throughput medicinal & discovery chemistry
- Improved reactivity & selectivity over homogeneous reagents / catalyst
- Compares very favourably to polymer-based reagents: no swelling, thermally stable, more easily scalabe, faster kinetics, compatible with all solvents and mechanically stable.

Here is the reaction mechanism:



Here are a selection of reactions that can be done using our reagents and oxidants:

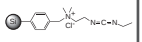
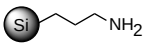
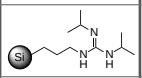
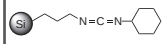
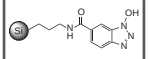
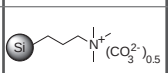
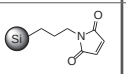
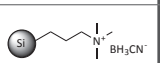
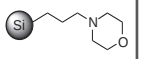
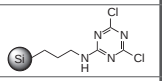
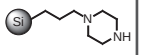
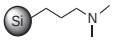
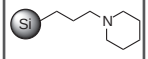
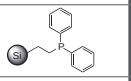
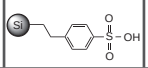
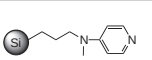
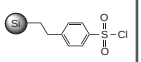
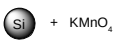
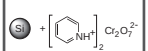
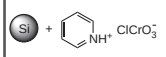
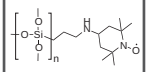
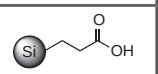
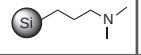
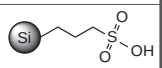
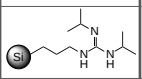
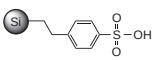
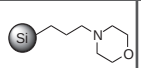
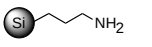
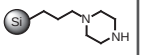
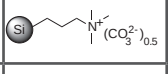
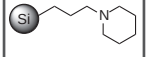
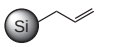
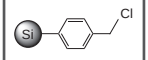
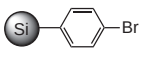
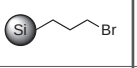
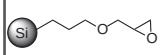
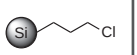
- Acylation / Esterification
- Alkylation / Etherification
- Amide Coupling
- Catalytic Hydrogenation
- Various Cross-Couplings
- Cyanation
- Deprotection of Ethers
- Ether Formation
- Fmoc, Bsmoc Deprotections
- Friedel-Crafts Alkylation
- Fries Rearrangement
- Grubbs Metathesis
- Michael Addition
- Tosylate Formation
- Urea Synthesis
- ***And so many more...***

Complete Overview of all Functionalized Silia*Bond* Reagents

Here is a global recapitulation of all SiliCycle's functionnalized silicas that can be used as reagents in organic synthesis.

- Silia*Bond* Catalysts & Reagents
- Silia*Bond* Oxidants
- Silia*Bond* Acids & Bases
- Silia*Bond* Linkers

Global Recapitulation of Silia*Bond* Reagents

	Name & Product Number	Structure	Loading (mmol/g) / Density (g/ml)	Name & Product Number	Structure	Loading (mmol/g) / Density (g/ml)
Catalysts & Reagents	Silia*Bond* $AlCl_3$ (*R74530B*)		≥ 1.60 0.781	Silia*Bond* EDC (*R70630B*)		≥ 0.32 0.770
	Silia*Bond* Amine (*R52030B*)		≥ 1.20 0.700	Silia*Bond* Guanidine (*R68230B*)		≥ 0.80 0.732
	Silia*Bond* Carbodiimide (*R70530B*)		≥ 0.91 0.751	Silia*Bond* HOBt (*R70730B*)		≥ 0.56 0.766
	Silia*Bond* Carbonate (*R66030B*)		≥ 0.46 0.608	Silia*Bond* Maleimide (*R71030B*)		≥ 0.64 0.644
	Silia*Bond* Cyanoborohydride (*R66730B*)		≥ 0.87 0.705	Silia*Bond* Morpholine (*R68030B*)		≥ 0.99 0.666
	Silia*Bond* Dichlorotriazine (*R52230B*)		≥ 0.60 0.781	Silia*Bond* Piperazine (*R60030B*)		≥ 0.83 0.671
	Silia*Bond* Dimethylamine (*R45030B*)		≥ 1.14 0.705	Silia*Bond* Piperidine (*R71530B*)		≥ 1.03 0.660
	Silia*Bond* Diphenylphosphine (*R39030B*)		≥ 0.75 0.588	Silia*Bond* Tosic Acid (*R60530B*)		≥ 0.54 0.698
	Silia*Bond* DMAP (*R75630B*)		≥ 0.53 0.674	Silia*Bond* Tosyl Chloride (*R44030B*)		≥ 0.63 0.761
Oxidants	Silia*Bond* $KMnO_4$ (*R23030B*)		10 % w/w 0.593	Silia*Bond* PDC (*R24530B*)		20 % w/w 0.651
	Silia*Bond* PCC (*R24030B*)		20 % w/w 0.693	Silia*Cat* TEMPO (*R723-100*)		≥ 0.70 0.550 - 0650
Acids & Bases	Silia*Bond* Carboxylic Acid (*R70030B*)		≥ 0.92 0.687	Silia*Bond* Dimethylamine (*R45030B*)		≥ 1.14 0.705
	Silia*Bond* Propylsulfonic Acid (*R51230B*)		≥ 0.63 0.728	Silia*Bond* Guanidine (*R68230B*)		≥ 0.80 0.732
	Silia*Bond* Tosic Acid (*R60530B*)		≥ 0.54 0.698	Silia*Bond* Morpholine (*R68030B*)		≥ 0.99 0.666
	Silia*Bond* Amine (*R52030B*)		≥ 1.20 0.700	Silia*Bond* Piperazine (*R60030B*)		≥ 0.83 0.671
	Silia*Bond* Carbonate (*R66030B*)		≥ 0.46 0.608	Silia*Bond* Piperidine (*R71530B*)		≥ 1.03 0.660
Linkers	Silia*Bond* Allyl (*R53530B*)		≥ 1.08 0.613	Silia*Bond* Phenylmethylchloride (*R56530B*)		≥ 1.14 0.637
	Silia*Bond* Bromophenyl (*R55030B*)		≥ 0.99 0.742	Silia*Bond* Propyl Bromide (*R55530B*)		≥ 1.39 0.748
	Silia*Bond* Glycidoxy (*R36030B*)		≥ 0.82 0.662	Silia*Bond* Propyl Chloride (*R59030B*)		≥ 1.39 0.751

SiliaBond Reagents & Oxidants Typical Reactions Selection Table

Here is a quick view of typical reaction examples in which SiliCycle functionalized silicas can be used as a quick, trendy and easy synthetic strategy.

Pure product can either be obtained by:

- using leach-free supported reagents, catalysts or oxidants
- purifying a reaction mixture, contaminated by excess homogeneous reagent or by a metal after using an homogeneous metal-based catalyst

SiliaBond Reagents & Oxidants Typical Reactions Selection Table

Typical Reactions		Best SiliaBond Reagent or Oxidant for Synthesis OR Best SiliaCat Catalyst for Catalysis	
Typical Reactions in Organic Synthesis			
Acylation / Esterification		SiliaBond DMAP SiliaBond $AlCl_3$	SiliaBond Tosic Acid
Alkylation / Etherification		SiliaBond Guanidine	SiliaBond $AlCl_3$
Amide Coupling	With acids, acid chlorides and amines	SiliaBond Carbodiimide SiliaBond Dichlorotriazine	SiliaBond EDC
	Using HOBt	-	
Catalytic Hydrogenation		SiliaCat Pd^0	SiliaCat Pt^0
Coupling Reactions Buchwald Amination, Heck Coupling, Kumada Coupling, Negishi Coupling, Sonogashira Coupling, Stille Coupling Suzuki Coupling and more...		SiliaCat DPP-Pd SiliaCat Pd^0 Please see SiliaCat section p. 27 for detailed protocoles and information	
Deprotection of Aromatic Ether		SiliaBond Tosic Acid	
Ether Formation		SiliaBond $AlCl_3$	SiliaBond Tosic Acid
Fmoc, Bsmoc Deprotection of Amino Acid		SiliaBond Piperazine	
Friedel-Crafts Alkylation		SiliaBond $AlCl_3$	
Fries-Speier Esterification		SiliaBond Tosic Acid	
Grubbs Metathesis		-	
Knoevenagel Condensation		SiliaBond Amine SiliaBond Dimethylamine	SiliaBond Piperidine SiliaBond Piperazine
Michael Addition		SiliaBond Dimethylamine	SiliaBond Guanidine
Nitro-Aldol (*or Henry*) Reaction		SiliaBond Carbonate	
Oxidation	Alcohols to acids	SiliaBond $KMnO_4$	
	Alcohols to ketones / aldehydes	SiliaCat TEMPO	SiliaBond PCC & PDC
Reduction (*Reductive Amination, Alkylation, etc.*)		SiliaBond Cyanoborohydride	
Sharpless Dihydroxylation		-	
Sulfonamide Synthesis		SiliaBond Dichlorotriazine SiliaBond EDC	
Tosylate Formation		SiliaBond Tosyl Chloride	
Urea Synthesis		SiliaBond DMAP	
Williamson Ether Synthesis		SiliaBond Guanidine	

Silia*Bond* Reagents & Oxidants Typical Reactions Selection Table		
Best Silia*Bond* Organic Scavenger to Remove Excess Reagent OR Best Silia*MetS* Metal Scavenger to Remove Excess Metal from Catalyst	**Typical Reactions**	
Various Silia*Mets* Metal Scavenger to remove metallic residues from homogeneous catalyst	**Acylation / Esterification**	
Various Silia*Mets* Metal Scavenger to remove metallic residues from homogeneous catalyst Silia*Bond* Carbonate to remove excess homogeneous HOBt	**Alkylation / Etherification**	
Silia*Bond* Amine to remove excess acid chloride Silia*Bond* Isocyanante or Tosic Acid to remove excess amine	With acids, acid chlorides and amines	**Amide Coupling**
Silia*Bond* Carbonate to remove excess homogeneous HOBt	Using HOBt	
Silia*MetS* Thiol, Thiourea or DMT to remove Pd Silia*MetS* DMT, Diamine or Triamine to remove Pt Silia*MetS* DMT, DOTA, Imidazole or TAAcONa to remove Ni	**Catalytic Hydrogenation**	
Silia*Bond* Isocyanante or Tosic Acid to remove excess amine Silia*MetS* Thiol, Thiourea or DMT to remove Pd Silia*MetS* DMT, DOTA, Imidazole or TAAcONa to remove Ni Silia*MetS* DOTA, Imidazole or TAAcONa to remove Cu Please see Silia*MetS* section p. 161 for detailed protocoles and information	**Coupling Reactions** Buchwald Amination, Heck Coupling, Kumada Coupling, Negishi Coupling, Sonogashira Coupling, Stille Coupling, Suzuki Coupling and more...	
-	**Deprotection of Aromatic Ether**	
-	**Ether Formation**	
Silia*Bond* Amine, DMAP, Piperazine, Silia*MetS* Diamine or Triamine to remove excess FMOC-Cl or Bsmoc-Cl	**Fmoc, Bsmoc Deprotection of Amino Acid**	
-	**Friedel-Crafts Alkylation**	
-	**Fries Rearrangement**	
Silia*MetS* DMT or Cysteine to remove Ru	**Grubbs Metathesis**	
-	**Knoevenagel Condensation**	
Silia*MetS* TAAcONa to remove Li Silia*MetS* Thiol, Thiourea or DMT to remove Pd	**Michael Addition**	
Silia*MetS* DOTA, Imidazole or TAAcONa to remove Cu	**Nitro-Aldol (*or Henry*) Reaction**	
-	Alcohols to acids	**Oxidation**
-	Alcohols to ketones / aldehydes	
Silia*Bond* Tosic Acid to remove excess borohydride or excess amine	**Reduction (*Reductive Amination, Alkylation, etc.*)**	
Silia*MetS* Thiol, DMT, Cysteine, Imidazole, TAAcOH or TAAcONa to remove Os	**Sharpless Dihydroxylation**	
Silia*Bond* Amine to remove excess sulfonyl chloride	**Sulfonamide Synthesis**	
-	**Tosylate Formation**	
Silia*Bond* Amine to remove excess isocyanate	**Urea Synthesis**	
-	**Williamson Ether Synthesis**	

Typical Reactions in Organic Synthesis

Silia*Bond* Acids & Bases Typical Reactions Selection Table
Silia*Bond* Linkers Typical Reactions Selection Table

Here is a quick view of typical reaction examples in which SiliCycle functionalized silicas can be used as a quick, trendy and easy synthetic strategy.

Silia*Bond* Reagents & Oxidants Typical Reactions Selection Table		
	Classification	**Best Silia*Bond* Acids & Bases**
Acids & Bases	**Acids**	Silia*Bond* Carboxylic Acid
		Silia*Bond* Propylsulfonic Acid
		Silia*Bond* Tosic Acid
	Bases	Silia*Bond* Amine
		Silia*Bond* Carbonate
		Silia*Bond* Dimethylamine
		Silia*Bond* Guanidine
		Silia*Bond* Morpholine
		Silia*Bond* Piperazine
		Silia*Bond* Piperidine
Linkers	**Synthesis of homemade functionalized silicas according to your very own application**	SiliaBond Allyl
		SiliaBond Bromophenyl
		SiliaBond Glycidoxy
		SiliaBond Phenylmethylchloride
		SiliaBond Propyl Bromide

SiliaBond Reagents & Oxidants Typical Reactions Selection Table

Typical Reactions & Applications Examples		
Acids & Bases	• Nucleophilic acyl substitutions such as esters hydrolysis, Fisher esterifications, amides hydrolysis, etc.	• A chromatographic phase week cation exchanger at pH ≥ 6.8 that can be eluted at a pH ≤ 2.8 (*please see p. 232*)
	• Nucleophilic acyl substitutions such as transesterifications, etc.	• Carbon-carbon coupling reactions
	• A chromatographic phase strong cation exchanger that is permenently negatively charged (*pKa < 1*) • Ionic scavenging (*please see p. 232)*	• Deprotections of aromatic ethers • Fries rearrangements
	• Organic scavenging of electrophiles (*please see p. 156 - 159)* • Ionic scavenging (*please see p. 156 - 159)*	• Nucleophilic-catalyzed reactions • Acid-catalyzed reactions such as Aldol reactions, Retro-Claisen reaction, Mannich reactions, etc.
	• Ionic scavenging (*please see p. 156 - 159)* • Nitro-Aldol (*Henry*) reactions & Michael additions	• Amine free-basing • Compatible with solvent-free conditions
	• Knoevenagel condensations	• Catch and release purification of compounds bearing a permanent negative charge such as salts of sulfonic acids
	• Alkylations • Strecker-type reactions • Etherifications such as Williamson synthesis	• Michael additions and more generally speaking 1,4 addition reactions • Ionic scavenging (*please see p. 156 - 159)* • Deprotonates moderately acidic hydrogens
	• Acid sponge • Enamine formations • Mannich condensations	• Less nucleophilic and less basic than piperidine hence forming stable chloramines
	• Deprotecting and scavenging agent for Fmoc and Bsmoc amino protecting groups	• Knoevenagel condensations • Ionic & nucleophile scavenger
	• Deprotecting and scavenging agent for Fmoc and Bsmoc amino protecting groups • Knoevenagel condensations	• Ketones to enamines conversions • Production of dipiperidinyl dithiuram tetrasulfide (*rubber vulcanization accelerator*)
Linkers	• Allylic oxidations • Ene reactions	• Tsuji-Trost reactions • Rancidification
	• Introduction of phenyl groups via Pd-catalyzed couplings	• Synthesis of Grignard reagents
	• Immobilization of molecules bearing amino, hydroxy, mercapto and thiocarboxylic acid groups • Ring-opening reactions & hydrolysis	• Reduction with tungsten hexachloride • Reduction with lithium aluminum hydride
	• Nucleophilic substitutions for introduction of phenyl linker	
	• Nucleophilic substitutions for introduction of n-propyl linker	

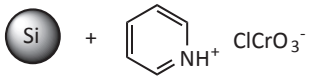
Oxidations

SiliaBond Pyridinium Chlorochromate (*R24030B*)
SiliaBond Pyridinium Dichromate (*R24530B*)

Description

SiliaBond Pyridinium Chlorochromate (*Si-PCC*)

Commonly used for the oxidation of alcohols to carbonyl compounds, selective oxidation of allylic and benzylic alcohols, organometallic oxidations, oxidative transpositions, oxidative cleavages, allylic and benzylic oxidation and oxidative cyclizations.[1-4] Using PCC immobilized onto silica gel provides anhydrous conditions that minimize the risk of side reactions and reduced yields. It greatly facilitates removal of polymeric reduced chromium by-products and is compatible with acid-sensitive protecting groups.[5,6] When used in conjunction with ultrasounds, kinetics are increased and the amount of oxidant required to complete the reaction is decreased.[7-9]



Category: Oxidant

Typical Application: Oxidation of alcohols to aldehydes / ketones

Loading: 20 % w/w	**Density**: 0.693 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous CH_2Cl_2

Storage: Keep cool (< *8°C*) and dry

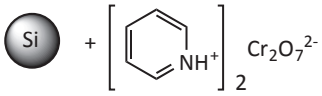
[1] *Org. Chem.*, **1989**, *54*, 5387
[2] Tetrahedron Lett., **2001**, *42*, 2141
[3] Synlett, **1999**, *10*, 1630
[4] Synth. *Commun.*, **1996**, *26*, 225
[5] *J. Org.Chem.*, **1993**, *58*, 2509
[6] *J. Chem. Educ.*, **1999**, *76*, 974
[7] *J. Org. Chem.*, **1983**, *48*, 666
[8] *Liebigs Ann. Chem.*, **1993**, 173
[9] *J. Org. Chem.*, **1992**, *57*, 3867

Description

SiliaBond Pyridinium Dichromate (*Si-PDC*)

Great alternative to *Si*-PCC in nucleoside and carbohydrate oxidation, particularly for fragile molecules.[1] SiliaBond PDC can also be used in conjunction with *tert*butylhydroperoxide for a variety of oxidative transformations.[2]

Si-PDC is a very convenient and effective reagent for oxidizing allylic and benzylic alcohols, saturated with acid-sensitive groups, such as cyclopropane rings or ketal functions.[3]



Category: Oxidant

Typical Application: Oxidation of alcohols to aldehydes / ketones

Loading: 20 % w/w	**Density**: 0.651 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous CH_2Cl_2

Storage: Keep cool (< *8°C*) and dry

[1] *J. Chem. Soc. Perkin Trans. I*, **1982,** 1967
[2] *J. Chem. Soc. Chem. Commun.*, **1993**, *7*, 651
[3] *Tetrahedron*, **1979**, *35*, 1789

SiliaBond Potassium Permanganate (*R23030B*)

Description

SiliaBond Potassium Permanganate (*Si-KMnO$_4$*)

This product is a strong oxidant that will oxidize alcohols and aldehydes to carboxylic acids. SiliaBond Potassium Permanganate increases recovery, facilitates work-up and expands the scope of the chemistry because it can be used in all organic solvents eliminating solubility issues.[1] With SiliaBond Potassium Permanganate, the manganese salt by-products stay adsorbed onto the silica.

Category: Oxidant

Typical Application: Oxidation of alcohols and aldehydes to acids

Loading: 10 % w/w	**Density**: 0.593 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous CH_2Cl_2

Storage: Keep dry

[1] *Synlett*, **2001**, *10,* 1555

Amide Coupling Reactions

The amide bond is the defining molecular structure of proteins and peptides. In addition, a report estimates that as many as 25 % of all synthetic pharmaceutical drugs contain an amide group.[1] Therefore, there is an ongoing scientific endeavor to develop efficient amidation methodologies.[2] Usually, the amide bond formation relies on the use of an excess of toxic coupling reagents such as carbodiimides or supernucleophiles. These chemicals produce a large amount of by-products, which tends to complicate the isolation and purification of the desired amide product.

The use of a reagent linked to an insoluble material has become a widely used tool since the introduction of the solid-phase synthesis concept.[3] Solid-phase reagents are valuable for amide coupling with a carboxylic acid because they generate less unwanted side products. Other advantages of using solid-supported reagents include improved stability, toxic chemical immobilization, the ability to run multiple transformations in a single pot and the flexibility to use batch reactions, microwave irradiation and flow chemistry.

[1] *J. Comb. Chem.*, **1999**, *1*, 55 [2] *Tetrahedron*, **2005**, *61*, 10827 [3] *J. Am Chem Soc.*, **1963**, *85*, 2149

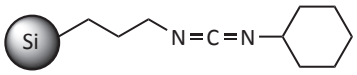
Silia*Bond* Carbodiimide (*R70530B*)

Description

Silia*Bond* Carbodiimide (*Si-DCC*)

1,3-Dicyclohexylcarbodiimide (*DCC*) has arguably become the most commonly used reagent in peptide synthesis and other amide bond-forming reactions of primary and secondary amines with carboxylic acids.[1] The major drawback associated with using DCC is the formation of the urea by-product (*DCU*) which remains in solution and requires additional purification steps to remove. However, by using covalently bonded DCC on silica, it is possible to avoid problematic purifications. Only a simple filtration step is needed to remove the unwanted DCU.

[1] *Chem. Rev.*, **1981**, *81*, 589



Category: Reagent

Typical Application: Amide coupling with acids, acyl chlorides and amines

Loading: ≥ 0.91 mmol/g	**Density**: 0.751 g/mL	**Endcapping**: Yes

Solvent Compatibility: Aprotic solvents

Storage: Keep cool (< *8°C*), dry and under argon

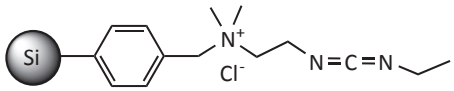
Silia*Bond* Ethyl-Dimethylamino Carbodiimide (*R70630B*)

Description

Silia*Bond* Ethyl-Dimethylaminopropyl Carbodiimide (*Si-EDC*)

A recent literature review shows that 1-ethyl-3 (*3-dimethylaminopropyl*) carbodiimide (*EDC*) has become recognized as one of the best reagents for amide coupling reactions. Unfortunately, using the EDC basic tertiary amine results in the formation of urea, which has to be separated from the product by acidic aqueous extractions.[1] By attaching EDC to silica, it is possible to avoid this potentially problematic work-up without sacrificing the useful carbodiimide reactivity. In fact, Silia*Bond* EDC behaves in a similar fashion as EDC in solution, but the by-product remains on the solid support.

[1] *The Peptides: Analysis, Synthesis, Biology; Academic: New York*, **1979**, *1*, 241



Category: Reagent

Typical Application: Amide coupling with acids, acyl chlorides and amines

Loading: ≥ 0.32 mmol/g	**Density**: 0.770 g/mL	**Endcapping**: Yes

Solvent Compatibility: Aprotic solvents

Format: Keep cool (< *8°C*), dry and under argon

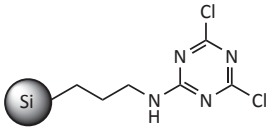
Silia*Bond* Dichlorotriazine (*R52230B*)

Description

Silia*Bond* Dichlorotriazine (*Si-DCT*)

2,4,6-trichloro[1,3,5]triazine (*cyanuric chloride*) has been used as a versatile reagent in alkyl chloride and acid chloride synthesis. This triazine has been especially useful as a coupling reagent for amide selective formation.[1] However, cyanuric chloride is toxic, corrosive and a severe eye, skin and respiratory tract irritant. By anchoring cyanuric chloride on a silica matrix, it is now possible to use this valuable reagent without worrying about its toxicity profile. Silia*Bond* DCT reacts in a similar manner as cyanuric chloride. In addition, excess reagent and by-product elimination is reduced to a simple filtration, which is particularly useful for products where toxicity is a concern such as in the synthesis of active pharmaceutical ingredients (*API*).

[1] *J. Org. Chem.*, **1997**, *62*, 982



Category: Reagent

Typical Application: Amide coupling with acids, acyl chlorides and amines

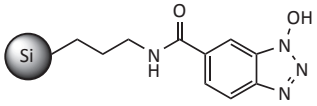
Loading: ≥ 0.60 mmol/g	**Density**: 0.781 g/mL	**Endcapping**: Yes
Solvent Compatibility: Aprotic solvents		
Storage: Keep cool (< *8°C*), dry and under argon		

Silia*Bond* HOBt (*R70730B*)

Description

Silia*Bond* HOBt (*Si-HOBt*)

Hydroxybenzotriazole (*HOBt*) has been used for increasing yield and decreasing racemization during chiral amide synthesis. However, dry HOBt can undergo exothermic decomposition. Bonding HOBt to silica eliminates this risk of explosion. Silia*Bond* HOBt can be easily activated and should ideally be used with a base such as *N,N*-diisopropylethylamine in the same conditions as in homogeneous solution. Moreover, this supported reagent can be reused a few times without adversely affecting its performance.



Category: Reagent

Typical Application: Avoiding or reducing racemization during chiral amide synthesis

Loading: ≥ 0.56 mmol/g	**Density**: 0.766 g/mL	**Endcapping**: Yes
Solvent Compatibility: Aprotic solvents		
Storage: Keep dry		

Reductive Aminations

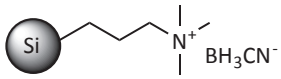
Reductive amination involves the conversion of a carbonyl group, most of the time a ketone or an aldehyde, to an amine via an intermediate imine or iminium. The intermediate imine is reduced by sodium cyanoborohydride. This is known as direct reductive amination and is carried out with reducing agents that are more reactive toward protonated imines (*or iminiums*) than ketones and are stable under moderately acidic conditions.

Silia*Bond* Cyanoborohydride (*R66730B*)

Description

Silia*Bond* Cyanoborohydride (*Si-CBH*)

Silia*Bond* Cyanoborohydride is the silica-bound equivalent of sodium cyanoborohydride. Bound cyanoborohydride is very useful in reductive amination and in the reduction of imines and aldehydes. However, when using the solution phase equivalent, cyanide contamination of the product is a concern. This problem is minimized with the use of silica-bound materials since the toxic cyanide residue remains on the silica. To see if any cyanide ion was leaching from the silica, 1 g of Silia*Bond* Cyanoborohydride was slurried in 10 mL of methanol for 24 h. Cyanide strips indicated less than 3 ppm in each test performed. In addition to providing superior conversions, acetic acid was not needed (*eliminating issues with acid labile groups*), the work-up required only a filtration and HCN nor NaCN were liberated during work-up.



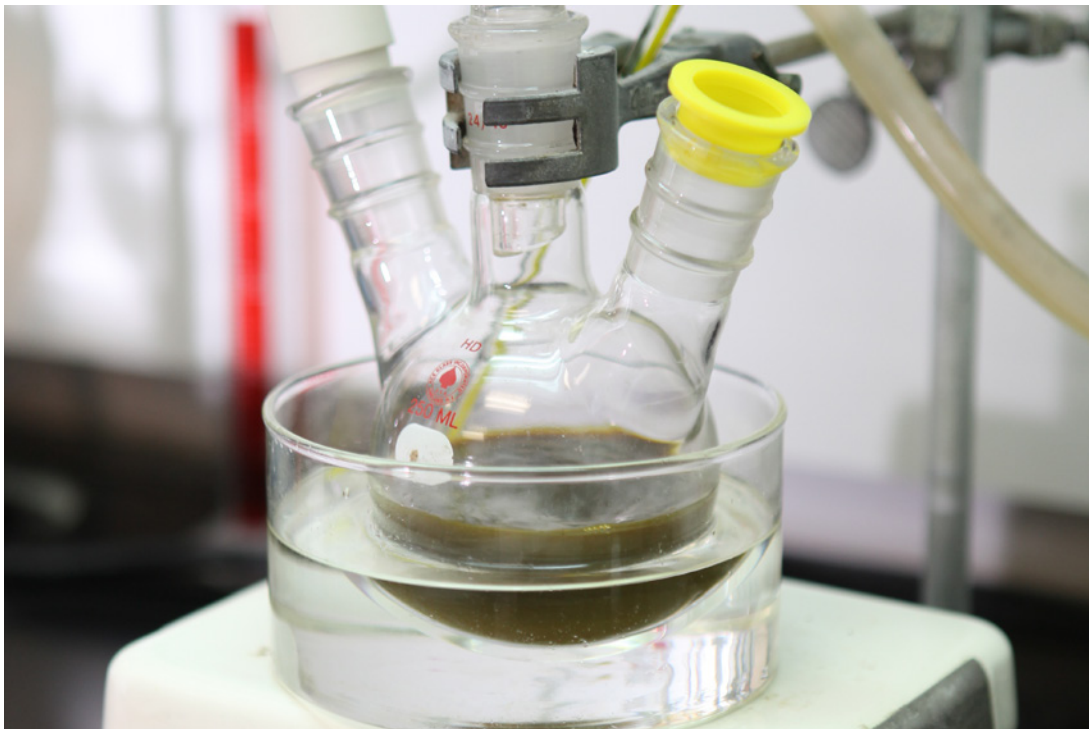
Category: Reagent

Typical Application: Reductive amination

Loading: ≥ 0.87 mmol/g	**Density**: 0.705 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep cool (< *8°C*), dry and under argon



Nitro-Aldol (*or Henry*) Reaction

The Henry reaction is commonly used to form carbon-carbon bonds by addition of nitroalkanes over aldehydes. This reaction is a useful technique in organic chemistry due to the synthetic utility of its corresponding products, as they can be easily converted to other useful synthetic intermediates such as nitroalkenes by dehydrogenation, α-nitro ketones by oxidation and β-amino alcohols by reduction. Usually, the Henry reaction is carried out in presence of bases in homogeneous solution, giving low yield due to side reactions such as retroaldol and Cannizarro reactions.

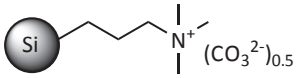
Silia*Bond* Carbonate (*R66030B*)

Description

Silia*Bond* Carbonate (*Si-CO_3*)

Used as a heterogenous catalyst in the Henry reaction, Silia*Bond* Carbonate is replacing the use of expensive and toxic heterogeneous catalysts. Silia*Bond* Carbonate in catalytic amounts drive the reaction forward to high yield with or without solvent.

Silia*Bond* Carbonate is also an excellent product for amine free-basing. Please see p. 112 for more information.



Category: Reagent or Catalyst

Typical Application: Nitro-Aldol reaction (*Henry reaction*), free basing of amines

Loading: ≥ 0.46 mmol/g	**Density**: 0.608 g/mL	**Endcapping**: Yes
Solvent Compatibility: Aprotic solvents		
Storage: Keep dry		

Silia*Bond* Piperazine (*R60030B*)

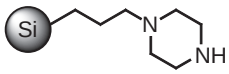
Description

Silia*Bond* Piperazine (*Si-PPZ*)

Silia*Bond* Piperazine (*Si-PPZ*) is a very useful solid-phase Knoevenagel catalyst. According to the results of a study, Si-PPZ is superior to its polystyrene-based equivalent.[1-3]

Silia*Bond* Piperazine is a useful deprotecting and scavenging agent for Fmoc and Bsmoc amino protecting groups, as well as a great electrophile scavenger.

Please see p. 157 for more information on Silia*Bond* Piperazine scavenging capabilities.



Category: Reagent or Catalyst

Typical Application: Knoevenagel synthesis, Fmoc and Bsoc deprotection, organic scavenger.

Loading: ≥ 0.83 mmol/g	**Density**: 0.671 g/mL	**Endcapping**: Yes
Solvent Compatibility: All solvents, aqueous and organic		
Storage: Keep cool (< *8°C*) and dry		

[1] *J. Org. Chem.*, **1983**, *48*, 666
[2] *J. Org. Chem.*, **1999**, *64*, 4324
[3] *J. Org. Chem.*, **2010**, *51*, 6670

Acylation & Esterification Reactions

Acylations are the addition of an acyl group (*RCO*) via electrophilic substitution, whereas esterifications are the formation of esters (*RCOOR*) from a derived carboxylic acid.

The typical acylation reaction is the Friedel-Crafts, and other acyl transfers include the Boekelheide, Kostanecki, Passerini reactions, the Pummerer rearrangement, etc. The typical esterification reaction is the Fischer reaction, and other ester synthesis include the Fisher-Speier modification, Mitsunobu reaction, the Steglich esterification, etc.

For both reactions DMAP (*4-dimethylaminopyridine*) is well-known as an acyl-transfer catalyst, to increase speed and yield of alcohol and phenol acylations over acetic and benzoic anhydrides. Tosic Acid, on the other hand, is a very popular acid catalyst for esterification & transesterification of esters and $AlCl_3$ is probably one of the most commonly used Lewis acid as a catalyst for Friedel-Crafts reactions.

Silia*Bond* Aluminum Chloride (*R74530B*)

Description

Silia*Bond* Aluminum Chloride (*Si-AlCl$_3$*)

Silia*Bond* Aluminum Chloride is the silica-supported version of the most widely used Lewis acid, aluminum chloride.[1] It is an effective catalyst for Friedel-Crafts alkylations[2-4] and acylations. It also catalyzes the formation of ethers. The silica-supported product has several advantages over the free catalyst.[5,6]

- It is a milder Lewis acid. $AlCl_3$ is so reactive that it often lacks selectivity and causes the formation of unwanted by-products.
- Si-$AlCl_3$ reduces over alkylation and increases shelf-life.
- Execution of the reaction is easier. The reagent is removed by a simple filtration, avoiding the destructive water quench which produces large amounts of hazardous waste.

Silia*Bond* Aluminum Chloride's activity can be determined by its color. The material should only be used when it's yellow or violet. The product turns white in presence of moisture and is no longer reactive.

Category: Reagent or Catalyst

Typical Application: Acylations, esterifications		
Loading: ≥ 1.60 mmol/g	**Density**: 0.781 g/mL	**Endcapping**: No
Solvent Compatibility: Anhydrous, degassed and organic solvents		
Storage: Keep cool (< *8°C*), dry and under argon		

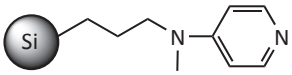
[1] *Acc. Chem. Res.*, **2002**, *35*, 791
[2] *Org. Proc. Res. Dev.*, **1998**, *2*, 221
[3] *J. Catal.*, **2000**, *195*, 237
[4] *J. Catal.*, **2000**, *195*, 412
[5] *Chem. Rev.*, **2003**, *103*, 4307
[6] *Tetrahedron*, **2003**, *59*, 1781

Silia*Bond* DMAP (*R75630B*)

Description

Silia*Bond* DMAP (*Si-DMAP*)

Silia*Bond* DMAP is the heterogeneous catalyst equivalent of 4-dimethylaminopyridine, which is used as a nucleophilic catalyst in a wide variety of reactions such as acylations and Baylis-Hillman reactions. These reactions are well known in organic synthesis and are very useful in various applications. Silia*Bond* DMAP has an advantage over its free counterpart as it can be removed by a simple filtration.



Category: Reagent or Catalyst

Typical Application: Acylations, esterifications

Loading: ≥ 0.53 mmol/g	**Density**: 0.674 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep cool (< *8°C*), dry and under argon

Silia*Bond* Tosic Acid (*R60530B*)

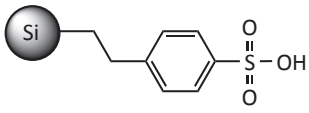
Description

Silia*Bond* Tosic Acid (*Si-SCX*)

Silia*Bond* Tosic Acid is in a class of strong acids used in different fields of synthetic organic chemistry. The aromatic ring makes it slightly more acidic than other supported sulfonic acids.

Silia*Bond* Tosic Acid used as an acid catalyst for Fischer-Speier esterification provides excellent conversion.

Silia*Bond* Tosic Acid can also be used as a metal scavenger. Please refer to page 151 for more details.



Category: Reagent or Catalyst

Typical Application: Esterification, deprotection of aromatic ethers

Loading: ≥ 0.54 mmol/g	**Density**: 0.698 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep dry

Alkylation & Etherification Reactions

Alkylation reactions are the transfer of an alkyl group from one molecule to the other via alkylating agents, that may have an electrophilic or nucleophilic character. Etherifications are a type of C-O bond formation reaction, usually from the S_N2 reaction between an organohalide and an alcohol.

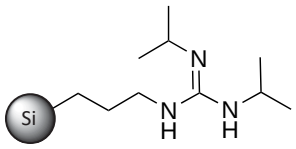
Just like for acylation reactions, the most common type of alkylation is the Friedel-Crafts reaction and the typical etherification reaction is the Williamson synthesis.

Silia*Bond* Guanidine (*R68230B*)

Description

Silia*Bond* Guanidine (*Si-GUA*)

Silia*Bond* Guanidine is a silica-bound guanidine moiety that is sufficiently basic to deprotonate moderately acidic hydrogens. It is most commonly used in Williamson synthesis, 1,4 addition reactions, Strecker-type reactions, etc.



Category: Reagent

Typical Application: Williamson ether synthesis, Strecker-type reactions, 1,4 addition reactions

Loading: ≥ 0.80 mmol/g	**Density**: 0.732 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep dry

Silia*Bond* Aluminum Chloride (*R74530B*)

Description

Silia*Bond* Aluminum Chloride (*Si-AlCl$_3$*)

As shown on the previous page, Silia*Bond* Aluminum Chloride is the silica-supported version of the widely used Lewis acid, aluminum chloride.[1] It is an effective catalyst for Friedel-Crafts alkylations[2-4] and acylations. It also catalyzes the formation of ethers. The silica supported product has several advantages over the free catalyst:[5,6]

- It is a milder Lewis acid. Homogeneous $AlCl_3$ is so reactive that it often lacks selectivity and causes the formation of unwanted by-products.
- The steric bulk of the silica reduces over alkylation and increases shelf-life.
- Execution of the reaction is easier. The reagent is removed by a simple filtration, avoiding the destructive water quench which produces large amounts of hazardous waste.

Silia*Bond* Aluminum Chloride's activity can be determined by its color. The material should only be used when it's yellow or violet. The product turns white in presence of moisture and is no longer reactive.

Category: Reagent or Catalyst

Typical Application: Acylations, esterifications

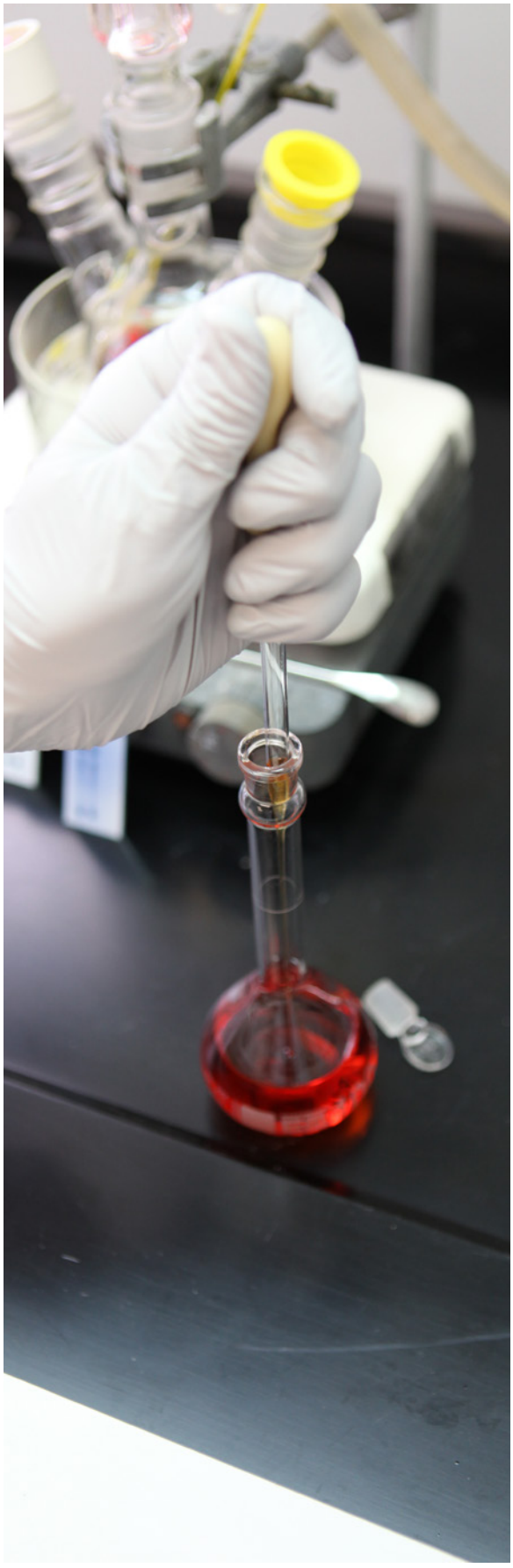
Loading: ≥ 1.60 mmol/g	**Density**: 0.781 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous, degassed and organic solvents

Storage: Keep cool (< *8°C*), dry and under argon

[1] *Acc. Chem. Res.*, **2002**, *35*, 791
[2] *Org. Process Res. Dev.*, **1998**, *2*, 221
[3] *J. Catal.*, **2000**, *195*, 237
[4] *J. Catal.*, **2000**, *195*, 412
[5] *Chem. Rev.*, **2003**, *103*, 4307
[6] *Tetrahedron*, **2003**, *59*, 1781

SiliaBond Reagents Compatibility with Different Technologies



Organic synthesis has traditionally been performed in batch: round-bottom flasks, test tubes, or closed vessels.

The general strategies and synthetic protocols used to construct organic molecules have remained relatively unchanged over the last few decades despite the many conceptual and technological advances that have arisen.

However, certain key enabling technologies, such as microwave heating and flow-based chemical processing, have seen rapid adoption and are greatly impacting on the synthetic routes used to prepare many of today's new chemical entities.

Nowadays, many existing syntheses have been re-examined and improved through the judicious application of modern chemical engineering principles.

In the following section, flow-based applications are identified by the following logo:

and microwave-based applications are identified by the following logo:

Flow Chemistry

What is Flow Chemistry?

Flow chemistry is a simple yet powerful technique: a chemical reaction is run in a continuously flowing stream, in opposition to a static volume contained in a vessel. Fluids containing the various reagents are pumped to join into a mixer and be submitted to different experimental conditions (*such as heating, cooling, pressure etc.*), in order to react.

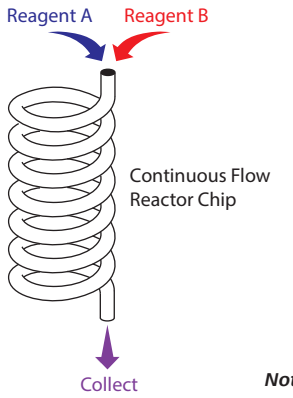
The main advantage of this new concept is that molecules enter, react and leave the system hence avoiding sustained exposition to conditions that would eventually lead to side reactions, by-products or impurities formation, etc.

In terms of reactivity, the strength of flow chemistry originates from the mixing. At large scale, mixing becomes much more powerful and heat exchange surface much more favorable than in a batch operation.

Doubling reaction size multiplies the surface by only 4, but the volume by 8. This volume-surface ratio is specially critical when hot spots arise (*low temperature reactions*), or when build-up next to the vessel's walls (*high temperature reactions*): temperature of the fluids is thus homogeneous.

Using silica-supported products in flow chemistry applications will ensure the following:

- Increase in R&D and manufacturing productivity
- Much higher reproducibility during scale-up because there is no issue of volume:surface ratio
- Precise control of mixing & temperature
- Minimal risk associated with hazardous reagents
- Separation of the catalyst from the products alleviates the need for any filtration (*or further handling*)
- Silia*Bond*, Silia*Cat* and Silia*MetS* can be used without degradation



***Note**: a reactor is needed*

Importance of Flow Chemistry

Flow chemistry is a relatively new technique that is being used more and more for large scale manufacturing because it only requires a small investment but enables the production of large quantities in shorter time and less space.

The use of supported catalysts in flow chemistry is even more recent. Supported catalysts are available on different supports such as polymers, charcoal, alumina and silica. They offer many advantages over the traditional homogeneous catalysts, including ease of handling and purification.

Silica presents many advantages such as no swelling, good mechanical and thermal stability and ease of scalability. SiliCycle has developed innovative silica-based catalysts (*Silia*Cat*, please see appropriate section p. 15*), reagents (*Silia*Bond*) and metal scavengers (*Silia*MetS*, *please see appropriate section p. 137*) that can be used in flow chemistry.

Microwave Applications

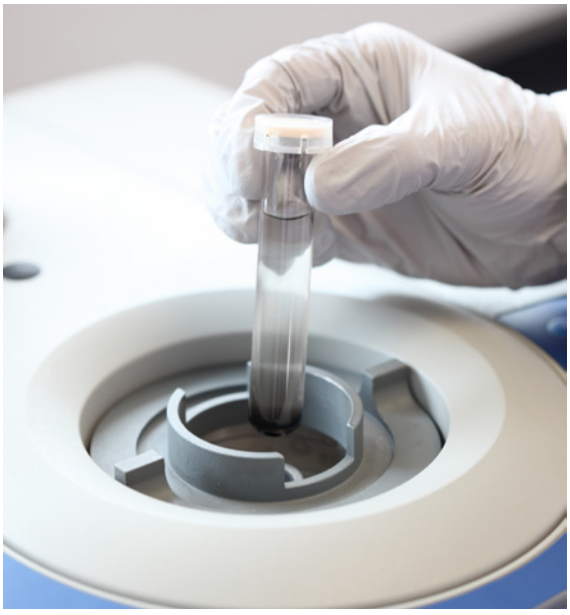
What is Microwave Chemistry?

It's been a while since chemists have known that molecules undergo excitation when exposed to electromagnetic radiations

Use of microwave or dielectric heating in organic chemistry has lead to extraordinary reaction rate enhancements. More recently the use of microwave radiation for heating reactions has even been expanded to inorganic and materials chemistry.

In the background of green chemistry, microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave-assisted reactions are fast, clean, economic and eco-friendly. This technique has frequently been proposed as the "technology of tomorrow".

- Faster kinetics: only a few minutes per reaction
- Higher yields and excellent purity
- Compatibility with many solvents
- Silia*Bond*, Silia*Cat* and Silia*MetS* can be used without degradation
- Wide variety of reactions and applications



Importance of Microwave-Assisted Synthesis

In last 2 decades, microwave synthesizer have taken organic chemistry by strom. Fast kinetics, higher yields, excellent purity, wide compatibility of solvents and their applicability to a variety of reactions and applications, make them very useful tools in the laboratory. After their introduction, chemists started to use supported reagents for solution-phase synthesis. The polymer-supported reagents commonly used, although very useful, have drawbacks in microwave synthesizers, namely swelling and heat instability. The high temperatures generated inside these synthesizers put stress on the resins. Also, because of the small reaction volumes, the swelling of the resins can be problematic. Silica-based products on the other hand, do not suffer from such shortcomings. They are heat resistant and they do not swell. In the following pages, we present different reactions (*amide synthesis, reductive amination, Henry reaction*) using Silia*Bond* Reagents as well as an electrophile and nucleophile that demonstrate the effectiveness of these reagents for microwave applications.

Application Notes and Case Studies

We have selected a few application cases to help understanding how our functionalized silicas can be introduced in your daily synthetic strategies.

Application Notes

You can read through our “Application Notes” section to learn more about different SiliCycle applications that were developed in our labs, but don’t take our word for granted and also check out customers Case Studies.

In the following section, application notes are identified by this logo:

Case Studies

Discover and learn what some of our customers are doing with our technology in the “Case Studies” section.

In the following section, case studies and applications developed by our customers are identified by this logo:

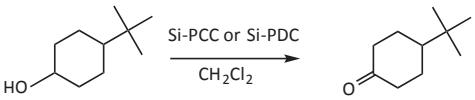
Nothing speaks more than lab examples and real-life experiences!

Oxidations

Oxidation of Alcohols to Ketones and Aldehydes (*Si-PDC or Si-PCC*)

General Procedure

Silia*Bond* PCC or Silia*Bond* PDC (*8.00 mmol; 2.0 equiv*) and acetic acid (*4.00 mmol; 1.0 equiv*) were added to a solution of alcohol in CH_2Cl_2 (*7.5 mL*). The resulting mixture was stirred for 6 h at room temperature. Ether (*15 mL*) was added and after stirring for another 2 min, the solution was filtered and the solids were washed with ether (*4 x 9 mL*). Concentration under vacuum afforded the desired product without further purification.



Oxidation of Alcohols Results

Silia*Bond* Oxidant	Conditions	Conversion[a] (%)
Silia*Bond* PCC	6 h, r.t.	100
Silia*Bond* PDC		100

[a] Conversion determined from GC-MS

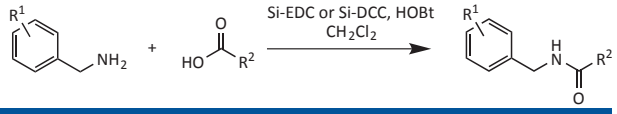
Amide Coupling Reactions

Synthesis of Capsaicin Analogues (*Si-DCC or Si-EDC*)

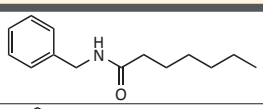
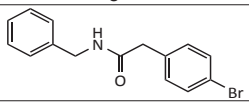
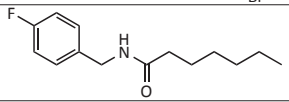
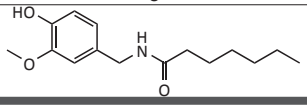
Capsaicin's potential clinical use as an analgesic and for its peripheral anti-inflammatory effects, as well as the discovery of an ultra-potent analogue (*resiniferatoxin*) has attracted significant interest in finding capsaicin synthesis routes.

General Procedure

The acid (*1.00 mmol; 1.0 equiv*) was placed in an oven-dried reaction vial with anhydrous CH_2Cl_2 (*10 mL*) under nitrogen. HOBt (*1.00 mmol; 1.0 equiv*) and Silia*Bond* DCC or Silia*Bond* EDC (*1.50 mmol; 1.5 equiv*) were added to the solution, which was then stirred briefly (*5 min*). The amine (*0.50 mmol; 0.5 quiv*) was then added to the reaction tube and the mixture was then stirred for 16 h at room temperature. Reaction was followed by GC-MS, and work-up consisted in a simple filtration on Büchner and washing with CH_2Cl_2 (*3 x 10 mL*). Solvent was evaporated to yield pure amide.



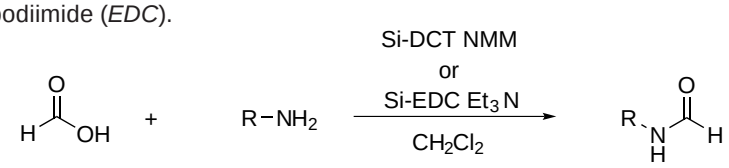
Capsaicin Analogues Reaction Results (*in %*)

Product	Yield[a] (*Purity*[b])	
	Si-DCC	*Si*-EDC
	99 (> *98*)	81 (> *98*)
	98 (> *98*)	88 (*95*)
	99 (> *98*)	99 (> *98*)
	98[c]	98[c]

[a] Yield calculated in crude product [b] Purity determined by GC-MS [c] Yield determined by GC-MS

Synthesis of Formylated Amino Acids (*Si-DCT or Si-EDC*)

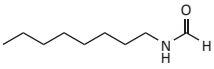
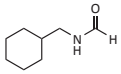
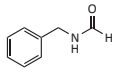
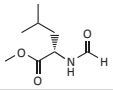
N-formylamino acid esters are useful derivatives for preparing selected *N*-formylamino acids, incorporating polyfunctional amino acids into peptides and for other useful starting material preparation. Formylated amino acids have been prepared in high yields by using Silia*Bond* Dichlorotriazine (*DCT*) and Silia*Bond* Ethyl-Dimethylaminopropyl Carbodiimide (*EDC*).



General Procedure

Formic acid (*0.90 mmol; 1.0 equiv*) was placed in an oven-dried reaction vial in anhydrous CH_2Cl_2 (*10 mL*) under nitrogen. To this solution was either added *[N-methylmorpholine (0.90 mmol; 1.0 equiv) and Silia*Bond* DCT (2.25 mmol; 2.5 equiv)]* or *[triethylamine (0.90 mmol; 1.0 equiv) and Silia*Bond* EDC (2.25 mmol; 2.5 equiv)]*. The mixture was then stirred briefly (*5 min*), and the amine (*0.45 mmol; 0.5 equiv*) was added to the vial and the reaction was stirred at room temperature for 16 h. Conversion to the desired formamide was monitored by GC-MS. Upon completion, the Silia*Bond* DCT or EDC was filtered and washed with 2 x 10 mL of CH_2Cl_2 to yield product.
No further purification was required.

Synthesis of Formylated Amino Acids Results (*in %*)

Product	Conversion[a] Si-DCT	Conversion[a] Si-EDC	Product	Conversion[a] Si-DCT	Conversion[a] Si-EDC
	99	93		99	99
	99	100		98	95

[a] Conversion determined by GC-MS

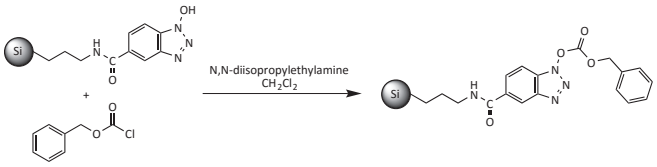
Amine Protection Using Benzylcarbamate Group (*Si-HOBt*)

Benzylcarbamate groups are one of the most used amine protecting functions because of the easy deprotection by hydrogenolysis. Silia*Bond* HOBt, as a key reactive, facilitates the protection step and can be reused a few times without loss of reactivity.

General Procedure

Silia*Bond* HOBt (*0.80 mmol; 1.0 equiv*) was introduced in an oven-dried flask containing anhydrous CH_2Cl_2. Benzylchloroformate (*3.20 mmol; 4.0 equiv*) was added to the suspension, followed by *N,N*-diisopropylethylamine (*3.20 mmol; 4.0 equiv*). The reaction mixture was stirred for 60 min at room temperature. Then, the suspension mixture was filtered, washed with CH_2Cl_2 (*2 x 10 mL*) and the Silia*Bond* HOBt was oven-dried for reuse.

Activation Reaction



Activation and Recycling Results (*in %*)

Entry	Yield[a]
Activation	96
1st Recycling	86
2nd Recycling	95
3nd Recycling	96

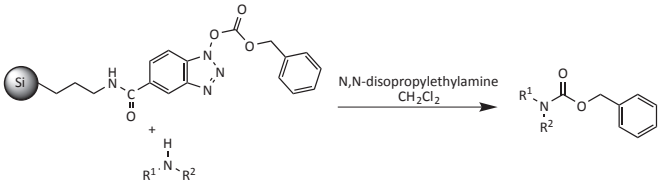
[a] Yield determined by GC-MS

Amine Protection Reaction (*Si-HOBt*)

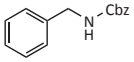
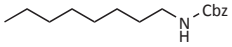
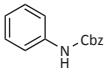
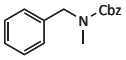
General Procedure

Same as previous

The dried, activated Silia*Bond* HOBt (*0.80 mmol; 1.0 equiv*) was placed in a flask containing anhydrous CH_2Cl_2 under nitrogen. To this suspension, the amine (*0.64 mmol; 0.8 equiv*) was added, and the reaction mixture was stirred for 4 to 16 h at room temperature.
The reaction suspension was filtered and washed with CH_2Cl_2 (*2 x 10 mL*).



Amine Protection Results (*in %*)

Product	Yield[a]	Product	Yield[a]
	98 (*4 h*)		93 (*4 h*) 98 (*16 h*)
	94 (*4 h*) 96 (*16 h*)		98 (*4 h*)
	81 (*16 h*)		93 (*16 h*)

[a] Yield determined from isolated product

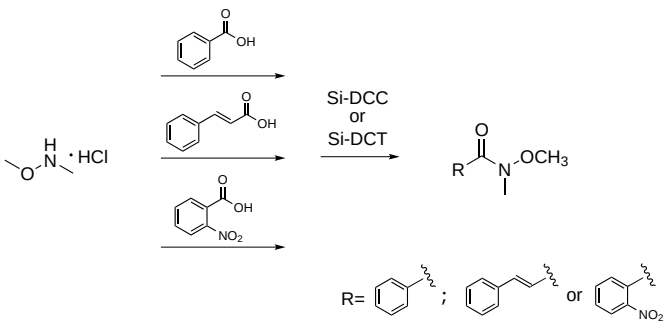
Weinreb and Acylsulfonamide Synthesis (*Si-DCC or Si-DCT*)

The Weinreb synthesis is a reaction often used in medicinal chemistry to produce amides. These functional groups are present in natural products and can be reliably reacted to form new carbon-carbon bonds or converted to other functions. In normal conditions, the Weinreb synthesis can tolerate a large variety of functional groups such as *N*-protected amines, sulfonates, alpha-beta saturation and silyl ethers.

General Procedure for Weinreb Synthesis

The acid (*0.21 mmol; 3.0 equiv*), DMAP (*0.21 mmol; 0.3 equiv*), pyridine (*0.25 mmol; 3.5 equiv*), *N,O,*-dimethylhydroxylamine hydrochloride (*0.07 mmol; 1.0 equiv*) and Silia*Bond* DCC or DCT (*0.32 mmol; 4.5 equiv*) in 10 mL of DCM were added to a dry vessel and stirred overnight at room temperature Excess acid was scavenged with Silia*Bond* Amine (*0.29 mmol; 4.0 equiv*) and excess amine, DMAP and pyridine were scavenged with Silia*Bond* Tosic Acid (*1.00 mmol; 14.0 equiv*).

Total volume of the mixture was adjusted to keep a ratio silica / solvent of 1 g / 5 mL. Scavengers were allowed to react for 1 h at room temperature prior to filtration, washing with DCM and evaporation of solvent.



Weinreb Synthesis Results (*in %*)

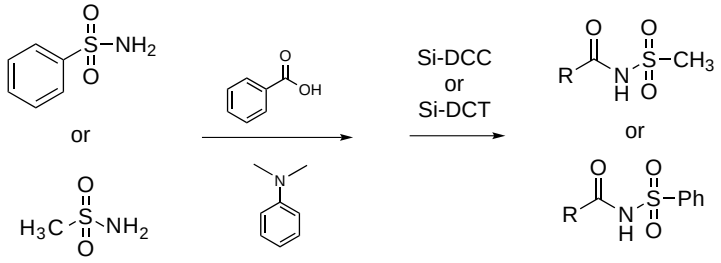
Amine	Acid	Yield[a] (*Purity*)[b]	
		Si-DCC	Si-DCT
N,O-Dimethylhydroxyamine Hydrochloride	Benzoic Acid	99 (*96*)	96 (*94*)
	t-Cinnamic Acid	87 (*95*)	82 (*70*)
	2-Nitrobenzoic Acid	> 99 (*93*)	92 (*79*)

[a] Yield determined from isolated product
[b] Purity determined by GC-MS

General Procedure for Acylsulfonamide Synthesis

Benzoic Acid (*0.27 mmol; 3.0 equiv*), DMAP (*0.27 mmol; 3.0 equiv*), sulfonamide (*0.09 mmol; 1.0 equiv*) and Silia*Bond* DCC or DCT (*0.41 mmol; 4.5 equiv*) were added to a 10 mL of (*4:1*) DCM / DMF mixture in a dry reaction vessel and stirred 24 h at room temperature Excess amine and DMAP were scavenged with Silia*Bond* Tosic Acid (*1.08 mmol; 12.0 equiv*).

Total volume of the mixture was adjusted to keep a ratio silica / solvent of 1 g / 5 mL. Scavengers were allowed to react for 2 h at room temperature prior to filtration, washing with DCM and evaporation of the solvent.



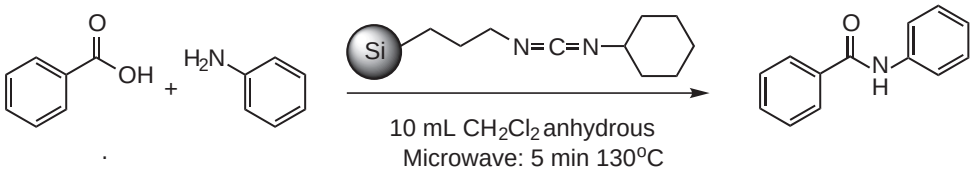
Acylsulfonamide Synthesis Results (*in %*)

Acid	Sulfonamide	Yield[a] (*Purity*)[b]	
		Si-DCC	Si-DCT
Benzoic Acid	Benzenesulfonamide	96 (*71*)	98 (*90*)
	Methanesulfonamide	79 (*53*)	71 (*82*)

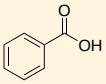
[a] Yield determined from isolated product
[b] Purity determined by GC-MS

Coupling of Benzoic Acid with Aniline (*Si-DCC*)

In the amide coupling between benzoic acid and aniline catalyzed by Si-DCC using 2 different synthetic approaches, better yields were acheived in both strategies, albeit with a little less purity in crude compound before further purification.



Amide Coupling Yield[a] (*Purity*)[b] in %

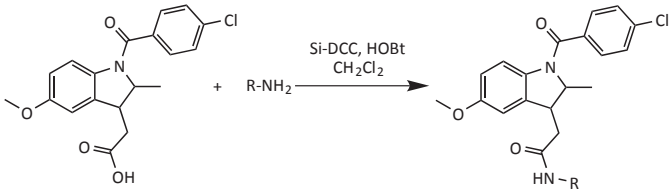
		*Si*-Carbodiimide (*Si-DCC*)	Microwave	Bulk (*room temperature, 24 h*)
1.5 equiv	1.0 equiv	2.0 equiv	73 (*88*)	53 (*99*)
2.0 equiv		3.0 equiv	95 (*95*)	81 (*98*)

[a] Determined from GC-FID,
[b] Refers to the isolated product

Synthesis of Amide Derivatives of Indomethacin (*Si-DCC*)

A report has shown that indomethacin primary and secondary amide analogues are potent compounds for human COX-2 specific inhibition. Silia*Bond* Carbodiimide can be used as a key reagent in its synthesis.

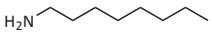
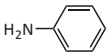
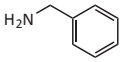
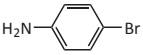
J. Med. Chem., **2000**, *43*, 2860-2870



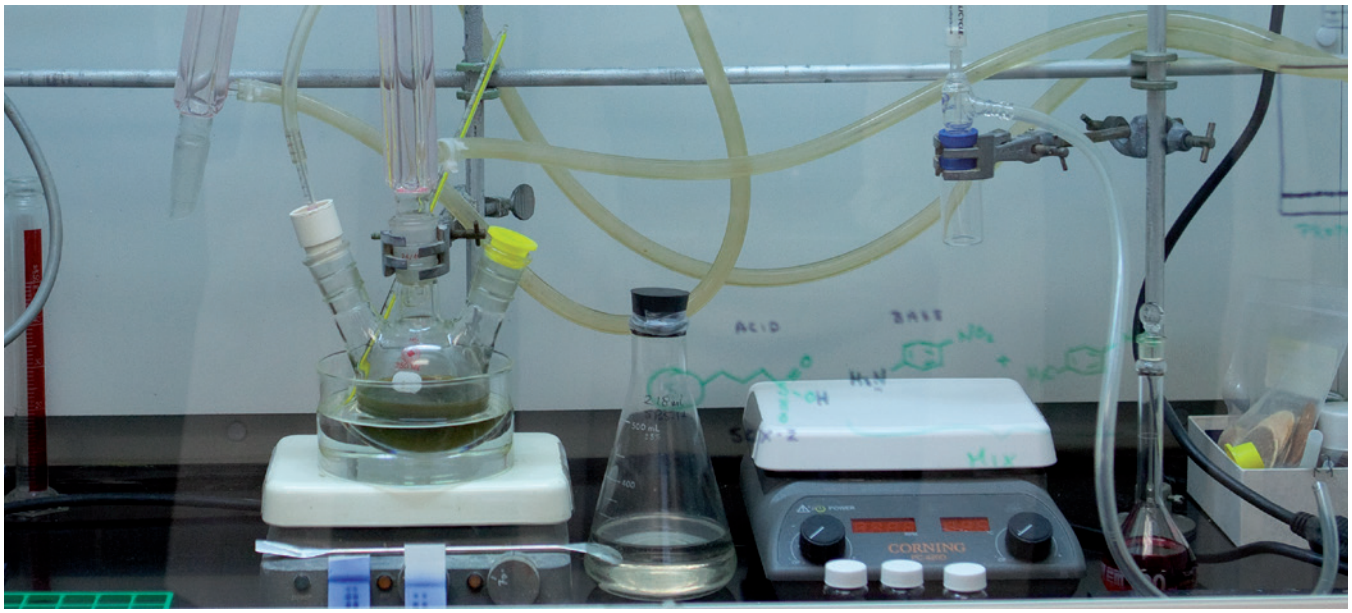
General Procedure

The indomethacin (*0.56 mmol; 1.0 equiv*) was placed in an oven-dried reaction vial in anhydrous CH_2Cl_2 (*5 mL*) under nitrogen. HOBt (*0.95 mmol; 1.7 equiv*) and the Silia*Bond* Carbodiimide (*1.12 mmol; 2.0 equiv*) were added, and the mixture was stirred briefly (*5 min*). Then, the amine (*0.56 mmol; 1.0 equiv*) was added to the vial and the reaction was stirred at room temperature for 16 h. Then, the crude product was directly purified on a short plug of silica gel (*hexane / EtOAc 1 / 1*) to yield pure amide.

Amide Derivatives Results

Amine	Yield[a] (*in %*)	Amine	Yield[a] (*in %*)
	90		94
	82		78

[a] Yield determined from isolated product



Reductive Amination

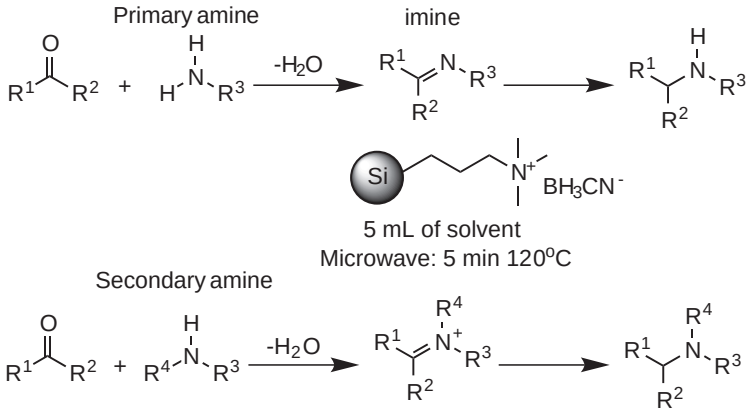
Reductive Aminations (*Si-CBH*)

General Procedure (*conventional - batch*)

In polypropylene tubes with a frit on the bottom, was weighed Silia*Bond* Cyanoborohydride (*1.14 mmol; 1.2 equiv*). The tubes were placed on SiliCycle's MiniBlock and 5 mL of THF was added in each tube. The appropriate ketones / aldehydes (*0.95 mmol; 1.0 equiv*) were added, followed by the amines (*1.90 mmol; 2.0 equiv*). The tubes were sealed with a teflon septum, and the stirring plate was turned on at 650 RPM for 16 hours. The agitation was then stopped, the septum removed and the solutions filtered through the frits, in identified collection tubes. Each solution was analyzed by GC-MS.

General Procedure (*microwave*)

In polypropylene tubes was weighed the carbonyl (*0.95 mmol; 1.0 equiv*), the amine (*1.90 mmol; 2.0 equiv*) and Silia*Bond* Cyanoborohydride (*1.14 mmol; 1.2 equiv*). THF was added (*5 mL*), and the reaction mixture was maintained at 120°C for 5 min in a microwave. The septum was then removed and the solutions filtered through frits, in identified collection tubes. Each solution was analyzed by GC-MS.



Reductive Amination (%) Results				
Amine (*2.0 equiv*)	Carbonyl (*1.0 equiv*)	Microwave (*120°C, 1.2 equiv Si-CBH*)[a] 5 min	Bulk (*r.t., 2.5 equiv Si-CBH*)[a] 1 h	24 h
Piperidine	Benzaldehyde	> 99	80	> 99
N,N-Benzylmethylamine		> 99	97	> 99
3-Phenyl-1-propylamine	Cyclohexanone	> 99	88	87

[a] Conversion determined by GC-MS

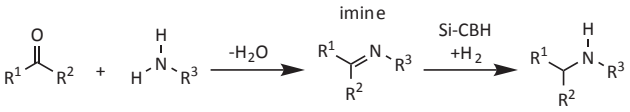
All reactions conducted with the microwave gave conversions that were equivalent to significantly higher, than when using traditional bulk conditions.

Reductive Aminations (*Si-CBH*)

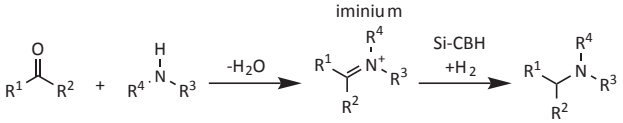
General Procedure

To Silia*Bond* Cyanoborohydride (*1.00 mmol; 2.0 equiv*) was added the solvent (*5 mL*), the aldehyde or ketone (*0.50 mmol; 1.0 equiv*) and the amine (*0.60 mmol; 1.2 equiv*). The reaction mixture was stirred at room temperature for 16 h. Each solution was then analyzed by GC-MS. Upon completion, Silia*Bond* CBH was simply filtered and washed off. Solvent was then evaporated to yield pure amide.

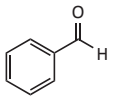
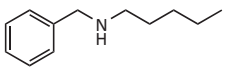
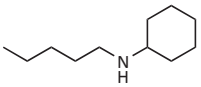
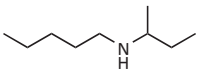
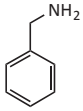
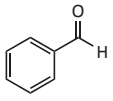
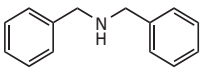
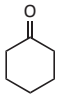
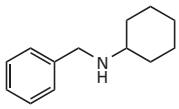
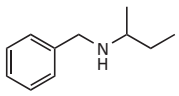
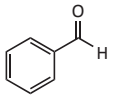
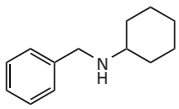
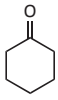
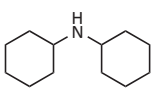
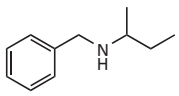
Reduction of Primary Amines



Reduction of Secondary Amines

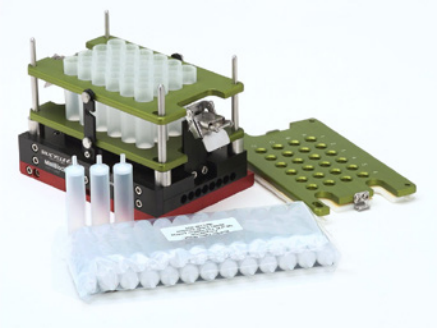


Reduction of Primary Amine Results

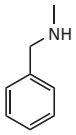
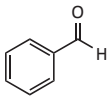
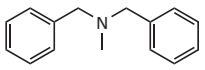
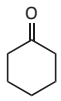
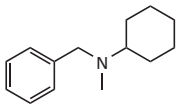
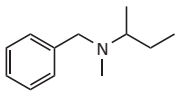
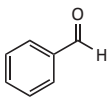
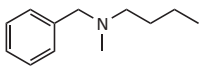
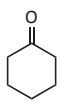
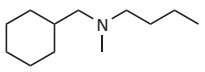
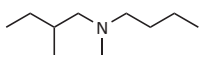
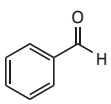
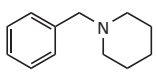
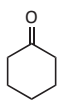
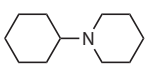
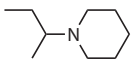
1° Amine	Carbonyl	Conditions (*room temperature, 16 h*) Product	in Acetonitrile		in Ethanol		in Methylene Chloride	
			Conversion Product (%)[a]	Imine (%)[b]	Conversion Product (%)[a]	Imine (%)[b]	Conversion Product (%)[a]	Imine (%)[b]
			27	25	64	11	69	12
			97	0	95	5	92	8
			92	0	84	7	78	9
			61	20	71	23	73	24
			92	2	83	17	81	13
			88	3	90	7	91	6
			66	21	97	0	100	0
			91	5	93	5	93	6
			90	0	92	6	86	7

[a] Conversion determined by GC-MS, [b]Unreacted imine was determined by GC-MS

All reactions were carried out using SiliCycle MiniBlock, all at once within a timeframe of 16 h.



Reduction of Secondary Amine Results

2° Amine	Carbonyl	Conditions (*room temperature 16 h*) Product	in Acetonitrile		in Ethanol		in Methylene Chloride	
			Conversion Product (%)[a]	SM[c] (%)[b]	Conversion Product (%)[a]	SM[c] (%)[b]	Conversion Product (%)[a]	SM[c] (%)[b]
			90	2	71	0	91	0
			92	5	79	17	93	3
			79	8	79	21	93	2
			94	6	67	0	79	0
			77	23	77	20	87	3
			70	25	61	26	44	2
			97	3	80	0	83	1
			85	15	69	19	88	6
			81	9	70	21	55	2

[a] Conversion determined by GC-MS, [b] Unreacted iminum was determined by GC-MS, [c] Starting Material

Reductive Amination

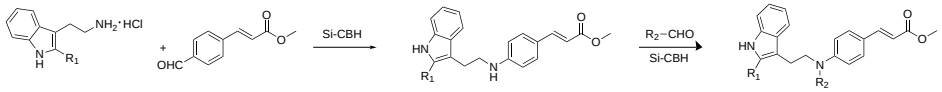
Synthesis of Histone Deacethylase Inhibitors (*Si-CBH*)

Journal of Medicinal Chemistry, **2011**, *54*, 4752-4772

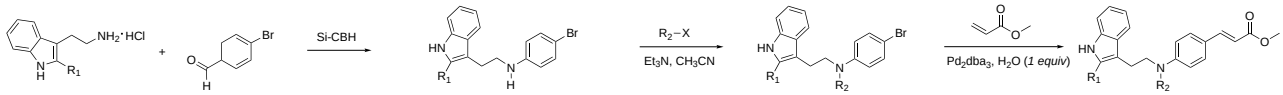
Histone deacethylase (*HDAC*) inhibitors have proven to show interesting potential in the treatment of various forms of cancer. Silia*Bond* Cyanoborohydride was used in the general synthesis of hydroxymate-based HDAC inhibitors:

- An acrylate was reacted with a bromo-benzaldehyde via reductive amination to yield an indole-carboxylic acid ethyl ester, using Silia*Bond* Cyanoborohydride (*route 2*).
- A tryptamine or tryptamine analogue was reacted with a formylcinnamate again via reductive amination to generate substituted amino cinnamates. Subsequent alkylation of the secondary amines in the corresponding tertiary amine was done via reductive amination using Silia*Bond* Cyanoborohydride (*route 1*) or via reaction with previously synthetized arylhalide (*route 2*).

ROUTE 1



ROUTE 2



General Procedure

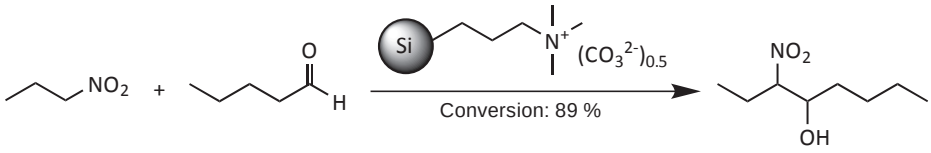
2-Fluoro-ethylamine hydrochloride (*1.10 mmol; 1.0 equiv*) was added to a solution of (*E*)-3-(4-formyl-phenyl)-acrylic acid methyl ester (*1.10 mmol; 1.0 equiv*) and acetic acid in DMF (*1:4*). The mixture was stirred at room temperature for 10 min. Silia*Bond* Cyanoborohydride (*1.10 mmol; 1.0 equiv*) was added and stirred at room temperature for another 10 min. The mixture was then heated via microwave irradiation at 150°C for 5 min, filtered and concentrated under vacuum. Typical total yields were between 7 and 46 %.

Nitro-Aldol (*or Henry*) Reaction

3-Nitrooctan-4-ol Synthesis via a Nitro-Aldol (*Si-CO_3*)

General Procedure

1-nitropropane (*1.12 mmol; 1.0 equiv*) was added to a solution containing THF (*5 mL*) and valeraldehyde (*1.12 mmol; 1 equiv*). Silia*Bond* Carbonate (*0.11 mmol; 0.1 equiv*) was added and the mixture was stirred at room temperature for 6 h. The reaction mixture was then filtered and washed with THF and the crude product was evaporated. Finally, pure product was obtained after flash chromatography purification using a mix of hexane / ethylacetate (*80/20*).



Nitro-Aldol (*or Henry*) Reaction Results (*in %*)

Entry	Solvent	Reaction Conditions	Conversion[a] (*Purity*)[b]
1	THF	0.1 equiv Si-CO_3 room temperature, 6 h	92 (*83*)[b]
2	CH_2Cl_2		76
3	Ethanol		90
4	Propanol		95
5	None		92
6	THF	0.1 equiv Si-CO_3 microwave 100 W, 100°C, 10 min	89

[a] Conversion determined by GC-MS, [b] Purity determined from the isolated product

Knoevenagel Condensations (*Si-PPZ*)

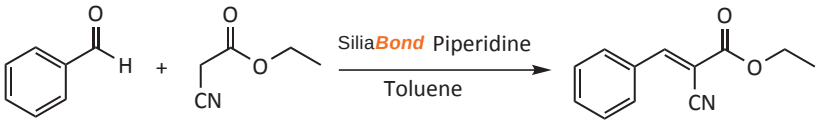
The Knoevenagel condensation between carbonyl compounds and methylene malonic esters produce several important products, including nitriles used in anionic polymerization and unsaturated ester intermediates employed in the synthesis of several therapeutic drugs. Alkali metal hydroxides, pyridine and piperidine are the traditional catalysts used in these reactions.

General Procedure (*conventional - batch*)

A mixture of benzaldehyde (*2.00 mmol; 1.0 equiv*), ethylcyanoacetate (*3.00 mmol; 1.5 equiv*) nd 10 mol % of Silia*Bond* Piperidine (*0.20 mmol; 0.1 equiv*) in 15 mL of toluene were stirred at 110°C for 20 h. The reaction mixture was filtered and the solvent was evaporated. The crude product obtained was analyzed by GC/MS.

General Procedure (*flow*)

The reactor was charged with Silia*Bond* Piperidine (*1.50 mmol; 0.1 equiv*) and heated at 110°C using toluene as solvent. A mixture of benzaldehyde (*15.00 mmol; 1 equiv*), ethylcyanoacetate (*22.50 mmol; 1.5 mmol*) in 110 mL of toluene was stirred at r.t. for 5 min. The mixture was then introduced in a glass bottle directly connected to the pump. Upon completion of the reaction, the reaction mixture was filtered and the crude product analyzed by GC/MS to determine the conversion ratio.



Knoevenagel Condensation Reaction Results

Entry	Catalyst (*mol %*)	Time (*h*)	Flow Conditions			Conversion (*%*) (*Yield %*)
			Flow (*µL/min*)	Vol. Reactor (*mL*)	Residence Time (*min*)	
1	10	20	Conventional (*Batch*)			98 (*80*)
2	55	2	50	0.7	14	99 (*82*)
3	10	20	100	2.4	24	100 (*90*)

At equivalent time reaction and catalyst mol %, flow conditions generate both significantly higher conversion and yields than traditional batch conditions. Higher reaction times were shown to yield better results than higher catalyst mol %. Yet, even in this last option, better conversion and yield were obtained.

Jasminaldehyde Synthesis via Aldol Reaction (*Si-PPZ*)

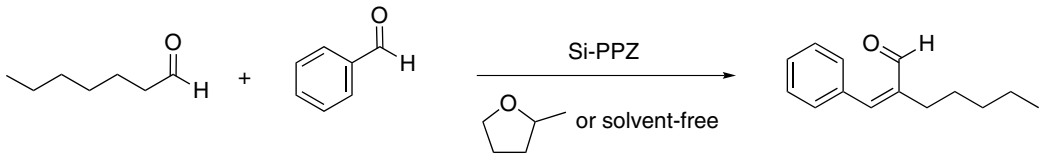
Catalysis Science & Technology, **2013**, *3*, 2732-2736

Jasminaldehyde is usally produced via an aldol C-C bond forming reaction, using typically a base such as NaOH.

One of the major drawback associated with the reaction between heptanal and benzaldehyde is the production of organic waste and by-product formation.

de María *et al.* have reported the synthesis of jasminaldehyde using Silia*Bond* Piperazine as an organocatalyst, both in bio-based solvents (*e.g.: 2-MeTHF*) and solvent-free conditions. Solvent-free conditions provided even better conversion.

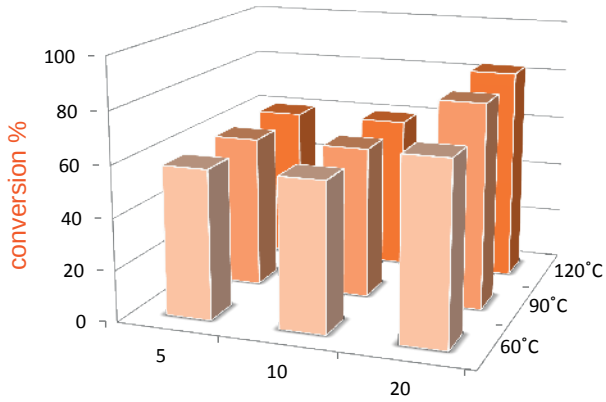
More over, selectivity remained unaltered during catalyst recycling.



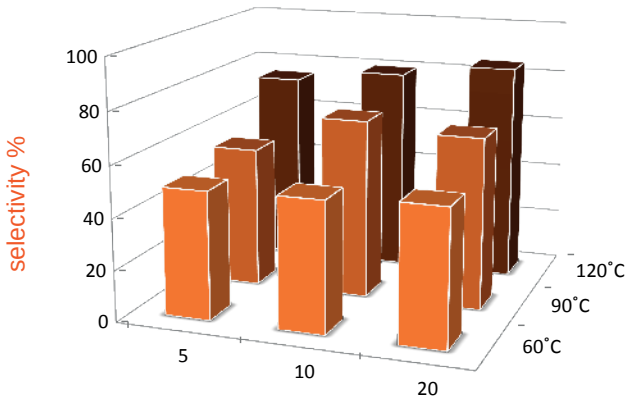
General Procedure

Heptanal (*0.42 mmol; 1.0 equiv*) was mixed with different amounts of benzaldehyde (*2.1 - 8.4 mmol; 5.0 - 20.0 equiv*). Reactions took place mostly in solvent-free conditions at 60 - 120°C, with variable catalyst loadings of Silia*Bond* Piperazine (*0.08 - 0.33 mmol; 0.2 - 0.8 equiv*). Reaction times were set from 8 to 18 h. For the work-up, the suspended catalyst was filtered and the reaction mixture analyzed by ^{1}H NMR to assess conversion and selectivity.

CONVERSION



SELECTIVITY



Conclusion

Silia*Bond* Piperazine as organocatalyst for the synthesis of jasminaldehyde was reported for the first time. Under optimized conditions high conversions and selectivities (*> 90 %*) were achieved in solvent-free conditions (*neat substrates*).

The immobilized catalyst proved to be reusable, and high selectivities remained within all catalytic cycles.

Acylation & Esterification Reactions

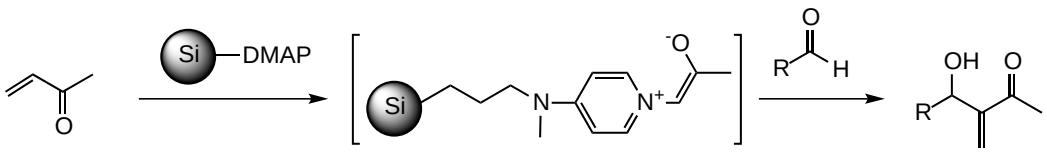
Baylis-Hillman Reaction (*Si-DMAP*): Comparative Study with PS-DMAP

Coupling of activated alkenes, generally alpha, 1-beta-unsaturated, with aldehydes is named the Baylis-Hillman reaction. This reaction is well known for the formation of carbon-carbon bonds under mild conditions and its compatibility with several functional groups. Furthermore, an organic base can be used to catalyze this reaction with similar success compared to using transition metals.

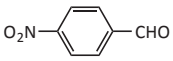
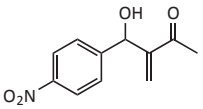
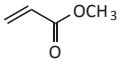
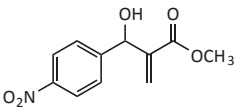
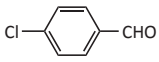
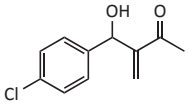
Results using silica-supported DMAP (*Si-DMAP*) were compared to those using polystyrene-bound DMAP (*PS-DMAP*).

General Procedure

Aldehyde (*1.00 mmol; 1.0 equiv*) was placed in a flask and THF, Silia*Bond* DMAP (*or PS-DMAP*) (*0.10 mmol; 0.1 equiv*), water and enone (*2.00 mmol; 1.0 equiv*) were added. The crude reaction mixture was stirred at room temperature for 6 to 96 h and conversion followed by GC-MS. The reaction mixture was then simply filtered on Büchner and washed with solvent to yield pure product after evaporation.



Baylis-Hillman Reaction Results

Aldehyde	Enone	Conditions	Product	Yield[a] (*in %*) Si-DMAP	Yield[a] (*in %*) PS-DMAP
		THF / H_2O (*3/1*) room temperature, 6 h 10 % *Si*- or *PS*-DMAP		**81**	37
		DMF / H_2O (*3/1*) room temperature, 90 min 10 % *Si*- or *PS*-DMAP		**75**	14
		CH_2Cl_2 room temperature, 24 h 10 % *Si*- or *PS*-DMAP		**74**	37
		No solvent room temperature, 96 h 24 % *Si*- or *PS*-DMAP		**71**	58
		THF / H_2O (3/1) room temperature, 96 h 19 % *Si*- or *PS*-DMAP		**63**	15

[a] Yield determined from the isolated product

It was thus demonstrated that Silia*Bond* DMAP was clearly superior than the corresponding polystyrene-bound DMAP.

Acylation & Esterification Reactions

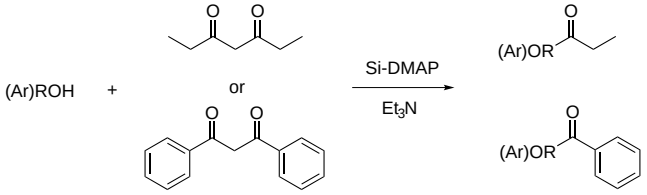
Acylation reactions can generate esters, using activated carboxylic acids (*acids chlorides*) and alcohols, even hindered tertiary alcohols.

General Procedure (*conventional - batch*)

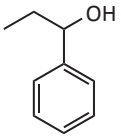
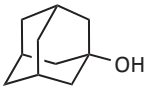
The alcohol (*4.00 mmol; 1.0 equiv*), acetic anhydride (*6.00 mmol; 1.5 equiv*) and triethylamine (*6.00 mmol; 1.5 equiv*) were stirred in 10 mL of CH_2Cl_2 at room temperature for 5 minutes. Two fractions of 5 mL solution were introduced into the reactor charged with Silia*Bond* DMAP (*0.36 mmol; 0.09 equiv*). Upon completion of the reaction, the mixture was analyzed by GC-MS to determine the conversion.

General Procedure (*flow*)

A mixture of the alcohol (*6.00 mmol; 1.0 equiv*), acetic anhydride (*9.00 mmol; 1.5 equiv*), triethylamine (*9.00 mmol; 1.5 equiv*) and Silia*Bond* DMAP (*0.30 mmol; 0.05 equiv*) in 15 ml of CH_2Cl_2 was stirred at room temperature for 90 minutes. The reaction was quenched by the addition of 0.5 mL of methanol, diluted with 25 mL Et_2O and washed twice with saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the solution was filtered and evaporated to give a colorless oil in a quantitative yield.



Acylation Reaction Results

Substrate	Reagent	Catalyst (*equiv*)	Time (*h*)	Flow Conditions: Flow (*µL/min*)	Flow Conditions: Vol. Reactor (*mL*)	Conversion (%) (*Yield %*)
2-Octanol	Ac_2O	5	2	Conventional (*Batch*)		99 (*98*)
		9	2 1	100 200	0.7	100 (*99*) 98 (*99*)
	Bz_2O	10	24	Conventional (*Batch*)		91
		9	14 6	25 12.5	0.7	97 (*95*) 95 (*93*)
	Ac_2O	5	1.5	Conventional (*Batch*)		99 (*98*)
		9	3 2 1	50 100 200	0.7	99 (*97*) 99 (*97*) 99 (*97*)
	Bz_2O	5	24	Conventional (*Batch*)		88
		9	6 3 2	25 50 100	2.38	99 (*97*) 99 (*94*) 98 (*88*)
	Ac_2O	6	24	Conventional (*Batch*)		67
		9	17 7 4	10 25 50	2.38	95 (*61*) 97 (*40*) 97 (*27*)

For all acylation reactions, better or equivalent conversions could be obtained using flow chemistry *vs* conventional batch chemistry and with shorter reaction times. In some cases, the isolated yields using flow chemistry were even higher than simple conversion using batch conditions.

Fischer-Speier Esterifications (*Si-SCX*)

The Fischer-Speier reaction is a classic organic process where a carboxylic acid is reacted with an alcohol in the presence of an acidic catalyst to form an ester. All carboxylic acids and only primary and secondary aliphatic alcohols can be used in this reaction. The most commonly used catalysts for this reaction are highly toxic such as H_2SO_4, tosic acid and scandium triflate. Also, a large excess of one of the reagents is used to push the equilibrium towards the product.

General Procedure

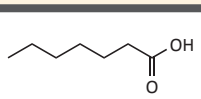
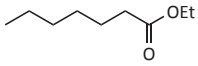
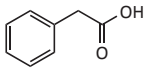
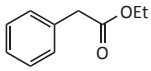
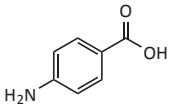
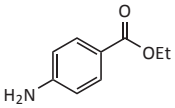
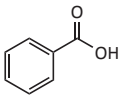
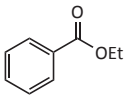
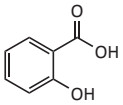
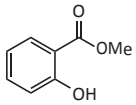
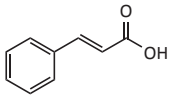
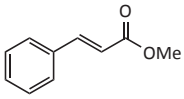
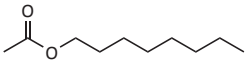
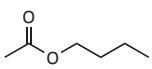
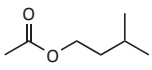
Method A

The carboxylic acid (*1.50 mmol; 1.0 equiv*) was added to a mixture of alcohol (*10 mL*) and Silia*Bond* Tosic Acid (*0.15 mmol; 0.1 equiv*). The reaction mixture was maintained at reflux for 16 h, then simply filtered on Büchner, washed with solvent to yield crude product after evaporation.

Method B

In a 250 mL round-bottom flask equipped with a Dean-Stark apparatus, the carboxylic acid (*16.3 mmol; 1.0 equiv*) was added to an alcohol (*65.20 mmol; 4 equiv*) and Silia*Bond* Tosic Acid (*1.63 mmol; 0.1 equiv*). The mixture was then heated to reflux for 20 to 24 h, then simply filtered on Büchner, washed with solvent to yield crude product after evaporation.

Fischer-Speier Esterification Results

Alcohol	Carboxylic Acid	Method	Ester	Conversion[a] (*in %*)
Ethanol		A		100
				100
		A (*72 h*)		40[c]
		B		94[c]
Methanol				89[c]
		A		98
1-Octanol				100
1-Butanol				100 (*99*)[b]
3-Methylbutanol				100

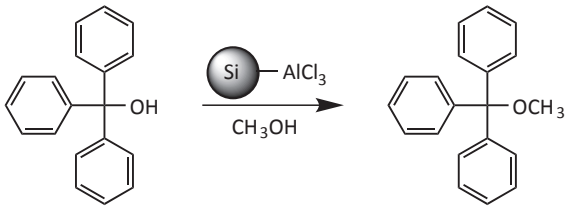
[a] Conversion determined by GC-MS, [b] *Si*-SCX recycled 3 times, [c] Conversion determined from the isolated product

S_{N_1} Acylation of Triphenylcarbinol (*Si-$AlCl_3$*): *Comparative Study with PS-$AlCl_x$*

General Procedure

Triphenylcarbinol (*2.00 mmol; 1.0 equiv*) was added to a solution of SiliaBond Aluminum Chloride (*2.30 mmol; 1.15 equiv*) in anhydrous methanol. The mixture was heated to 60°C until completion of the reaction (*followed by TLC, 90 min*). The catalyst was then removed by filtration and the product analyzed by ^{1}H NMR.

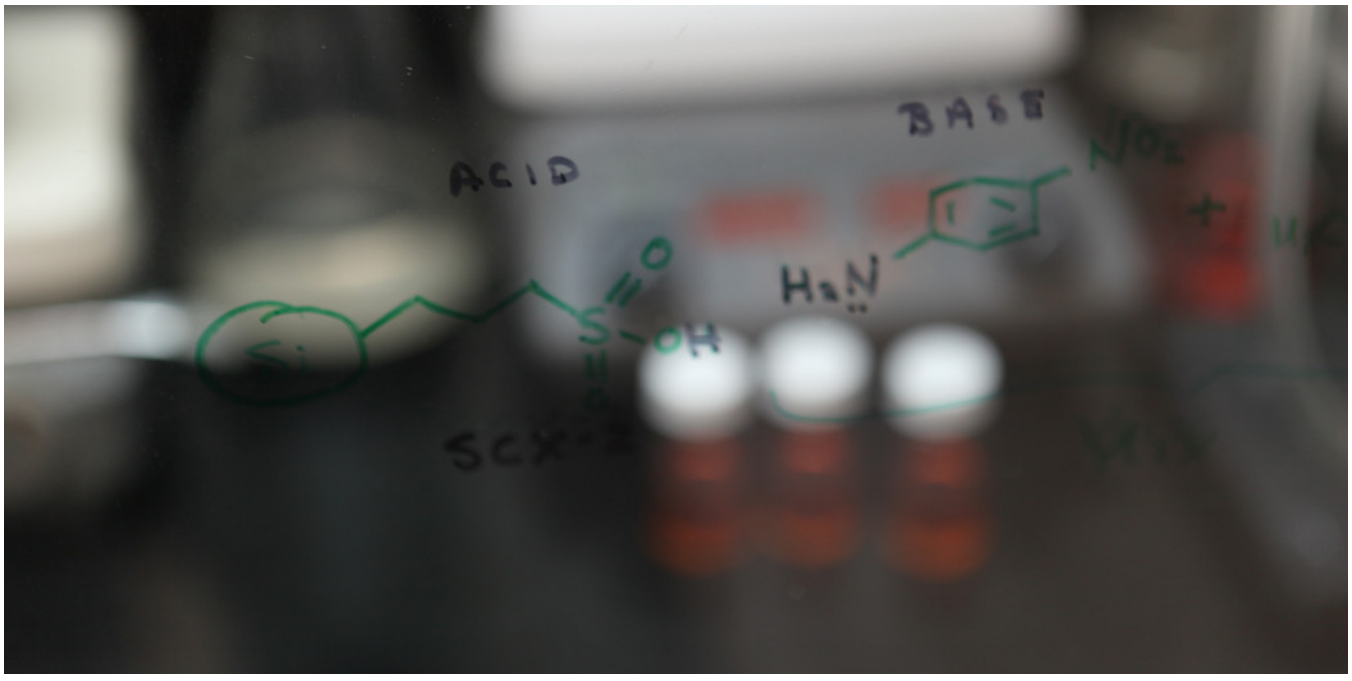
Using the same protocol, a comparison between SiliCycle's silica-supported SiliaBond Aluminum Chloride (Si-$AlCl_3$) and the competition's Polymer-bound Aluminum Chloride (PS-$ALCl_x$) was done.



Friedel-Crafts Acylation Results

Alcohol	Catalyst	Conversion[a] (*in %*)
Triphenylmethanol $(Ph)_3OH$	*Si*-$AlCl_3$	**95**
	PS-$AlCl_x$	81
Tert-Butyl Alcohol $(CH_3)_3OH$	*Si*-$AlCl_3$	**60**
	PS-$AlCl_x$	0
Benzyl Alcohol $PhCh_2OH$	*Si*-$AlCl_3$	**40**
	PS-$AlCl_x$	0

[a] Conversion determined by ^{1}H NMR



Synthesis of pyran-based macrocycles (*Si-DCC*)

Proceedings of the National Academy of Sciences of the United States of America., **2011**, *108*, 6751-6756

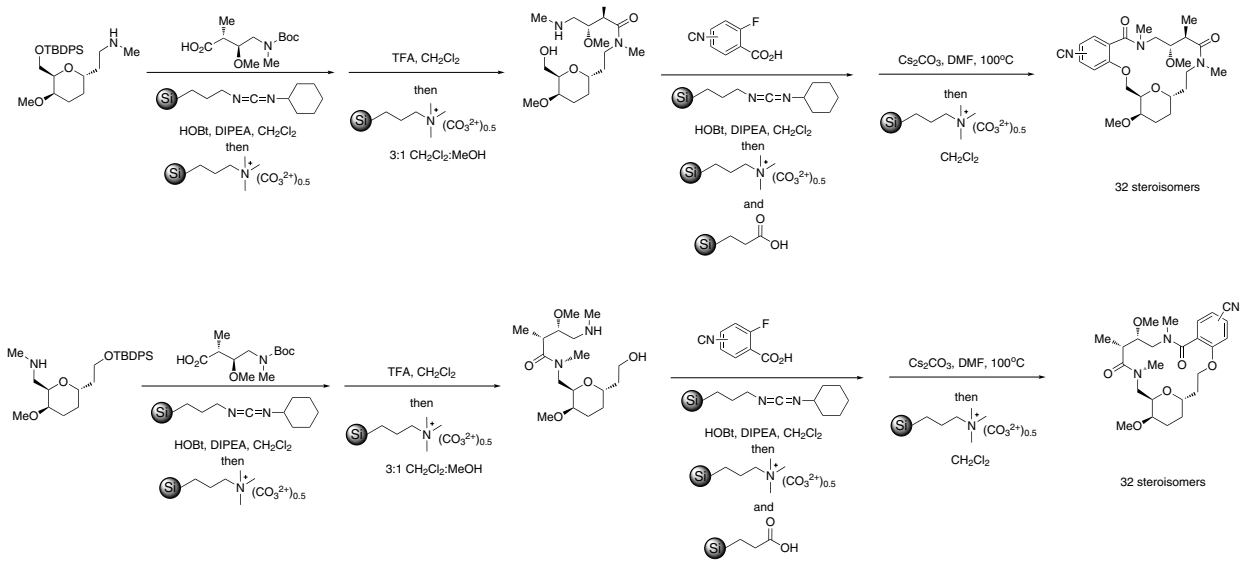
Stereogenic centers in molecules of complex structure are well-known to be key compounds going from discovery to clinical chemistry. In this context, a library of highly structural complex macrocycles with a pyran structure was synthetized with Silia*Bond* Carbodiimide (*Si-DCC*) as a key reagent.

352 macrocycles with ring cycles of 14, 15 and 16 members were produced in parallel synthesis using SiliCycle MiniBlock and MiniBlock XT. Silia*Bond* Carbonate (*Si-CO$_3$*) and Silia*Bond* Carboxylic Acid (*Si-WCX*) were used in the purification process.

The synthetic pathway comprises 2 main steps:

- The acylation of pyran amines with excess of a Boc-protected aminobutanoic acid in the presence of Silia*Bond* Carbodiimide together with homogeneous HOBt. The amino alcohol was deprotected, then unreacted acid was removed using Silia*Bond* Carbonate.
- A selective acylation of the deprotected amino alcohol - again deprotected with Silia*Bond* Carbonate - with either the *ortho*- or *para*- regioisomer of a cyano-fluorobenzoic acid, to yield an S_NAr amide precursor. Again, benzoic acid was scavenged using Silia*Bond* Carbonate and further clean up with Silia*Bond* Carboxylic Acid was done to remove any excess amine or potential o-acylation by-products.

For more information on purification steps using Silia*Bond* Organic Scavengers, please see p. 141



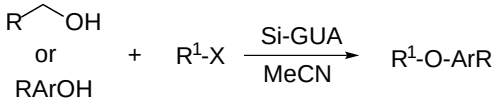
General Procedure

Acylation: The crude amino alcohols, cyano-fluorobenzoic acid 4-o or 4-p (*0.14 mmol; 1.0 equiv*), Silia*Bond* DCC (*0.19 mmol; 1.4 equiv*) and DIEA (*0.09 mmol; 0.7 equiv*) were combined in 2 % dimethylformamide (*DMF / DCM 3.0 mL*), and stirred at room temperature overnight. In cases where acylation was slow, additional Silia*Bond* DCC (*0.19 mmol; 1.4 equiv*) and a solution of HOBt (*0.04 mmol; 0.3 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 Silia*Bond* CO_3 (*0.18 mmol; 1.4 equiv*) and Silia*Bond* WCX (*0.18 mmol; 1.4 equiv*) for 30 min and then filtered and evaporated for 4 h.

Alkylation & Etherification Reactions

General Williamson Ether Synthesis (*Si-GUA*)

The Williamson etherification is a standard reaction to synthesize asymmetric ethers from alcoholates, prepared from primary and secondary alcohols or phenols with base, in the presence of primary alkyl halides. Because of the high reactivity of alcoholates, they need to be produced during the reaction by strong bases.



General Procedure

The alcohol (*0.15 mmol; 1.0 equiv*) was added to acetonitrile (*4 mL*) and Silia*Bond* Guanidine (*0.05 mmol; 0.3 equiv*). The solution was stirred for 1 h at room temperature. Next, the alkyl halide (*0.12 mmol; 0.8 equiv*) was transferred to the reaction mixture, which was again stirred for 16 h at 60°C. Finally, the mixture was filtered, washed with 2 mL of acetonitrile and crude product was obtained after evaporation of solvents. Conversion was measured by GC-MS.

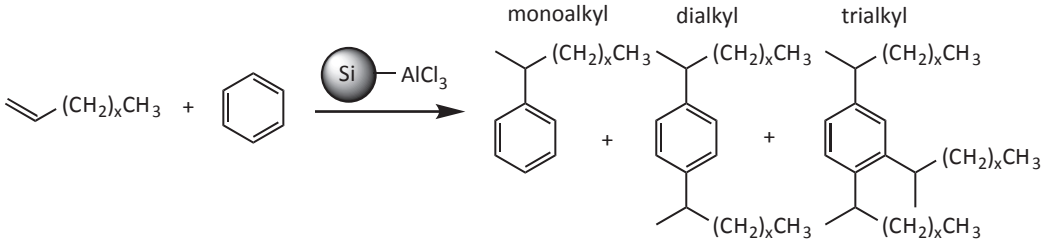
When using 1-iodopentane, yields ranging from 79 to 89 % were acheived with various alcohols, and from 75 to 94 % when using benzylbromide.

Friedel-Crafts Alkylation of Benzene (*Si-AlCl$_3$*): Comparative Study with Homogeneous AlCl$_3$

For decades, sulfonated linear alkylbenzenes (*LABs*) have been among the most prolific detergents. LAB synthesis is carried out by Friedel-Crafts alkylation of benzene by linear olefins using hydrogen fluoride or aluminum chloride as catalyst. However, the use of these catalysts presents severe problems. For example, aluminum chloride is difficult to separate after reaction and produces a large amount of waste effluent.

General Procedure

Silia*Bond* AlCl$_3$ (0.04 mmol; *0.03 equiv*) was stirred into anhydrous benzene (*typical reaction solvent volume: 5 mL/g of Silia*Bond* AlCl$_3$*). The alkene (*1.18 mmol; 1.0 equiv*) was slowly added (*a small exothermic reaction could be observed*). After the addition was completed, the catalyst was removed by filtration and washed 3 times with anhydrous benzene.



Friedel-Crafts Alkylation Results

Alkene	Catalyst	Alkene Conversion[a] (*in %*)	Selectivity Towards Alkylbenzene (*in %*)		
			Mono	Di	Tri
1-Hexene	AlCl$_3$	100	59	31	10
	Si-AlCl$_3$	100	**71**	28	1
1-Decene	AlCl$_3$	100	69	23	9
	Si-AlCl$_3$	100	**80**	20	0

[a] Conversion determined by GC-MS

As seen in the above table, althought all reactions could be run to completion, selectivity toward the mono-alkylbenzene was much improved when using Si-AlCl$_3$, compared to homogeneous AlCl$_3$.

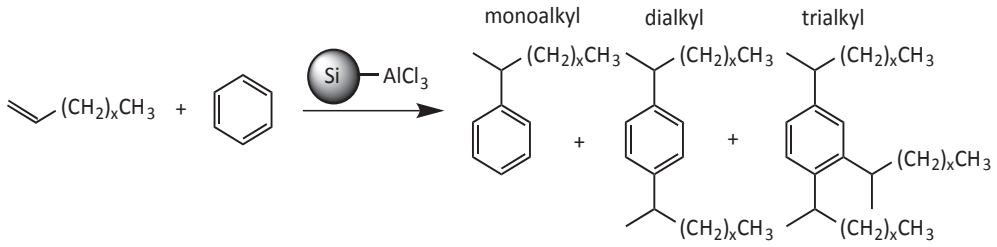
Comparative Study of Alkylation in Flow Chemistry

General Procedure (*conventional - batch*)

1-decene (*1.00 mmol; 1.0 equiv*) was added slowly (*over 30 min*) to a mixture of anhydrous benzene (*20 mmol; 20 equiv*) and Silia*Bond* $AlCl_3$ (*0.20; 0.2 equiv*). After the addition, the catalyst was removed by filtration and the crude product was analyzed by GC-MS.

General Procedure (*flow*)

A mixture of 1-decene (*1.00 mmol; 1.0 equiv*) and anhydrous benzene (*20 mmol; 20 equiv*) was pumped in a reactor charged Silia*Bond* $AlCl_3$ (*0.2 mmol; 0.2 equiv*). After completion of the reaction the mixture was analyzed by GC-MS.



Friedel-Crafts Alkylation Results

Ratio 1-Decene vs Benzene	Catalyst (*equiv*)	Time (*min*)	Flow Conditions			Conversion & Selectivity (%)			
			Flow (*µL/min*)	Vol. Reactor (*mL*)	Res. Time (*min*)	Conv.	Mono	Di	Tri
1:20	0.2	30	Conventional (*Batch*)			100	85	15	0
		20	250	0.76	3	100	89	11	0

Albeit both methodologies gave complete conversion, better selectivity could be reach using the microwave.

Deprotection Reactions

Deprotection of Methoxymethyl Groups (*Si-SCX*)

MOM groups are used as a protecting group for alcohols. The group can be removed using an acid. In this application Silia*Bond* Tosic Acid (*SCX*) has been used to deprotect alcohols previously protected by chloromethyl methyl ether.

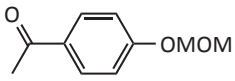
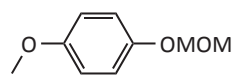
General Procedure (*conventional - batch*)

A mixture of 1-(4-(MOM)phenyl)ethanone (*2.50 mmol; 1.0 equiv)* and Silia*Bond* Tosic Acid (*0.13 mmol; 0.05 equiv)* in 10 mL of toluene / H_2O (*10:0.5*) was stirred at 65°C for 4 h. The reaction mixture was filtered and the solvent was evaporated. The crude product obtained was analyzed by GC-MS.

General Procedure (*flow*)

The reactor was filled with the desired amount of Silia*Bond* Tosic Acid and stirred at r.t. or heated at 65°C using toluene as solvent. A solution of 12.5 mmol of 1-(4-(MOM)phenyl)ethanone in 50 mL of toluene was introduced in a glass bottle connected directly to a pump. A second glass bottle, connected to another pump, was filled with solvent. The flow for the two pumps was different: 100 µL/min for the first pump and 20 µL/min for the second pump. Upon completion of the reaction, the mixture was evaporated and the crude product was analyzed by GC-MS.

Deprotection of Methoxymethyl (*MOM*) Group using Silia*Bond* SCX Results

Substrate	Catalyst (*equiv*)	Time (*h*)	Solvent	Flow Conditions: Flow (*µL/min*)	Flow Conditions: Vol. Reactor (*mL*)	Conversion (*%*) (*Yield %*)
	0.5	2	Toluene / MeOH (*0.25M*)	Conventional (*Batch*)		100 (*90*)
	0.05	4				93 (*83*)
	0.44	2	Toluene / MeOH (*0.25M*)	100	2.4	100 (*100*)
	0.1	9		120		100 (*99*)
	0.5	3	CH_2Cl_2 (*0.1 M*)[a]	50		98 (*91*)
	0.5	2		100		97 (*90*)
	0.35	2	Toluene / MeOH (*0.25M*)	100	2.4	99 (*88*)

[a] at room temperature

At equivalent conditions, better yields could be obtained using flow chemistry. Even when using a fifth of the catalyst mol %, better yields were achieved, albeit needing higher reaction times.

Ordering Information for Batch Reactor Mode (*Bulk*)

All Reagents are available in the following sizes: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc. Up to multi-ton scale!

All Particle Size and Pore Size are respectively 40 - 63 µm and 60 Å. Other matrices are available upon request.

SiliaBond Reagents

Reagent Name	Reagent Product Number
SiliaBond $AlCl_3$	R74530B
SiliaBond Amine	R52030B
SiliaBond Carbodiimide	R70530B
SiliaBond Carbonate	R66030B
SiliaBond Cyanoborohydride	R66730B
SiliaBond Dichlorotriazine	R52230B
SiliaBond Dimethylamine	R45030B
SiliaBond Diphenylphosphine	R39030B
SiliaBond DMAP	R75630B
SiliaBond EDC	R70630B
SiliaBond Guanidine	R68230B
SiliaBond HOBt	R70730B
SiliaBond Maleimide	R71030B
SiliaBond Morpholine	R68030B
SiliaBond Piperazine	R60030B
SiliaBond Piperidine	R71530B
SiliaBond Tosic Acid	R60530B
SiliaBond Tosyl Chloride	R44030B

SiliaBond Oxidants

Oxidant Name	Oxidant Product Number
SiliaBond $KMnO_4$	R23030B
SiliaBond PCC	R24030B
SiliaBond PDC	R24530B

SiliaBond Acids & Bases

Acid / Base Name	Acid / Base Product Number
SiliaBond Carboxylic Acid	R70030B
SiliaBond Propylsulfonic Acid	R71230B
SiliaBond Tosic Acid	R60530B
SiliaBond Amine	R52030B
SiliaBond Carbonate	R66030B
SiliaBond Dimethylamine	R45030B
SiliaBond Guanidine	R68230B
SiliaBond Morpholine	R68030B
SiliaBond Piperazine	R60030B
SiliaBond Piperidine	R71530B

SiliaBond Linkers

Linker Name	Linker Product Number
SiliaBond Allyl	R53530B
SiliaBond Bromophenyl	R55030B
SiliaBond Glycidoxy	R36030B
SiliaBond Phenylmethylchloride	R56530B
SiliaBond Propyl Bromide	R55530B
SiliaBond Propyl Chloride	R59030B

Ordering Information: Available Kits

For screening purposes, especially if you are new to this technology, we have convenient kits for testing various funtionalities and various experimental conditions, to select the ones that best fit your synthetic application.

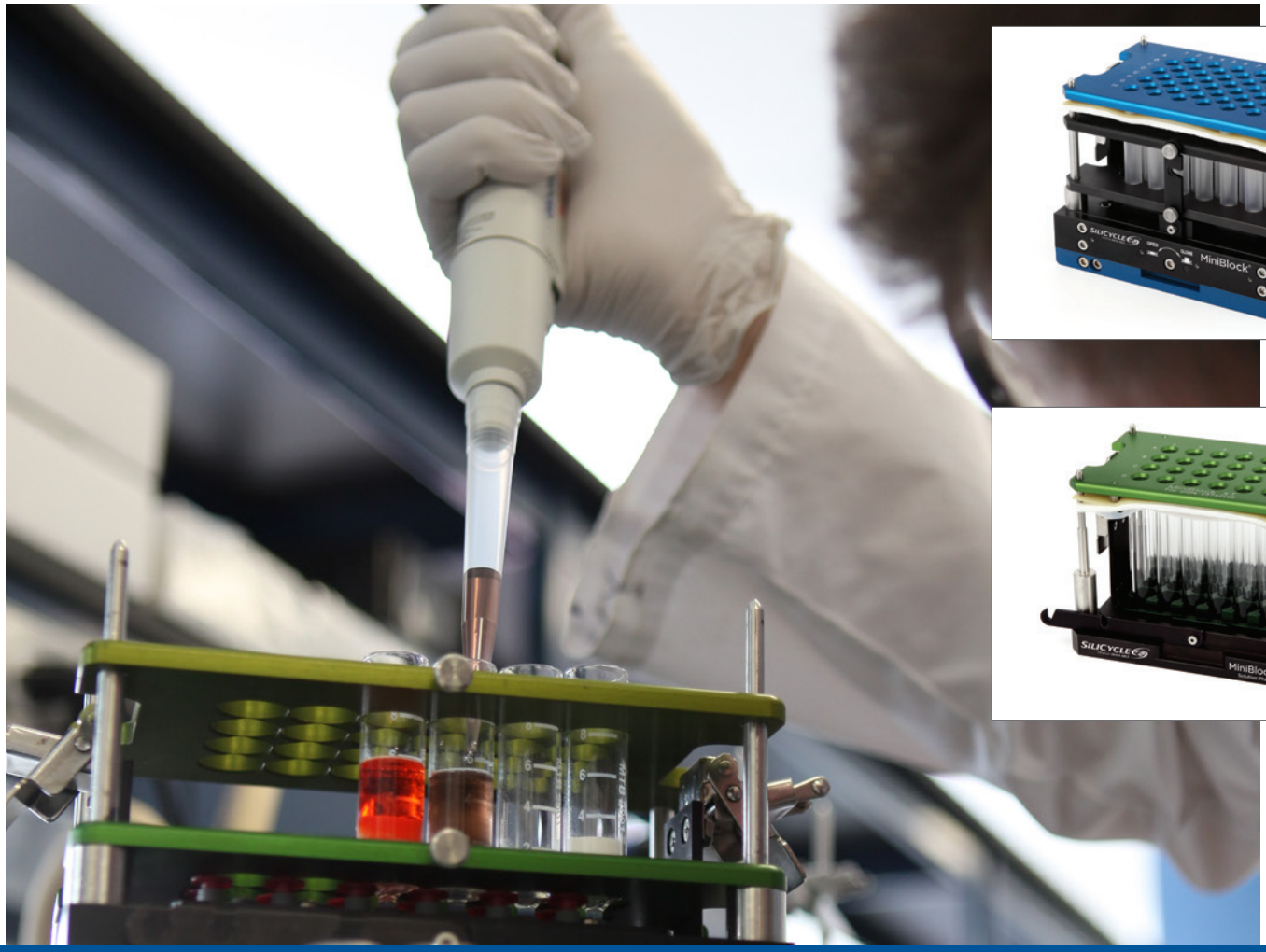
All these kits are procurable in 5 g, 10 g, 25 g, 50 g and 100 g formats
(*custom formats are also available, contact us for more details*).

How to Order

Simply note the **Product Number** which starts with "**K**", add a dash mark and your choice of format, e.g.: **K30330B-10G** to obtain **10G** of each one of the scavenger listed in the kit.

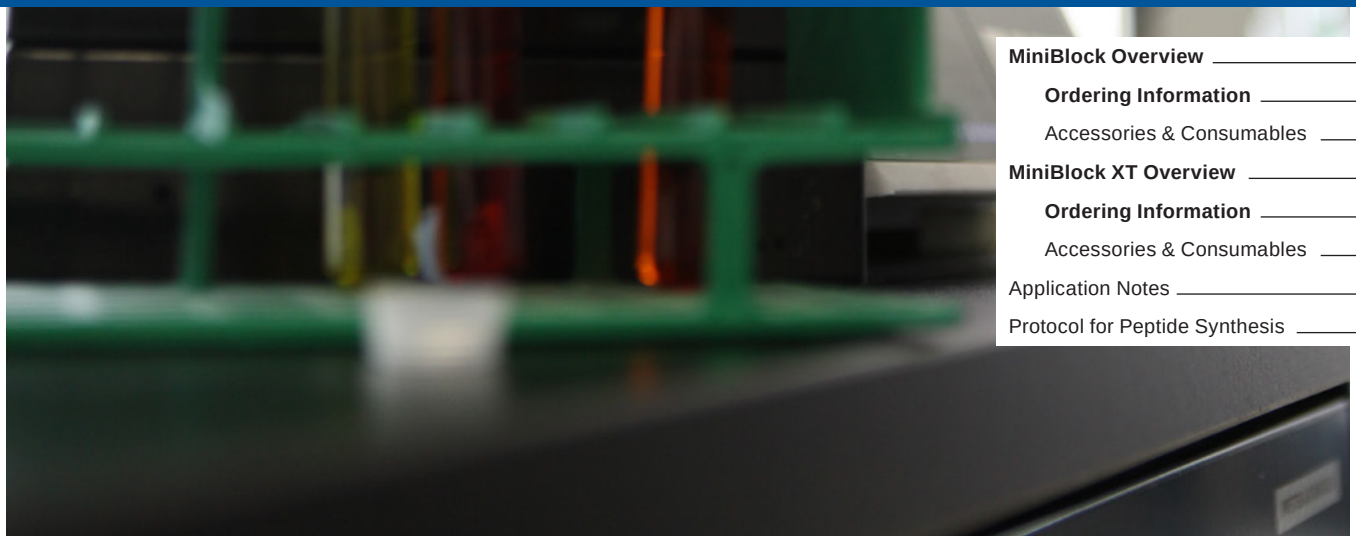
All following kits have all been designed for definite needs:

SiliaBond Kits		
Kit Name	**Kit PN**	**Composition**
SiliaBond Base Kit	K31630B	Amine, Carbonate, Dimethylamine, Diethylamine, Morpholine, Pyridine & Guanidine
SiliaBond Oxidant Kit	K30330B	Potassium Permanganate, TEMPO, Pyridinium Chlorochromate & Pyridinium Dichromate
SiliaBond Reversed-Phase Kit	K32530B	C8 mono, C18 (*17 %*), C18 (*17 %*) Mono, C18 (*23 %*), Cyano & Phenyl
SiliaBond Acid Kit	K31330B	Carboxylic Acid, Propylsulfonic Acid, TAAcOH & Tosic Acid
SiliaBond Reagent Kit	K32230B	Carbodiimide, Cyanoborohydride, Dichlorotriazine, DMAP, EDC & HOBt
SiliaBond Ion Exchanger Kit	K31430B	WAX, WCX, SCX-2, SCX, SAX & TMA Acetate



Parallel Synthesis

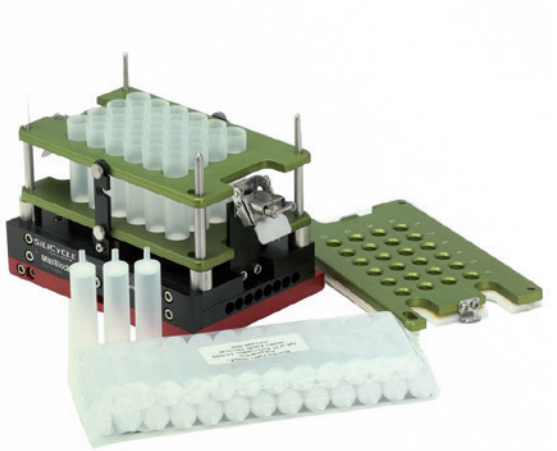
SiliCycle MiniBlock® Family Multifunctional Platforms



SiliCycle MiniBlock Parallel Synthetizer

SiliCycle MiniBlock: Multifunctional Synthesis & Purification Platform

- Designed for route scouting in peptide synthesis, scavenging studies, screening of reaction conditions, synthesis optimization, removal of excess reagents, side-products and catalysts
- Productivity enhancement: eliminates tedious work-up and purification issues
- Compatible with our full range of products, from synthesis through purification



Multifunctional Platform

SiliCycle MiniBlock is an easy to use reaction block designed to run multiple syntheses in parallel and screen for optimal conditions. It is the only compact parallel synthesizer that allows synthesis via solid or solution-phase, as well as filtration and purification to be carried out on the same platform.

Reactors

Patented reactor with built-in valve design. Available in 48, 24, 12 and 6-Positions arrays for reaction vessel volumes respectively of 4 mL, 10 mL, 20 mL and 40 mL.

Shaking and Washing Stations

High performance orbital shaker with integrated basins for wash and rinse capability. Customized and configured to provide vigorous vortex mixing for 1 (*Micro Shaker*) or 2 (*Compact Shaker*) reactors.

Parallel Synthesis & Purification

SiliCycle MiniBlock is ideal for parallel synthesis and post-reaction clean-up using Silia*Prep* MB pre-packed SPE cartridges, with either chromatographic phases or metal and organic scavengers. You just have to stack one reactor onto a second one to filter and purify your extracts.

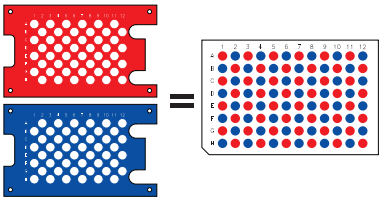
Typical Reactions Performed

The SiliCycle MiniBlock Family is widely used by chemists in all departments and sectors of activity. The flexibility of the design allows you to rapidly configure these compact parallel reactors to fit the needs of your chemistry, whether it requires inert conditions, refluxing or cooling, allowing complete freedom to choose a synthetic route:

- Peptide Synthesis
- Acylation & Alkylation
- Sulfonylation
- Reduction
- Reductive Amination
- Heterocycle Formation
- Enolate Formation
- S_NAr
- Suzuki Coupling
- Saponification
- Metallation
- Grignard Reaction
- Heck Reaction
- Stille Reaction
- Sonogashira

SiliCycle MiniBlock: Multifunctional Synthesis Platform

96 Format
Red and Blue 48-Positions MiniBlock combine to produce 96 compounds.



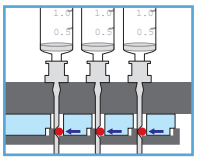
Inert Conditions
Continuous inert gas flow enables air / moisture sensitive reactions. Easily add reagents through the septum layer.

Agitation and Washing
Customized shaker allows precision vortex mixing of reactions. Built-in washing capability allows rapid washing of products while reaction blocks remain on the shaker.

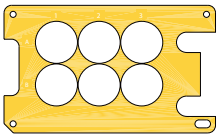
Products Collection
Collect products from SiliCycle MiniBlock cleanly and efficiently with just the turn of a key.

Two Colors Available
Reactor base can be chosen either red or blue.

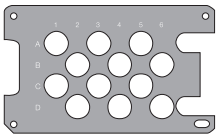
Unique Built-In Valve
Provides rapid bottom filtration - no need to invert or disassemble the reactor. Saves time and prevents cross-contamination.



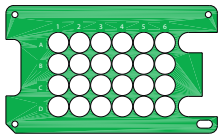
40 mL - 6 vessels



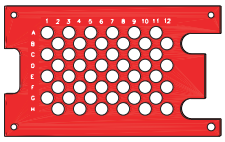
20 mL - 12 vessels



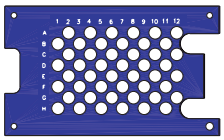
10 mL - 24 vessels



4 mL - 48 vessels



4 mL - 48 vessels



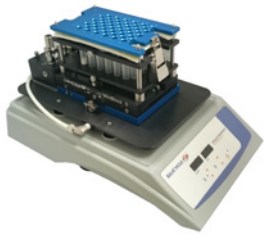
Configure Your SiliCycle MiniBlock to Suit Your Needs
SiliCycle MiniBlock can synthesize compounds in individual vessels from 4 mL to 40 mL, all delivered into racks with microplate footprints. This flexibility provides a smooth, seamless work-flow from synthesis to screening.

« SiliCycle MiniBlock's performance has been outstanding even under the most stringent reaction conditions. Many of these require completely inert and anhydrous conditions at temperatures as low as -70°C. »

Prof. Dieter Enders from Aachen University, Aachen, Germany

SiliCycle MiniBlock Micro Synthesis Sets

These Micro Synthesis Sets contain all components necessary for 6, 12, 24 or 48 parallel reactions. Reactor base can be chosen in either red or blue color.



Package Contents	
Quantity	**Description**
1	SiliCycle MiniBlock Reactor (*choose format, array and volume below*)
1	New Micro Shaking Station (*choose voltage below*)
1	Vacuum Collection Base
1	Tall Tube Extender
1	Micro Consumable Kit (*detailed below*)
1	Tool Kit (*4 keys & pliers*)

SiliCycle MiniBlock Micro Synthesis Sets Ordering Information		
Product Number 115V	**Product Number 230V**	**Description**
17120148	**17240148**	Micro Synthesis Set 48-Positions (*4 mL*): Red
17120248	**17240248**	Micro Synthesis Set 48-Positions (*4 mL*): Blue
17120124	**17240124**	Micro Synthesis Set 24-Positions (*10 mL*): Red
17120224	**17240224**	Micro Synthesis Set 24-Positions (*10 mL*): Blue
17120112	**17240112**	Micro Synthesis Set 12-Positions (*20 mL*): Red
17120212	**17240212**	Micro Synthesis Set 12-Positions (*20 mL*): Blue
17120106	**17240106**	Micro Synthesis Set 6-Positions (*40 mL*): Red
17120206	**17240206**	Micro Synthesis Set 6-Positions (*40 mL*): Blue

Micro Consumable Kit Contents						
Product Number	**MiniBlock Configuration**	**Reaction Tubes Qty / Box**	**Pinch Tubes Inserts Qty / Box**	**Multi-Layer Septa Qty / Box**	**Red Plugs Qty / Box**	**Compression Cords Qty / Box**
17000048	48-Positions	200 Polypropylene, 4 mL*	50	5	50	8
17000024	24-Positions	200 Polypropylene, 10 mL*				
17000012	12-Positions	12 Glass, 20 mL				
17000006	6-Positions	6 Glass, 40 mL				

* Glass reaction tubes can be ordered separately. See page 124.
Note: Collection racks and tubes / vials are sold separately. Contact us for details.

SiliCycle MiniBlock Compact Synthesis Sets

These Compact Synthesis Sets contain all components necessary for 6 to 96 parallel reactions. Reactor bases can be chosen as one of each color (*red and blue*) or both the same color.

Red / Blue combination is required for collection into a 96-Positions format.

Package Contents	
Quantity	**Description**
2	SiliCycle MiniBlock Reactor (*choose format, array and volume below*)
1	New Compact Shaking Station (*choose voltage below*)
1	Vacuum Collection Base
2	Tall Tube Extender
1	Counter Weight for Shaking Station
1	Air Push Assist Device
2	Micro Consumable Kit (*see previous page*)
2	Tool Kit (*4 keys & pliers*)

SiliCycle MiniBlock Compact Synthesis Sets Ordering Information		
Product Number 115V	**Product Number 230V**	**Description**
13820013	**13820095**	Compact Synthesis Set 48-Positions (*4 mL*): 1-Blue 1-Red
13820011	**13820094**	Compact Synthesis Set 48-Positions (*4 mL*): 2-Blue
13820012	**13820093**	Compact Synthesis Set 48-Positions (*4 mL*): 2-Red
13820048	**13200194**	Compact Synthesis Set 24-Positions (*10 mL*): 1-Blue 1-Red
13820049	**13200195**	Compact Synthesis Set 24-Positions (*10 mL*): 2-Blue
13200187	**13820053**	Compact Synthesis Set 24-Positions (10 *mL*): 2-Red
13820086	**13820083**	Compact Synthesis Set 12-Positions (20 *mL*): 1-Blue 1-Red
13820084	**13820082**	Compact Synthesis Set 12-Positions (*20 mL*): 2-Blue
13820085	**13820081**	Compact Synthesis Set 12-Positions (*20 mL*): 2-Red
13820092	**13820089**	Compact Synthesis Set 6-Positions (*40 mL*): 1-Blue 1-Red
13820090	**13820088**	Compact Synthesis Set 6-Positions (*40 mL*): 2-Blue
13820091	**13820087**	Compact Synthesis Set 6-Positions (*40 mL*): 2-Red

Note: Collection racks and tubes / vials are sold separately. Contact us for details.

Accessories & Consumables Available for your SiliCycle MiniBlock

Accessories & Consumables Ordering Information	
Product Number	**Description**
Heat Transfer Blocks*	Heating / cooling block, allowing uniform cooling to -40°C and heating to 120°C (*requires glass reaction tubes*).
13742005	Reflux Layer (*Heat Transfer Block*): 48-Positions (*Black*)
13742059	Reflux Layer (*Heat Transfer Block*): 24-Positions (*Green*)
13742060	Reflux Layer (*Heat Transfer Block*): 12-Positions (*Silver*)
13742061	Reflux Layer (*Heat Transfer Block*): 6-Positions (*Gold*)
Insulation Wrap*	Ensures maximal uniformity between reactors when working under extreme temperatures.
13200240	Insulation Wrap for SiliCycle MiniBlock
Inerting / Purging Manifolds (*48-Positions*)*	Internal septum prevents loss by evaporation and facilitates reagent addition or reaction sampling. Inert atmosphere is maintained at all times. Can be operated in continuous purging or static pressure modes.
13742183	Inerting / Purging Manifold: 48-Positions (*Blue*)
13742182	Inerting / Purging Manifold: 48-Positions (*Red*)
Purging / Evaporating Manifolds*	Provides superior performance for maintaining inert atmosphere while providing a cost effective option for evaporating solvents.
13200950	Purging / Evaporating Manifold: 24-Positions
13200951	Purging / Evaporating Manifold: 12-Positions
13200957	Purging / Evaporating Manifold: 6-Positions
Positive Pressure Manifolds	Provides positive pressure to all reaction tubes to assist draining.
13742018	Positive Pressure Manifold: 48-Positions (*Blue*)
13742019	Positive Pressure Manifold: 48-Positions (*Red*)
13742109	Positive Pressure Manifold: 24-Positions (*Blue*)
13742110	Positive Pressure Manifold: 24-Positions (*Red*)
Transfer Adapters	Allows the transfer of products from one reactor to another.
16004569	Blue Transfer Adapter
16004567	Red Transfer Adapter
Reaction Vessels	Polypropylene or borosilicate glass reaction vessels with frit.
13521028	48-Positions Polypropylene Reaction Vessel, 4 mL, 50 / Box
13521118	24-Positions Polypropylene Reaction Vessel, 10 mL, 25 / Box
13521058	48-Positions Borosilicate Glass Reaction Vessel, 4 mL, 50 / Box
13521062	24-Positions Borosilicate Glass Reaction Vessel, 10 mL, 25 / Box
13521067	12-Positions Borosilicate Glass Reaction Vessel, 20 mL, 12 / Box
13521071	6-Positions Borosilicate Glass Reaction Vessel, 40 mL, 6 / Box

* These accessories are the same for SiliCycle MiniBlock and SiliCycle MiniBlock XT.

SPE Development Kits for SiliCycle MiniBlock

To allow you to purify your samples directly after synthesis on SiliCycle MiniBlock, we offer SPE cartridges of 500 mg / 4 mL and 1 g / 10 mL, in every phase available from SiliCycle.

The table below presents our SPE development kits, to help you choose the right media.

SPE Development Kits Details		
Product Number	**Description**	**Phases**
KSPMB-K2000-045P	Silia*Prep* MB, Silica-Based Chromatography Development Kit, 500 mg (*4 mL*), 8 cartridges of each phase.	Silica, C18, Cyano, Diol, Diatomaceous Earth
KSPMB-K2000-100S	Silia*Prep* MB, Silica-Based Chromatography Development Kit, 1,000 mg (*10 mL*), 4 cartridges of each phase.	
KSPMB-K2001-045P	Silia*Prep* MB, Silica-Based Ion Exchange Development Kit, 500 mg (*4 mL*), 8 cartridges of each phase.	SCX, SCX-2, WCX, SAX, SAX-2, WAX
KSPMB-K2001-100S	Silia*Prep* MB, Silica-Based Ion Exchange Development Kit, 1,000 mg (*10 mL*), 4 cartridges of each phase.	
KSPMB-K2002-045P	Silia*Prep* MB, Silica-Based Metal Scavenging Development Kit, 500 mg (*4 mL*), 6 cartridges of each phase.	Thiol, DMT, Thiourea, Triamine, TAAcOH, TAAcONa, Imidazole, DEAM
KSPMB-K2002-100S	Silia*Prep* MB, Silica-Based Metal Scavenging Development Kit, 1,000 mg (*10 mL*), 3 cartridges of each phase.	
KSPMB-K2003-045G	Silia*Prep* MB, Polymeric Development Kit, 200 mg (*4 mL*), 6 cartridges of each phase.	HLB, DVB, SCX, WCX, SAX, WAX
KSPMB-K2003-100P	Silia*Prep* MB, Polymeric Development Kit, 500 mg (*10 mL*), 3 cartridges of each phase.	

Note: other sorbent weights can be offered on a custom basis, contact us for more information.

« SiliCycle MiniBlocks are so widely accepted by our medicinal chemists that 70 % of all current programs now use high-throughput chemistry. »

Dr. Harold Weller from Bristol-Myers Squibb, Princeton, NJ, USA

SiliCycle MiniBlock XT: For Reflux Capability and Faster Synthesis

SiliCycle MiniBlock XT is an easy to use reaction block designed for synthesis and screening reactions. Applications include synthesis of small organic molecules, optimization of critical process parameters and screening for optimal reaction conditions.

SiliCycle MiniBlock XT Reactors

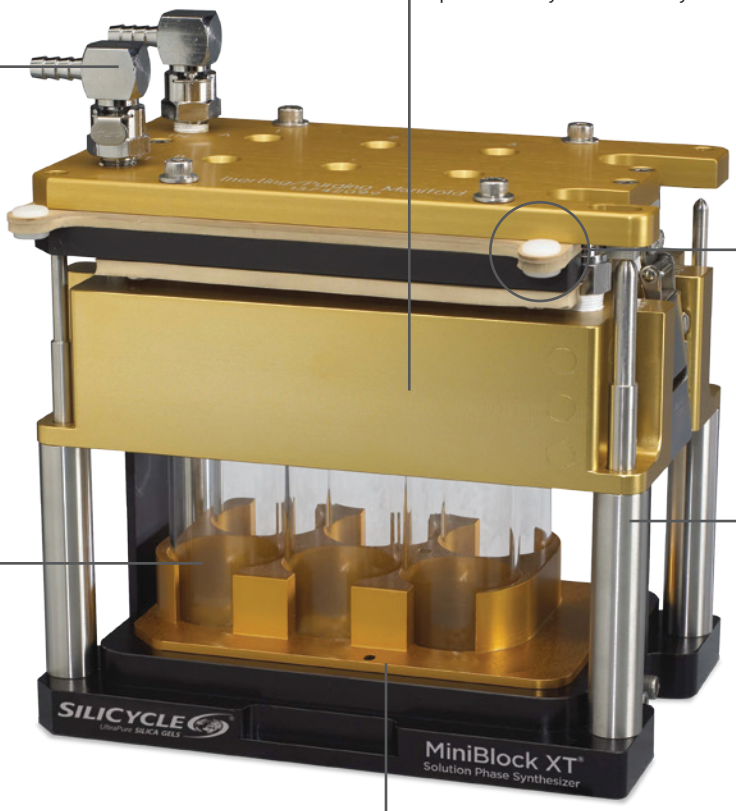
Reactors are available in 48, 24, 12 and 6-Positions arrays for reaction vessel volumes respectively of 11.5 mL, 18 mL, 55 mL and 110 mL.

Shaking and Heating

Shaking and heating are provided by a standard hotplate stirrer, requiring minimal hood space.

Inert Conditions
Continuous inert gas flow enables air / moisture sensitive reactions. Easily add reagents through the septum layer.

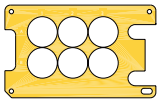
Efficient Reflux
A single reflux jacket cools all vessels. No need for individual condensers. Fittings are provided for quick and easy connection to your cooling liquid.



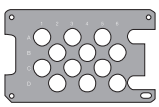
Easy Reaction Setup
All vessels are sealed with a single septum layer and allow easy access to reactions.

Configure Your SiliCycle MiniBlock XT to Suit Your Needs
Easily configure the SiliCycle MiniBlock XT to choose the scale and number of experiments based on your project requirements.

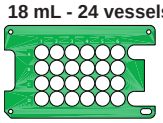
110 mL - 6 vessels



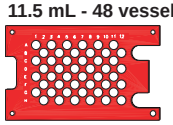
55 mL - 12 vessels

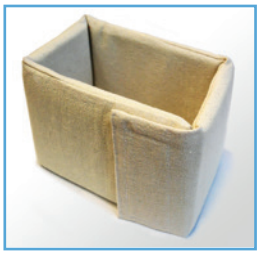


18 mL - 24 vessels



11.5 mL - 48 vessels





Heating and Cooling
Temperature uniformity and reproducibility is within 1°C at 80°C when using the insulation wrap.

Modular Racks
Readily interchangeable reaction vessel racks enable simple conversion between 6, 12, 24 and 48-Positions arrays. The 24 and 48-Positions vessel racks are compatible with parallel centrifugal evaporators.

SiliCycle MiniBlock XT Basic Kit

Affordable reaction block, designed for synthesis and screening with precision heating and refluxing (*temperature range: -70°C[a] to 160°C[b]*). Available in 6, 12, 24 and 48-Positions arrays. All needed consumables are included, except the hotplate stirrer*. Fully upgradable for reflux and inerting capabilities.

[a] Requires Low Temperature Bath
[b] Requires Heat Dispersion Adapter

Package Contents: 1 x XT Basic Reactor Frame
1 x Vessel Rack
1 x Vessel Rack Removal Tool
1 x Top Plate
5 x Multi-Layer Septa for Top Plate (*pre-scored*)

SiliCycle MiniBlock XT Basic Kit Ordering Information

Product Number	Description	Reaction Vessels Qty	Reaction Vessels Volume	Magnetic Stir Bars Qty	Magnetic Stir Bars Shape
13742234	XT Basic Kit, 48-Positions	100	11.5 mL	50	Egg
13742233	XT Basic Kit, 24-Positions		18 mL	30	Cross
13742232	XT Basic Kit, 12-Positions		55 mL	15	
13742231	XT Basic Kit, 6-Positions	24	110 mL	8	

SiliCycle MiniBlock XT Complete Kit

Basic Kit with reflux and inerting capabilities. Available in 6, 12, 24 and 48-Positions arrays. All needed consumables are included, except the hotplate stirrer.*

Package Contents: 1 x XT Basic Reactor Frame
1 x Vessel Rack
1 x Vessel Rack Removal Tool
1 x Top Plate
5 x Multi-Layer Septa for Top Plate (*pre-scored*)
1 x Reflux Layer
1 x Inerting Manifold
5 x Sealing Gaskets
5 x Inner / Piercing Septa

SiliCycle MiniBlock XT Complete Kit Ordering Information

Product Number	Description	Reaction Vessels Qty	Reaction Vessels Volume	Magnetic Stir Bars Qty	Magnetic Stir Bars Shape
13200991	XT Complete Kit, 48-Positions	100	11.5 mL	50	Egg
13742125	XT Complete Kit, 24-Positions		18 mL	30	Cross
13742124	XT Complete Kit, 12-Positions		55 mL	15	
13742123	XT Complete Kit, 6-Positions	24	110 mL	8	

* Hotplate stirrer available separately, product number 13511161 (*115V*) or 13511164 (*230V*)

SiliCycle MiniBlock XT Set, Including Hotplate Stirrer

A complete synthesis system (*Complete Kit with hotplate stirrer*) for 6, 12, 24 or 48 parallel solution-phase reactions. Compact unit enables reflux and controlled temperature synthesis (*temperature range: -70°C[a] to 160°C[b]*). All needed consumables are included.

[a] Requires Low Temperature Bath
[b] Requires Heat Dispersion Adapter

Package Contents	
Quantity	**Description**
1	Hotplate Stirrer, 115V or 230V
1	Heat Dispersion Adapter for Hotplate Stirrer
1	XT Basic Reactor Frame
1	Vessel Rack
1	Vessel Rack Removal Tool
1	Inerting Manifold
1	Reflux Layer
5	Sealing Gaskets
5	Inner / Piercing Septa
1	Top Plate
5	Multi-Layer Septa for Top Plate (*pre-scored*)

SiliCycle MiniBlock XT Set Ordering Information						
Product Number 115V	**Product Number 230V**	**Description**	**Reaction Vessels**		**Magnetic Stir Bars**	
			Qty	**Volume**	**Qty**	**Shape**
16004645	**16004646**	XT Set, 48-Positions	100	11.5 mL	50	Egg
13742118	**13742122**	XT Set, 24-Positions		18 mL	30	Cross
13742108	**13742121**	XT Set, 12-Positions		55 mL	15	
13742107	**13742119**	XT Set, 6-Positions	24	110 mL	8	

Accessories & Consumables Available for your SiliCycle MiniBlock XT

Accessories & Consumables Ordering Information	
Product Number	**Description**
Reflux Layers* Heating / cooling block, allowing uniform cooling to -40°C and heating to 120°C (*requires glass reaction tubes*).	
13742005	Reflux Layer (*Heat Transfer Block*): 48-Positions (*Black*)
13742059	Reflux Layer (*Heat Transfer Block*): 24-Positions (*Green*)
13742060	Reflux Layer (*Heat Transfer Block*): 12-Positions (*Silver*)
13742061	Reflux Layer (*Heat Transfer Block*): 6-Positions (*Gold*)
Heat Dispersion Adapter Focuses heat from the hotplate stirrer to the XT reactor for uniform temperature distribution to all reaction vessels.	
13742106	Heat Dispersion Adapter for SiliCycle MiniBlock XT
Insulation Wrap* Ensures maximal uniformity between reactors when working under extreme temperatures.	
13200240	Insulation Wrap for SiliCycle MiniBlock XT
XT Low Temperature Bath Insulated tray for sub-ambient temperature control of XT reactor. Maintains dry ice / acetone temperature for approximately 4 h without refilling. Can be placed on top of magnetic stirrer for mixing reaction components.	
13742180	XT Low Temperature Bath for SiliCycle MiniBlock XT
Inerting / Purging Manifolds (*48-Positions*)* Internal septum prevents loss by evaporation and facilitates reagent addition or reaction sampling. Inert atmosphere is maintained at all times. Can be operated in continuous purging or static pressure modes.	
13742183	Inerting / Purging Manifold: 48-Positions (*Blue*)
13742182	Inerting / Purging Manifold: 48-Positions (*Red*)
Purging / Evaporating Manifolds* Provides superior performance for maintaining inert atmosphere while providing a cost effective option for evaporating solvents.	
13200950	Purging / Evaporating Manifold: 24-Positions
13200951	Purging / Evaporating Manifold: 12-Positions
13200957	Purging / Evaporating Manifold: 6-Positions
Vessel Racks Readily interchangeable racks in automation friendly microtiter plate formats. Windows allow to see the reactions.	
13260544	Vessel Rack: 48-Positions
13260545	Vessel Rack: 24-Positions
13260546	Vessel Rack: 12-Positions
13260547	Vessel Rack: 6-Positions
13742151	Vessel Rack Removal Tool: press the button and lock into the rack for removal from frame (*make sure the rack cooled down before removal*)
Reusable Reaction Vessels Borosilicate glass reaction vessels.	
16004001	48-Positions Reaction Vessel, 11.5 x 110 mm, 11.5 mL, 100 / Box
13742149	24-Positions Reaction Vessel, 17 x 110 mm, 18 mL, 100 / Box
13742148	12-Positions Reaction Vessel, 24 x 150 mm, 55 mL, 100 / Box
13742146	6-Positions Reaction Vessel, 34 x 150 mm, 110 mL, 24 / Box

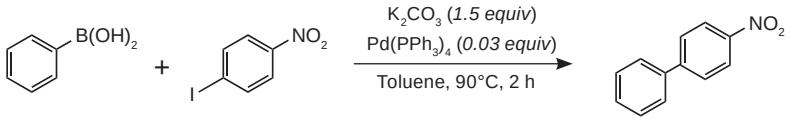
* These accessories are the same for SiliCycle MiniBlock and SiliCycle MiniBlock XT.

Applications Developed Using SiliCycle MiniBlock Family

Metal Scavenging Screening Using Silica-Supported Silia*MetS* Metal Scavengers

SiliCycle MiniBlock is ideal for optimizing post-reaction removal of metal residues. It enables quick screening of metal scavenging conditions using Silia*MetS* Metal Scavengers. The influence of solvent, temperature, reaction time, number of equivalent and nature of the metal scavenger can be quickly and efficiently evaluated in parallel.

Post-Suzuki-Miyaura Coupling Scavenging



4 x 9 Scavengers = 36 Conditions Evaluated at the Same Time, on a Single Station (*in %*)				
Metal Scavengers	**Scavenging Efficiency after 4 hours**			
	1 equiv - 22°C	4 equiv - 22°C	1 equiv - 80°C	4 equiv - 80°C
Silia*MetS* DMT	89	91	69	**99**
Silia*MetS* Diamine	66	78	65	**99**
Silia*Bond* Amine	39	42	56	93
Silia*MetS* Imidazole	53	56	60	97
Silia*MetS* TAAcOH	25	24	33	35
Silia*MetS* TAAcONa	34	34	56	72
Silia*MetS* Thiol	38	42	51	79
Silia*MetS* Thiourea	60	64	63	82
Silia*MetS* Triamine	53	57	56	**99**

Residual Pd content after work-up: 147 ppm.

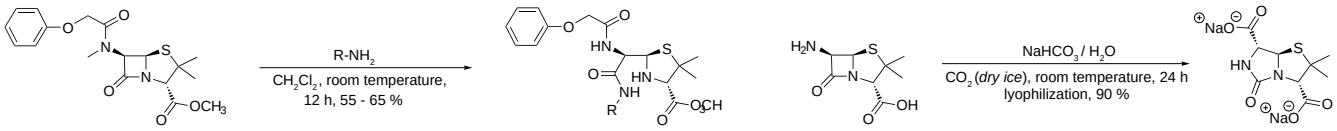
Download the poster here: www.silicycle.com/media/pdf/Poster_MiniBlock_Pittcon_2015_web.pdf

Synthesis of New Penicillin Derivatives as Drug-Like Molecules

Two efficient parallel synthetic methods were developed on **SiliCycle MiniBlock** and **SiliCycle MiniBlock XT** to quickly generate a number of new penicillin derivatives.

The first one is based on the β-lactam ring opening of penicillin V methyl ester to form thiazolidine amides. Various primary amines are used to attack the carbonyl group (*aliphatic, aromatic and heterocyclic*).

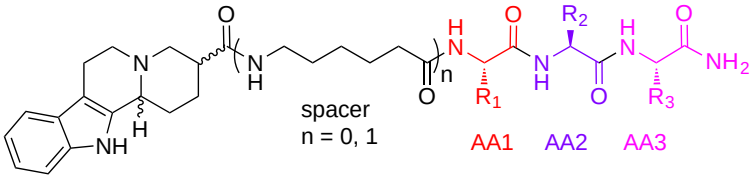
The second one consists in a β-lactam ring rearrangement of 6-aminopenicillanic acid into 8-hydroxypenillic acid, followed firstly by an esterification (*using various aliphatic and aromatic halides*) and secondly by an alkylation at the N-position (*using two aromatic bromides*).



Authors: Liu (*University of Kansas*) & co-workers
Publication: *Chinese Chemical Letters*, **2015**, *26*, 113-117

A Solid-Phase Combinatorial Synthesis of Indoloquinolizidine-Peptides

It was proven that the identification of bioactive compounds can effectively be achieved via solid-phase synthesis of combinatorial libraries. This publication validates the application of indoloquinolizidine-peptides combinatorial library to fine-tune the pharmacological profiles of multiple ligands at D1 and D2 dopamine receptors. Various peptides around the indoloquinolizidine core were explored and a library of 80 new indoloquinolizidine-tripeptides was made. The library synthesis was done with a **SiliCycle MiniBlock** and 80 final indoloquinolizidine-peptides were isolated in very high purities (> *90 %*) after simple solid-phase extraction on a SCX cartridge.



Authors: Royo (*University of Barcelona*) & co-workers
Publication: *European Journal of Medicinal Chemistry*, **2015**, *97*, 173-180

Rapid Analogue Library Synthesis for Drug Discovery

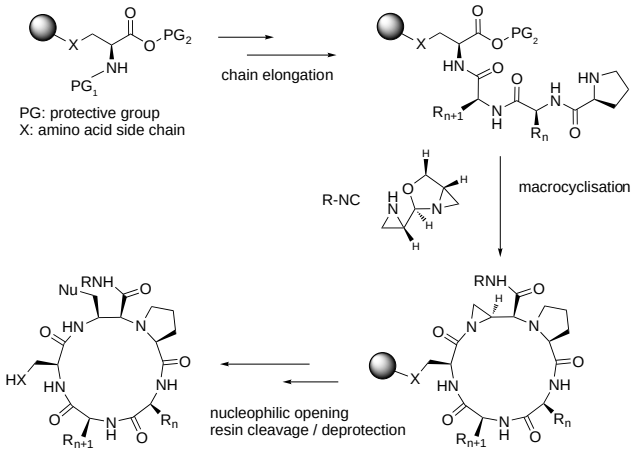
Solution-phase and solid-phase parallel synthesis of combinatorial libraries are valuable tools in drug discovery, for both rapidity of execution and ease of increasing molecular complexity.

In this paper, the Bristol-Myers Squibb Pharmaceutical Research Institute verified the impact on productivity of a centralized library synthesis service, to support lead optimization programs. They managed to reduce the library synthesis cycle time from eight weeks to two, by reducing most waste times. For example, they used **SiliCycle MiniBlock** and **SiliCycle MiniBlock XT** for rapid parallel synthesis. Various reactions were carried out with these equipments: synthesis of amides, ureas, sulfonamides, carbamates, alkylations, displacement reactions and Suzuki reactions.

Authors: Weller (*Bristol-Myers Squibb Pharmaceutical Research Institute*) & co-workers
Publication: *Journal of Combinatorial Chemistry*, **2006**, *8*, 664-669

Solid-Phase Parallel Synthesis of Functionalised Cyclic Peptidomimetics

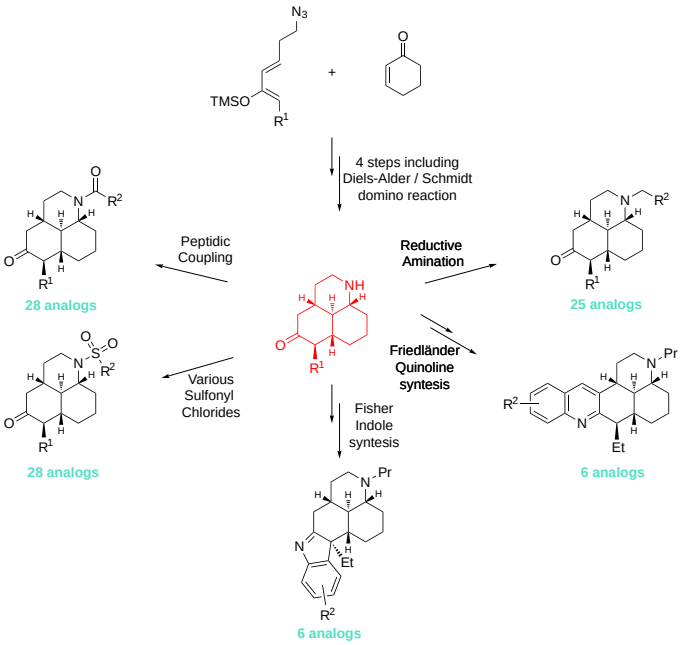
A **SiliCycle MiniBlock XT 24-Positions** was used to generate a library of several hundred macrocyclic peptidomimetics. The synthesis is entirely implemented on solid-phase, to minimize transfers and speed-up the process. This synthesis allows a single chemist to obtain 48 macrocycles in 2 weeks (*before purification and lyophilisation*), with great diversity in terms of ring size (*9 to 18-membered rings*) and amino acids contained in the ring (*nature and stereochemistry*).



Authors: Marsault (*Sherbrooke University*) & co-workers
Publication: *Chem. Eur. J.*, **2015**, *21*, 9249-9255

Diels-Alder Reactions of Azide-Containing Silyloxydienes

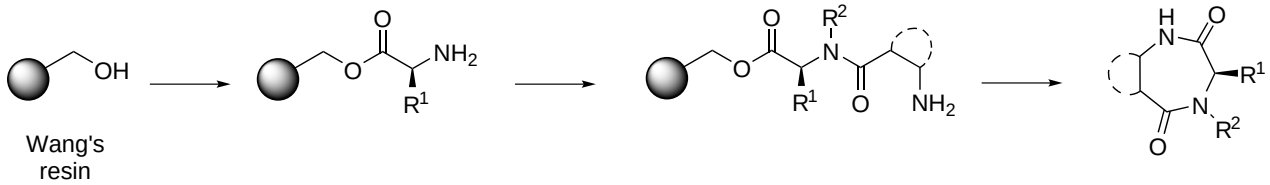
An elegant and divergent synthesis scheme was designed to prepare a series of analogs of potentially bioactive compounds. A 6,6,6-tricyclic amine building block was prepared through a Diels-Alder cycloaddition / Schmidt rearrangement domino sequence. Taking advantage of the **MiniBlock XT** unique capabilities in parallel synthesis, this scaffold was derivatized into 5 classes of analogs, for a total of 95 novel compounds. These structures will be screened against the Sigma-1 and Sigma-2 receptors to determine their biological activities.



Authors: Aubé (*UNC Eshelman School of Pharmacy*) & co-workers
Publication: *Tetrahedron*, **2016**, *72*, 3766-3774

Solid-Phase Synthesis via a Cyclization / Release Strategy

A series of analogues based on a 6,7-cycloalkane-fused 1,4-diazepane-2,5-dione scaffold was swiftly prepared, following a solid-phase synthethic approach using a **SiliCycle MiniBlock parallel reactor**. With Wang's resin as support, α- and alicyclic β-amino acid building blocks where synthesized, incorporating several functionnalities. Submitting these intermediates to a cyclization / release strategy, the target cyclic α,β-dipeptides were obtained in good yields and crude purities. This approach allowed the efficient synthesis of 26 analogues of a model library of homodiketopiperazines.

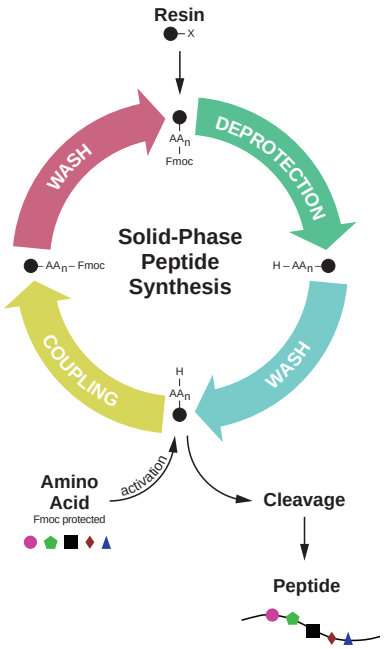


Authors: Van der Eycken (*Ghent University*) & co-workers
Publication: *Tetrahedron*, **2016**, *72*, 148-160

« If parallel synthesis is part of your chemistry plan, then the SiliCycle MiniBlock should be at the top of your list of hardware platform options. Designed for chemists by chemists, MiniBlock offers true parallel processing as opposed to actually being a collection of batch reactions. All chemical operations, including recovery from the reaction vessel, filtration and solid-phase extraction are carried out simultaneously without ever having to handle individual reactions. »

Dr. Conrad Santini from Baylor College of Medicine, Houston, TX, USA

Experimental Protocol for Peptide Synthesis



SiliCycle MiniBlock can be your ally in solid-phase peptide synthesis, saving a lot of precious time during all washing and filtration steps. You will find below the recommended protocol to follow as a starting point. Optimization steps can be undertaken, depending on your peptide sequence.

1. Put your starting resin in the SiliCycle MiniBlock reaction vessels (*in this example, we consider an amino-protected starting resin*).
2. Add 20 % piperidine (*in DMF*) to remove the Fmoc protecting group on the amino side, then shake for 5 min.
3. Filter the crude by opening the bottom valve of your MiniBlock (*do not forget to close it again after*).
4. Repeat steps 2 & 3 to ensure complete Fmoc removal.
5. Wash the resin 3 times with DMF to remove all remaining Fmoc and piperidine traces (*filter through your MiniBlock between each wash*).
6. Weigh the next N-protected amino acid you want to add on the chain, dissolve it in DMF and add it to the reaction vessels.
7. Add base to the reaction vessels to deprotonate the terminal -COOH of your new amino acid (*for example triethylamine*).
8. Add coupling agent, dissolved in DMF, to the reaction vessels (*for example EDC, DCC or DIC*).
9. Shake for 30 minutes to 12 hours, depending on the peptide length and steric properties of the new amino acid. You can repeat this step and even heat up the reactor to ensure the complete coupling.
10. Wash the resin 6 times with DMF to remove all remaining base, coupling agent and excess amino acid.
11. Repeat steps 2 to 10 to add your next amino acid, until your peptide sequence is completed.
12. OPTIONAL: After coupling your last amino acid, cleave the final Fmoc group by adding 20 % piperidine in DMF. If you want an Fmoc-protected peptide at the N-terminal position, skip this step.
13. Wash the resin 6 times with DMF and then 6 times with DCM to remove impurities (*such as Fmoc-cleavage residue*), let dry under nitrogen for 10 minutes.
14. Add cleavage solution to the reaction vessels (*for example TFA*) and shake at room temperature for 2 hours.
15. Collect the cleavage solution into adequate tubes. You can use the vacuum collection base to be sure to collect all the cleavage solution. You can repeat steps 14 & 15 to ensure a complete cleavage.
16. Wash the resin 2 times with the cleavage solution and once with DCM (*combine all cleavage and washing fractions*).
17. Evaporate TFA or precipitate your peptide in ACN.
18. Purify your peptide by Flash Chromatography or Preparative HPLC (*you can use one of our pre-packed SiliaSep C18 flash cartridges for example*).

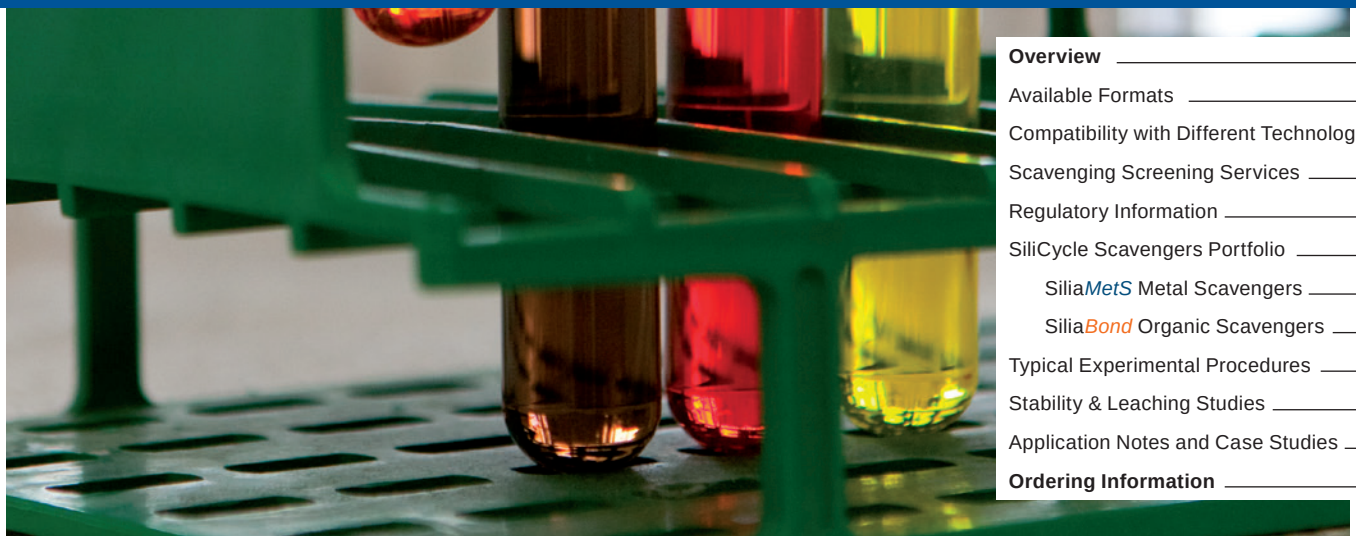
« We have been using the SiliCycle MiniBlock for peptides cleavage, not only it is convenient to set up and fast in delivery, it also allows us to tailor our cleavage protocol for different peptides so higher yields can be achieved. »

Yi Gong from C3-Jian, Marina Del Rey, CA, USA

Specialized Purification

Scavenging Solutions

SiliaMetS® Metal Scavengers
SiliaBond® Organic Scavengers



Metal and Organic Scavengers Overview

Scavenging Technologies: Creativity for Utmost Benefits

- Technology innovated by SiliCycle researchers
- Increased R&D and manufacturing productivity
- Amazingly versatile (*solvents, pH, compatible in batch flow, microwave, etc.*)
- Green and environmentally friendly technology
- Broadest scope of metals & organics to be scavenged

Since ancient times, chemists have been searching for techniques and tools to separate, isolate and purify chemical substances from one another to improve the quality of life. It's been a long road since the alchemists of the Middle-Ages understood that their search for the philosophers' stone would depend, at least in part, on good separation of elements.

SiliCycle grafted technology enables more powerful purification processes to help reach new purity standards. Our solutions are extremely versatile and customizable, hence suitable for a use in a vast array of industries, facing different contamination issues.

Discover what the scavenging technology from SiliCycle has to offer and how it can assist you in these times of environmental changes, tighter quality control and regulatory compliance.

Easier, Cleaner, Faster, Efficient Purification Processes Using Metal & Organic Scavengers

- Almost two decades of know-how in silica-grafting and scavenging technology
- Broadest portfolio of scavengers with associated applications
- Great variety of formats for all purifications scales: from laboratory to plant scale
- Successful technology for a variety of fields, such as pharmaceuticals, organic chemistry labs, agrochemicals, mining, fine chemicals, water and waste treatment
- Great compatibility with a myriad of experimental conditions, solvents, pH and temperatures
- Strong chemical, physical, thermal and mechanical stability

SiliCycle Has Pioneered the Field of Functionalized Silica, So You Can Benefit From Our Scavenging Expertise

Challenging purifications in chemistry can be overcome creatively and elegantly.

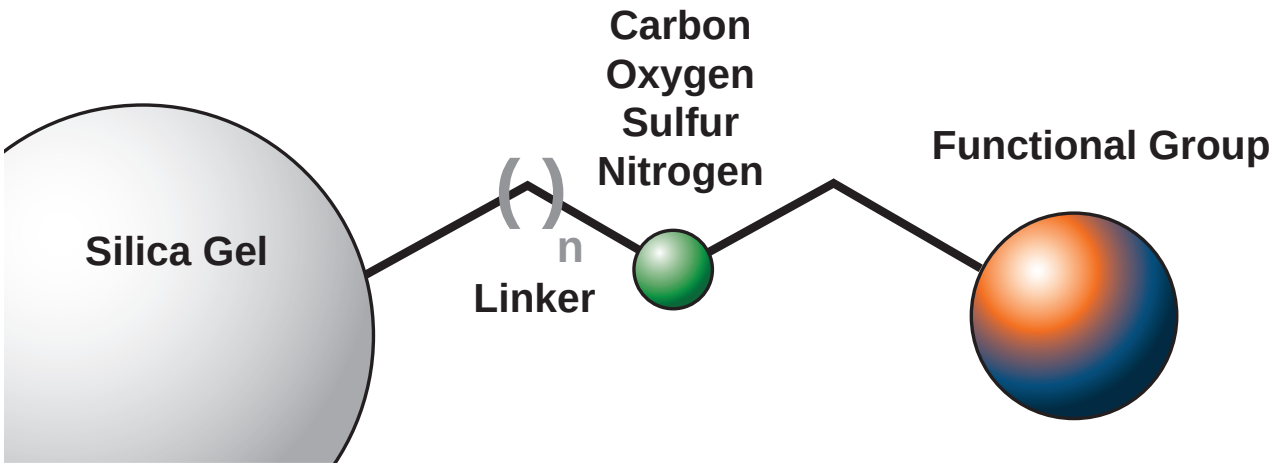
At SiliCycle, silica gels are functionalized with various molecules featuring scavenging properties toward different metals and / or organics.

We name our metal scavengers Silia*MetS* and our organic scavengers Silia*Bond*.

This technology combines the benefits of classical, century-old purification techniques, while integrating new assets that are becoming more and more critical in modern industries. New purification procedures need to be more selective, more efficient, quicker and greener.

It is because of today's strive for greater performance while respecting environmental concerns that silica-based scavengers were developed; they are a powerful tool with an eco-friendly twist:

- Reduced purification steps
- No swelling
- No cross-contamination
- Less solvent needed
- Efficient precious metal recovery



Typical Structure of our Functionalized Silicas with Various Organic Groups

Why Choose Silica-Based vs Polymer-Based Scavengers

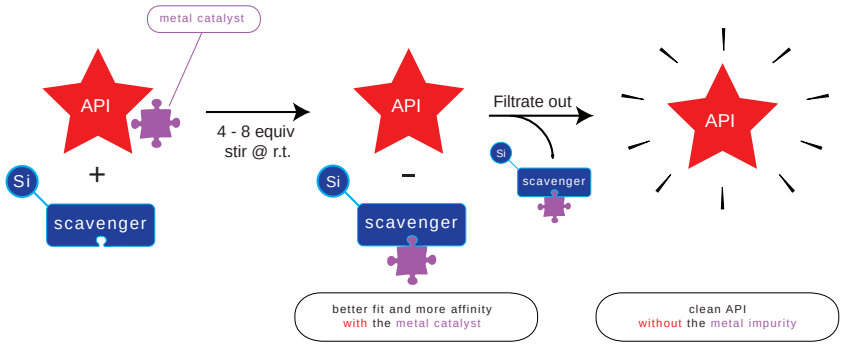
Silica-based scavengers have been proven to be the purification solution of choice over all. Silica matrices show strong advantages over polymeric resins in purification, such as:

- No swelling
- Faster kinetics
- Solvent independence
- Ease of use
- Mechanical stability
- Thermal stability
- Format flexibility
- Controlled & precise loading

New Pharmaceutical Challenges in Purification

SiliCycle Helps You Achieve Your Goals

In recent years, the time pressure associated with quickly bringing drug candidates to market has increased the number of transition metal-catalysed reactions progressing from lead optimisation to early scale-up. The removal of post-reaction metal residues has become a major issue in the pharmaceutical industry. Purification of APIs (*Active Pharmaceutical Ingredients*), or Product of Interest from residual metal catalyst by traditional methods (*chromatography, activated carbon, distillation, etc.*) often leads to problems such as high costs, time loss, low efficiency and reduced API yields. To overcome these limitations, SiliCycle's Scavenger Solutions have significantly changed how chemists can purify APIs. Here is the scavenging mechanism:

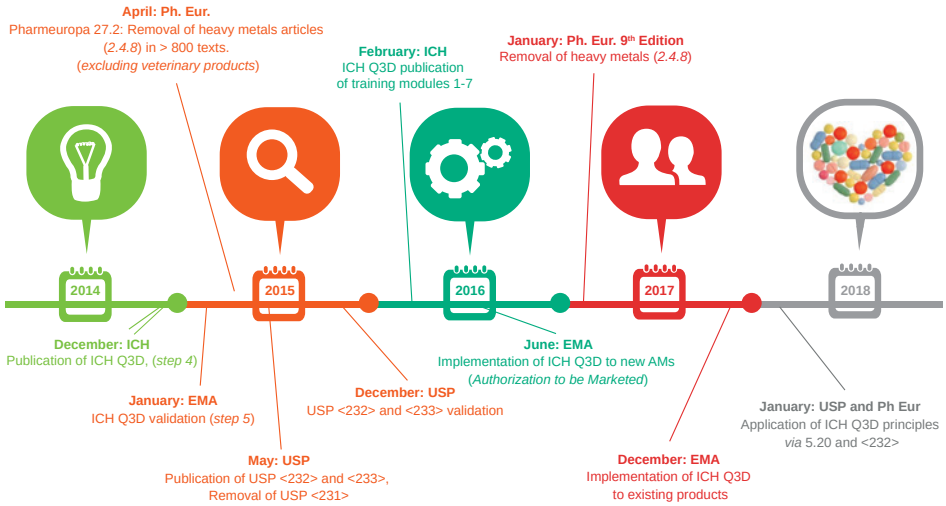


Scavengers for Metal Impurities (*SiliaMetS*)

New ICH-Q3D Heavy Metal Regulation Ready for Implementation in the Pharmaceutical Industry

Since June 2013, the International Conference on Harmonisation (*ICH*) has been working on its Q3D guidelines on metal elemental impurities in new drugs and new formulations containing known ingredients. After many revisions and improvements, the final version of the Q3D guidelines was finally accepted and signed off by the ICH Steering Committee in December 2014, hence requiring the entire manufacturing industry and supply chain to meet more stringent regulations.

Since December 2015, twenty-four (*24*) metals - well-known to act as catalysts or present in solvents - have been indicted and associated with great health risks, and have been assigned distinctive PDE (*Permitted Daily Exposure*) limits. For example, now that ICH Q3D contains Lithium and Barium, we no longer talk of heavy metals impurities but elemental impurities.



There is no doubt that these new guidelines will be one of the next major challenges to address for production plants and QC labs of the pharmaceutical industry. Take advantage of SiliCycle's expertise and knowledge in the field of grafting technologies to efficiently address this new regulation.

Scavengers for Organic Impurities (*SiliaBond*)

The Importance of Organic Contaminant Removal From APIs

Using excess reagents in organic synthesis is a very common strategy to maximise conversion and product yield. But the benefits of this approach can rapidly be outshined when comes the need to purify the final reaction mixture from excess reagents.

In addition, even reagents used in stoechiometric amounts can lead to an uncomplete reaction, and this is far more common than the other way around.

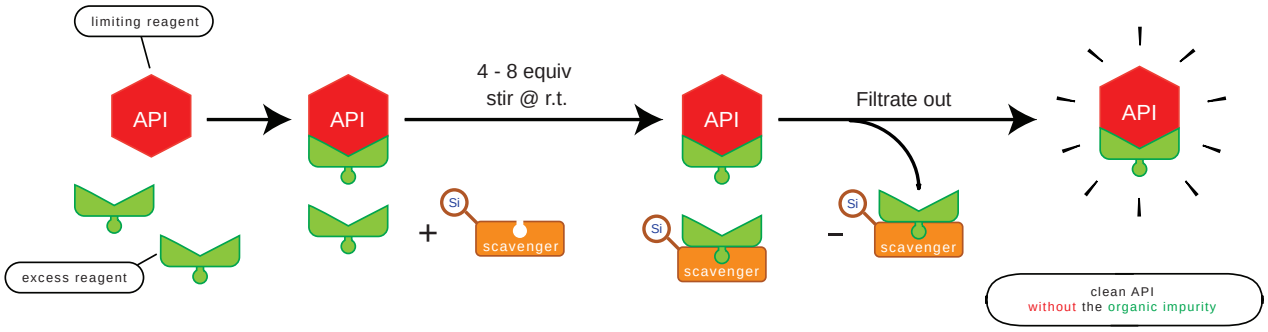
These reagents can either contaminate the API with potentially genotoxic impurities or environmental hazards, or jeopardize subsequent reactions by their reactivity. Indeed, such reagents usually bear nucleophilic, electrophilic, acidic or basic functional groups.

There is a very strong need in organic chemistry and high-throughput screening for simpler work-up and purification processes. Our range of organic scavengers have been widely acknowledged and adopted by early R&D teams up to manufacturing.

Two Ways Silia*Bond* Organic Scavengers Can Help You Purify Your API From Organic Contaminants

Method 1: Direct scavenging of the undesired compound to isolate the API

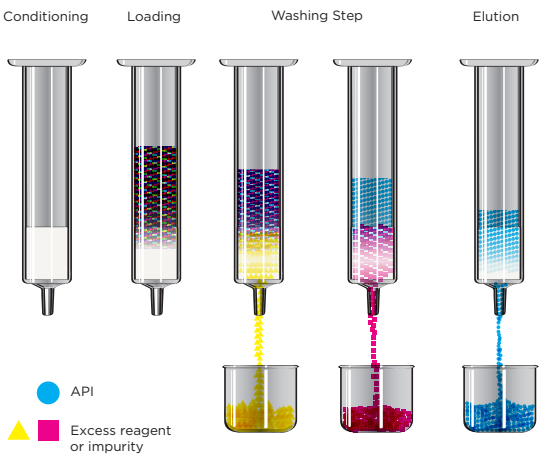
- Silica is bound with a functional group, that will specifically react with a product: either excess reagents (*unreacted*) or impurities.
- The API is recovered by simple filtration as demonstrated on the following scheme:



Method 2: Catch and release of the API

Silia*Bond* scavenger is packed in a SPE cartridge:

- **Conditioning step:** with six to ten hold-up volumes of solvent
- **Loading step:** API is loaded and trapped onto the cartridge bed
- **Washing step:** cartridge is washed to filter excess reagents and / or other impurities
- **Elution step:** API is eluted, recovered and purified



Scavenging Solutions

Different Formats for Different Applications

Scavengers as Bulk Silica

All our scavengers can be used in bulk directly in your reaction flask or reactor.

- All scavengers are available in the following format size: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc. Up to multi-ton scale!
- All our scavengers have, by default, the same silica backbone: our Silia*Flash* R10030B.
  - Particle Size: 40 - 63 µm
  - Pore Size: 60 Å
- All our Silia*Flash* silica gels of various particle sizes and pore sizes are available as silica backbones upon request. Please visit our Silia*Flash* chapter p. 213 for all details.

Scavengers in Silia*Prep* SPE Cartridges

All our scavengers are available in pre-packed SPE cartridges. Please refer to our Silia*Prep* Ordering Information p. 208 to learn about the different formats available.

Scavengers in Silia*Sep* Flash Cartridges

All our scavengers are available pre-packed in Flash cartridges (*please see p. 208*). Please take a look at our Silia*Sep* chapter p. 205 for more information on small-scale cartridges (*research or discovery labs*); and to p. 253 to learn about large-scale purifications on the kilo-scale cartridges (*up to 2.7 kg of crude reaction material applicable to cartridges*).

Packings can also be tailored to your available equipment & scales.

Scavengers as Guard Columns (*for HPLC*)

Silia*Chrom* HPLC Guard Columns are designed to effectively protect both analytical and preparative HPLC columns. The usage of this shorter column is highly recommended to prolong column lifetime and does not alter chromatography. All metals can be prejudicial and very damaging to your column and detector, complicating purification steps, often making them longer, more laborious and less effective.

Crude reaction mixtures can now directly be injected without further metal removal, which will save precious time for the chemist. Another great benefit is that there is much less risk of corroding the equipment by injecting dirty samples.

Silia*Chrom* Guard Columns are cost effective and easy to use as a pre-filter to remove contaminants prior to injection. In liquid chromatography, contaminants introduced into the column can cause:

- Higher backpressure
- Resolution loss
- Baseline noise or drift
- Peak shape changes
- Irreversible damages (*column + system*)

SiliCycle is the only one on the market to offer protective guard cartridges filled with metal scavengers to protect your HPLC columns and system from damageable metallic impurities.

Silia*Chrom* Guard Column Dimensions

Silia*Chrom* Guard Columns are available in lengths of 10 - 20 mm and three internal diameters (*ID: 4.0, 10 and 21.2 mm*). The Guard Column internal diameter should be the same as the HPLC column or one size smaller. Never use a guard column with a larger ID than the HPLC column (*risk of efficiency loss*).

Silia*Chrom* Scavenger Guard Columns		
Guard Column Name	**Palladium's Favorite Metal Guard Column**	**Universal Metal Guard Column**
Scavenger Packing #	K346	K307
Effective Scavenger Can also Remove these Metals	**Pd** **Ag, Cr, Hg, Ir, Ni, Os, Pt, Rh, Ru** Cd, Co, Cu, Fe, Pb, Sc, Sn, W, Zn	**Ca, Cd, Cs, Co, Cr, Cu, Fe, Ir, La, Li, Mg, Mn, Ni, Os, Pd, Pt, Rh, Ru, Sc, Sn, W, Zn** Ag

Silia*Chrom* Scavenger Guard Column Formats				
Particle Size of Sorbent (*µm*)	**Formats Available (*internal diameter x length in mm*)**			
	4.0 x 10	**4.0 x 20**	**10 x 10**	**21.2 x 10**
5	05E-A-N010	05E-A-N020	05E-A-Q010	05E-A-T010
10	07E-A-N010	07E-A-N020	07E-A-Q010	07E-A-T010

Please visit our Ordering Information section p. 209 to learn about the different formats that are available and how to build your own part number.

Compatibility with Different Technologies

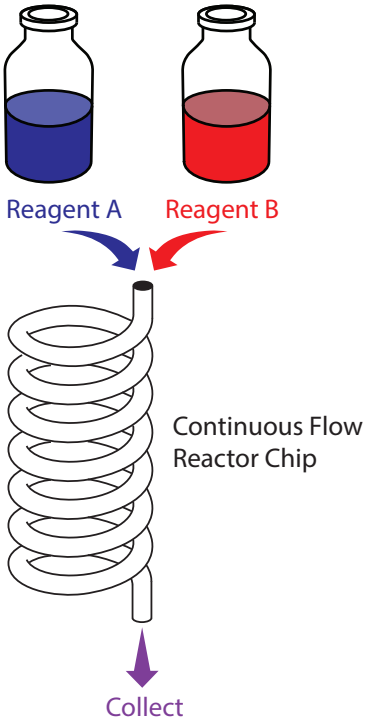
Functionalized Scavengers in Flow Chemistry

Flow chemistry is a relatively new technique that is being used more and more for large scale manufacturing because it only requires a small investment but enables the production of large quantities in a short time. The use of supported scavengers in flow chemistry is even more recent, but is generally more reliable and safer than batch procedures.

Supported scavengers are available on different supports such as silica, polymers, charcoal and alumina. They offer many advantages over the traditional homogeneous scavengers, including ease of handling and purification. Silica presents no swelling, much higher mechanical and thermal stability and ease of scalability than polymer.

Scavenging can be achieved using Silia*MetS* or Silia*Bond* in flow chemistry applications. Simply place the silica-based scavenger inside the solid-phase reactors provided with your flow system (*such as the Syrris Asia® Solid Phase Chemistry Reactors*) and let the solution to be purified flow through these reactors.

Multiple reactors can be placed in series and reactors can be heated to obtain optimum scavenging results.



In this catalog, all application notes and case studies using flow chemistry technology are identified by this logo:

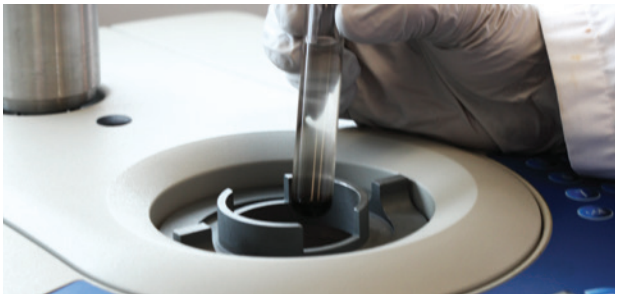
Scavengers in Microwave-Assisted Chemistry

Fast kinetics, higher yields, excellent purity, wide compatibility of solvents and their applicability to a variety of reactions and applications are just some of the advantages that make scavengers very important tools in the laboratory.

After their introduction, chemists started to use supported reagents for solution-phase synthesis, and later on heterogeneous scavengers for post-reaction purification.

Commonly used polymer-supported reagents, although very useful, have drawbacks when used in microwave synthesizers, namely swelling and heat instability. The high temperatures generated put stress on the resins. Also, because of the small reaction volumes, the swelling of the resins can be problematic. ***Silica-based products, on the other hand, do not suffer from such shortcomings. They are heat resistant and they do not swell.***

Metal and organic removal impurity using Silia*MetS* and Silia*Bond* can also be done under microwave irradiation to provide excellent scavenging efficiency in just minutes. Simply mix into a microwave tube the scavenger, the API dissolved in a suitable solvent, and set-up the system with chosen parameters. Usually, five minutes are sufficient for complete scavenging.

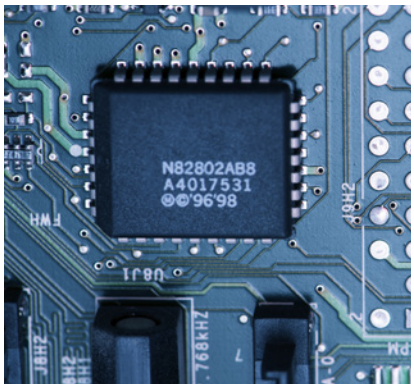


In this catalog, all application notes and case studies using microwave technology are identified by this logo:

Scavengers in Industry

Because our technology is flexible, versatile and customizable to suit your particular needs, these are some of the markets we have been helping over the years:

- Pharmaceutical
- Chemistry
- Electronics
- Mining
- Semi-conductors
- Optical fibers
- Metal recycling
- Universities & Research centers
- Natural extracts



Metal & Organic Scavenging Screening Services

This service was specially designed for scientists that are either confronted with a residual impurity that needs to be discarded, or in lower in concentration.

With increasing regulatory requirements (*FDA, ICH*) for residual levels of metal catalysts and organic potentially genotoxic impurities (*PGI compounds*), the removal of post-reaction metal residues has become a major issue in the industry. SiliCycle offers an unparalleled range of metal scavengers with its Silia*MetS* line, which significantly facilitates this purification process.

Our scavenging screening services are innovative as they provide solutions to quickly develop the most efficient metal scavenging process providing both time and cost savings. Confidentiality is assured, as in most cases the solution involves working with API and other patented materials, and easy technology transfers are guaranteed.

1. NDA signed for confidentiality purpose
2. Scavenging questionnaire completed by customer and revised by our experts
3. Communications to determine the objectives of the service
4. Customer's sample sent to SiliCycle
5. Initial lab-scale screening to select the most efficient scavengers and generate data
6. Optimization of the conditions
7. Scale-up trials and purity evaluation
8. Preparation of the report and wrap up meeting to present results to customer
9. Detailed experimental procedure for easy technology transfer & plant trials

Full Process Scale

We can also offer an exclusive partnership program designed to run on Full Process Scale. We will be working with you, in function of your needs. This process optimization work can be carried out and optimized as a slurry in your reactor followed by filtration (*bulk mode*), or via a cartridge in a flow design.

Please discover our full range of R&D Services in pages 287 to 303

Over the years, SiliCycle has developed a number of screening services to assist customers in their project and help identify solutions for purification problems, at all stages & scales, from R&D to production.

Regulatory Information

Regulatory Documents & Information

The SiliCycle scavengers have been used for over a decade in pilot plants and production units under cGMP conditions by the pharmaceutical industry as well as CMOs and CROs. They have ran their own analysis proving that silica-based scavengers can safely be used, both in reactors or cartridges, without leaching that would compromize the purity of their precious compound.

SiliCycle is committed to high quality standards and always strives to provide superior quality products. In doing so, all products are manufactured in an ISO 9001:2008 compliant facility and subjected to stringent quality control.

SiliCycle provides a Certificate of Analysis with all its products, certifying that every lot has been manufactured and tested in accordance with SiliCycle specifications. Moreover, samples from every lot are kept for subsequent analysis.

All products are shipped with the following information:

- Certificate of Analysis (*molecular loading, surface coverage, volatile content, etc.*)
- Material Safety Data Sheet (*MSDS*)
- Technical information

All products can be shipped with the following information, under request:

- BSE / TSE declaration (*non animal-derived*)
- GMO-Free Certificate
- Melamine-Free Certificate

Regulatory Support File

SiliCycle can work with you to fill and provide customized regulatory documents, including specific analytical tests in line with your needs.

Our Regulatory Support Files (*RSF*) are documents that include both proprietary and non-proprietary information on performance, chemical / thermal / mechanical stability, extractable & leachable compounds, SOPs, scale-up procedures, batch history, analytical methods and more. RSF documentation can be obtained through a Non-Disclosure Agreement (*NDA*).

For any inquiries, please contact regulatorysupport@silicycle.com

SiliCycle Scavenger Portfolio

We have the largest portfolio of grafted scavengers on the market and the largest spectrum of functionalities. Our charts will enable you to navigate through our products portfolio swiftly and two-entry tables have specifically been worked out to help you choose which scavenger best relates to your application.

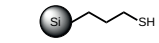
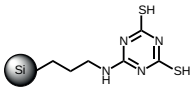
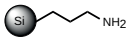
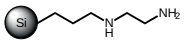
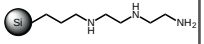
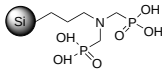
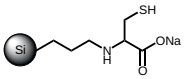
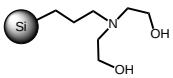
All Silia*MetS* / Silia*Bond* Scavengers can be used in a pH range of 2 to 12 and most of them can withstand temperatures up to 150°C.

Standard scavengers are grafted on 40 - 63 µm, 60 Å silica gel.

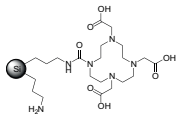
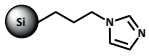
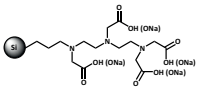
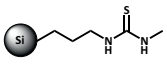
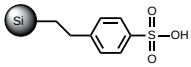
All functionalities are also available on any other of our bare silica gels, with various particle and pore diameters.

Please check *"Bulk Silica Gels - Silia*Flash *& Silia*Sphere*"* chapter, p. 213.

Silia*MetS* Metal Scavengers Portfolio

Silia*MetS* Metal Scavengers Technical Information				
Scavengers	**Structure**	**Brief Description**	**Metals Removed**[1]	**Typical Characteristics** [2, 3]
Silia*MetS* Thiol **PN: R51030B** Loading: ≥ 1.20 mmol/g Endcapping: Yes		Silia*MetS* Thiol is our most versatile and robust metal scavenger for a variety of metals under a wide range of conditions.	**Ag, Hg, Os, Pd & Ru** Cu, Ir, Pb, Rh & Sn	Color: White Density: 0.682 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* DMT **PN: R79030B** Loading: ≥ 0.50 mmol/g Endcapping: Yes		Silia*MetS* DMT is the silica-bound equivalent of 2,4,6-trimercaptotriazine (*trithiocyanuric acid, TMT*). It is a versatile metal scavenger for a variety of metals and the preferred metal scavenger for ruthenium catalysts and hindered Pd complexes (*i.e. Pd(dppf)Cl$_2$*).	**Ir, Ni, Os, Pd, Pt, Rh & Ru** Cd, Co, Cu, Fe, Sc & Zn	Color: Light brown Density: 0.732 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Amine **PN: R52030B** Loading: ≥ 1.20 mmol/g Endcapping: Yes		Also known for their electrophile scavenging efficiencies and their base reagent qualities, Silia*MetS* Amine, Diamine and Triamine have also proven to be very useful for the scavenging of the following metals: Pd, Pt, Cr, W and Zn.	**Cd, Cr, Pd, Pt, Rh & Ru** Co, Cu, Fe, Hg, Pb, W & Zn	Color: Off-white Density: 0.700 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* Diamine **PN: R49030B** Loading: ≥ 1.28 mmol/g Endcapping: Yes			**Cr, Pd, Pt, W & Zn** Cd, Co, Cu, Fe, Hg, Ni, Pb, Ru & Sc	Color: Off-white Density: 0.728 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* Triamine **PN: R48030B** Loading: ≥ 1.11 mmol/g Endcapping: Yes			**Cr, Pd, Pt, W & Zn** Ag, Cd, Co, Cu, Fe, Hg, Ni, Os, Pb, Rh, Ru & Sc	Color: Off-white Density: 0.736 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* AMPA **PN: R85130B** Loading: ≥ 0.80 mmol/g Endcapping: Yes		Silia*MetS* AMPA is an aminomethyl-alkylphosphonic acid ligand known for its excellent metal-bonding properties. It is particularly efficient to remove Al, Sb, Ni, La, and also very effective for Co, Cu, Fe, Mg and Zn scavenging from reaction intermediates or final APIs.	**Al, Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Mg, Nd, Ni, Pm, Pr, Sb, Sm, Tb, Tm, V & Yb** Co, Cu, Fe, Mg & Zn	Color: Yellow Density: 0.707 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 1 Year
Silia*MetS* Cysteine **PN: R80530B** Loading: ≥ 0.30 mmol/g Endcapping: Yes		Silia*MetS* Cysteine is the silica-bound equivalent of the amino acid cysteine. It is a versatile scavenger for a variety of metals and the preferred metal scavenger for tin residues. By attaching the molecule to the backbone via the amino group, the thiol group remains free and accessible for higher metal scavenging efficiency.	**Cd, Fe, Ir, Os, Ru, Sc & Sn** Ca, Cr, Cs, Cu, La, Mg, Pd, Pt, Rh & Zn	Color: Orange Density: 0.665 g/mL Solvent Compatibility: 2 Prolonged Storage: 1 Shelf Life: 1 Year
Silia*MetS* DEAM **PN: R54430B** Loading: ≥ 0.85 mmol/g Endcapping: Yes		Silia*MetS* DEAM is a versatile scavenger designed to remove trace metal of Ti, Zn, Fe and Ag as well as boronic acids from reaction intermediates or final APIs.	**Ag, Fe, Sn, Ti & Zn**	Color: Off-white Density: 0.691 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years

Silia*MetS* Metal Scavengers Technical Information

Scavengers	Structure	Brief Description	Metals Removed[1]	Typical Characteristics [2, 3]
Silia*MetS* DOTA **PN: R91030B** Loading: ≥ 0.38 mmol/g Endcapping: Yes		Silia*MetS* DOTA is a silica-supported tetracarboxylic acid and its various conjugate bases. DOTA molecule is a well-adopted complexing agent. Linked to various metals, so formed-complexes are used as contrast agents in cancer treatments or other medical applications.	**Ca, Cu, Gd, La, Ni & Zn** Co, Fe, Mg, Pd, Pt & Rh	Color: Light yellow Density: 0.681 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 1 Year
Silia*MetS* Imidazole **PN: R79230B** Loading: ≥ 0.96 mmol/g Endcapping: Yes		Silia*MetS* Imidazole is a versatile metal scavenger for a variety of metals including Cd, Co, Cu, Fe, Ni, Os, Pd and Rh.	**Cd, Co, Cu, Fe, Ir, Li, Mg, Ni, Os, W & Zn** Cr, Pd & Rh	Color: Off-white Density: 0.681 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* TAAcOH **PN: R69030B** Loading: ≥ 0.41 mmol/g Endcapping: No		Silia*MetS* TAAcOH & TAAcONa are supported versions of EDTA in their acid and sodium salt forms. These two products are effective metal scavengers for Ca, Mg, Li, Ir, Cs, Os, Sn, Pd, Ni and Cu. Silia*MetS* TAAcOH is effective for metals in low or zero oxidation states, compared to Silia*MetS* TAAcONa which is useful for metals in higher oxidation states (≥ *2*).	**Ca, Co, Ir, Li, Mg, Ni, Os, Ru & Sc** Cr, Cs, Fe, Pd, Rh & Sn	Color: Off-white Density: 0.635 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* TAAcONa **PN: R69230B** Loading: ≥ 0.41 mmol/g Endcapping: No			**Ca, Cd, Cs, Cu, Fe, Ir, La, Li, Mg, Ni, Os, Rh, Sc & Sn** Cr, Pd, Ru & Zn	Color: Off-white Density: 0.712 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* Thiourea **PN: R69530B** Loading: ≥ 1.07 mmol/g Endcapping: Yes		Silia*MetS* Thiourea is a versatile metal scavenger for all forms of palladium and is widely used in the pharmaceutical industry. Once complexed with a transition metal, it has been reported to be an effective catalyst.	**Pd & Ru** Ag, Cu, Fe, Os, Rh, Sc & Sn	Color: Off-white Density: 0.767 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Tosic Acid **PN: R60530B** Capacity: ≥ 0.54 meq/g Endcapping: Yes		Silia*Bond* Tosic Acid is in a class of strong acids used in different fields of synthetic organic chemistry. The aromatic ring makes it slightly more acidic than other supported sulfonic acids.	**Fe, Rh & Sn** Ag, Cu, Ni, Pd, Pt, Ru & Zn	Color: Off-white Density: 0.698 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years

[1] **Scavenging Efficiency:** Best scavenger for the removal of a particular metal is indicated in **Navy Blue**
Good scavenger indicated in **Pale Blue**

[2] **Solvent Compatibility**: 1- All solvents, aqueous and organic
2- All organic solvents

[3] **Prolonged Storage**: 1- Keep dry
2- Keep cool (< *8°C*) and dry
3- Keep cool (< *8°C*), dry and under inert atmosphere

Potentially Genotoxic Impurities (PGI) Scavenger
Contact Us for More Information

Scavenging Solutions

Silia*MetS* Metal Scavengers Selection Table

Best scavenger: ■ | Good scavenger: ●

Silia*MetS* Metal Scavengers Selection Table								
	Scavenger	Silia*MetS* Thiol (*Si-Thiol*) PN: R51030B	Silia*MetS* DMT (*Si-DMT*) PN: R79030B	Silia*Bond* Amine (*Si-WAX*) PN: R52030B	Silia*MetS* AMPA (*Si-AMPA*) PN: R85130B	Silia*MetS* Cysteine (*Si-CYS*) PN: R80530B	Silia*MetS* DEAM (*Si-DEAM*) PN: R54430B	Silia*MetS* Diamine (*Si-DIA*) PN: R49030B
	Loading (*mmol/g*)	≥ 1.20	≥ 0.50	≥ 1.20	≥ 0.80	≥ 0.30	≥ 0.85	≥ 1.28
	Typical Tap Density (*g/mL*)	0.682	0.732	0.700	0.707	0.665	0.691	0.728
Metals to be scavenged	Ag	■					■	
	Al				■			
	Ca					●		
	Cd		●	■		■		●
	Ce				■			
	Co		●	●	●			●
	Cr			■		●		■
	Cs					●		
	Cu	●	●	●	●	●		●
	Fe		●	●	●	■	■	●
	Gd				■			
	Hg	■		●				●
	Ir	●	■			■		
	La				■	●		
	Li							
	Mg				●	●		
	Ni		■		■			●
	Os	■	■			■		
	Pb	●		●				●
	Pd	■	■	■		●		■
	Pt		■	■		●		■
	Rh	●	■	■		●		
	Ru	■	■	■		■		●
	Sc		●			■		●
	Sn	●				■	■	
	Ti						■	
	W			●				■
	Zn		●	●	●	●	■	■

SiliaMetS Metal Scavengers Selection Table

SiliaMetS DOTA (Si-DOTA) PN: R91030B	SiliaMetS Imidazole (Si-IMI) PN: R79230B	SiliaMetS TAAcOH (Si-TAAcOH) PN: R69030B	SiliaMetS TAAcONa (Si-TAAcONa) PN: R69230B	SiliaMetS Thiourea (Si-THU) PN: R69530B	SiliaMetS Triamine (Si-TRI) PN: R48030B	SiliaBond Tosic Acid (Si-SCX) PN: R60530B	Scavenger	Metals to be scavenged
≥ 0.38	≥ 0.96	≥ 0.41	≥ 0.41	≥ 1.07	≥ 1.11	≥ 0.54 meq/g	Loading (*mmol/g*)	
0.681	0.681	0.635	0.712	0.767	0.736	0.698	Typical Tap Density (*g/mL*)	
				●	●	●	Ag	
							Al	
■		■	■				Ca	
	■		■		●		Cd	
							Ce	
●	■	■			●		Co	
	●	●	●		■		Cr	
		●	■				Cs	
■	■		■	●	●	●	Cu	
●	■	●	■	●	●	■	Fe	
■							Gd	
					●		Hg	
	■	■	■				Ir	
■			■				La	
	■	■	■				Li	
●	■	■	■				Mg	
■	■	■	■		●	●	Ni	
	■	■	■	●	●		Os	
					●		Pb	
●	●	●	●	■	■	●	Pd	
●					■	●	Pt	
●	●	●	■	●	●	■	Rh	
		■	●	■	●	●	Ru	
		■	■	●	●		Sc	
		●	■	●		■	Sn	
							Ti	
	■				■		W	
■	■		●		■	●	Zn	

Scavenging Solutions

Silia*MetS* Metal Scavengers Selection Guide

When selecting a metal scavenger, every parameter must be considered: metal catalyst, solvent, residual reagents, by-products, structure of the API (*or molecule of interest*) and temperature. The following tables, shown below, will help in selecting the most efficient scavenger for a specific metal and application. However, since some parameters may affect the efficiency of the scavenging, we highly recommend performing a preliminary screening experiment using the Silia*MetS* Metal Scavenger Kit.

SiliCycle also offers a confidential Metal Scavenger Screening Service. Contact us to take advantage of our expertise in metal removal.

Silia*MetS* Metal Scavengers Selection Guide (*Catalyst Only in Solution*)

Catalyst, Solvent & Conditions (*% of catalyst scavenged*)								
Silia*MetS*	$Pd(OAc)_2$	$Pd_2(allyl)_2Cl_2$	$Pd_2(dba)_3$	$Pd(PPh_3)_4$	$PdCl_2(dppf)$	Grubbs 1st Gen.	Grubbs 2nd Gen.	Hoveyda-Grubbs 1st
	DMF	DMF	DMF	DMF	DMF	DMF	DMF	DMF
	4 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 22°C	8 equiv, 16 h, 80°C	8 equiv, 16 h, 80°C	8 equiv, 16 h, 80°C
Silia*MetS* Thiol	> 99	> 99	98	98		96	99	93
Silia*MetS* Thiourea	> 99	> 99	98	91		98	96	98
Silia*MetS* Cysteine	not screened	not screened	not screened	98	not screened	not screened	not screened	not screened
Silia*MetS* DMT	98	> 99 [22°C]	> 99	> 99	Pd: 94, Fe: 92	> 99 [4 equiv]	99 [4 equiv]	98 [4 equiv]
Silia*Bond* Amine	98	> 99	97			97		
Silia*MetS* Diamine	> 99	> 99	> 99	90		99	94	98
Silia*MetS* Triamine	> 99	90	> 99	80		95		95
Silia*MetS* Imidazole	not screened	not screened	not screened	not screened		not screened	not screened	not screened
Silia*MetS* TAAcOH	98	93	97 [80°C]					
Silia*MetS* TAAcONa	97		80 [80°C]					

Note: other catalysts results are available on request (*metal screened but not shown: calcium, cobalt, cesium, copper, iron, iridium, lanthane, tin & tunsgten. Contact us!*)

Silia*MetS* Metal Scavengers Selection Guide (*Catalysts Scavenging in a Reaction*)

Catalyst, Solvent, Conditions & Reaction				
Silia*MetS*	$PdCl_2(PPh_3)_2$, CuI (*in DME*)	$Pd(OAc)_2$, P(o-tol)$_3$ (*in i-PrOH, H_2O*)	$RhCl(PPh_3)_3$ (*in Toluene*)	$FeCl_3.6H_2O$ (*in THF*)
	8 equiv, 4 h, 22°C	5 equiv, 4 h, 40°C	65 equiv, 4 h, 22°C	5 equiv, 4 h, 22°C
	Sonogashira Coupling	Suzuki Coupling	Wilkinson Hydrogenation	Michael Addition
Silia*MetS* Thiol	Pd: 89, Cu: 29	98		
Silia*MetS* Thiourea	Pd: 72, Cu: 80	92	81	82
Silia*MetS* Cysteine		84	88	> 99
Silia*MetS* DMT	Pd: 98, Cu: > 99	> 99	94	98
Silia*Bond* Amine		80	93	98
Silia*MetS* Diamine		80		> 99
Silia*MetS* Triamine				98
Silia*MetS* Imidazole		88	92	98
Silia*MetS* TAAcOH			81	98
Silia*MetS* TAAcONa			88	> 99

Scavenging > 99 %	Scavenging 95 - 99 %	Scavenging 90 - 94 %	Scavenging 80 - 89 %

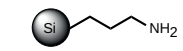
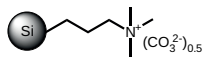
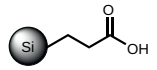
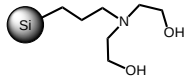
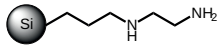
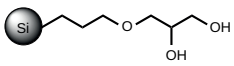
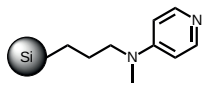
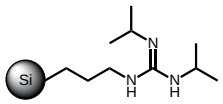
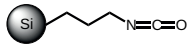
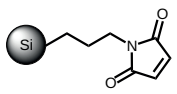
Catalyst, Solvent & Conditions (*% of catalyst scavenged*)							
Hoveyda-Grubbs 2nd	TPAP	$Ni(acac)_2$	Wilkinson's Cat.	$[Rh(OAc)_2]_2$	H_2PtCl_6	$Pb(OAc)_2.3H_2O$	$Zn(OAc)_2.2H_2O$
DMF	DCM	DMF	DMF	DMF	DMF	DMF	DMF
8 equiv, 16 h, 80°C	4 equiv, 16 h, 22°C	4 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 80°C	4 equiv, 4 h, 22°C	4 equiv, 4 h, 22°C
	96		> 99 [16 h]	97	80 [16 h]	97	> 99
	> 99		99	97			97 [80°C]
not screened	not screened	92	88	not screened	99		> 99
99 [4 equiv]	> 99	97	> 99	> 99	> 99	99	94
	> 99		> 99	> 99			> 99
90	97	99	> 99	> 99 [22°C]	> 99	81	> 99
95	> 99	93	97	97 [22°C]	97	> 99 [80°C]	> 99
	not screened	91 [80°C]	90	97 [22°C]	not screened		> 99
	> 99	> 99	97	96 [16 h]			
	> 99	> 99	88	> 99 [16 h]		90	> 99

Catalyst, Solvent, Conditions & Reaction			
CuCN (*in DMF*)	Iridium Crabtree's Cat. (*in DCM*)	$LaCl_3.LiCl$ (*in DMF*)	$PhCH_2ZnCl$ (*in THF*)
10 equiv, 4 h, 22°C	4 equiv, 4 h, 22°C	1 equiv, 4 h, 22°C	4 equiv, 4 h, 80°C
Rosemund von-Braun Cyanation	Alkene Hydrogenation	1,2-Addition on Ketone	Negishi Coupling
94			
> 99			
> 99	86	Li: 75, La: > 99	91
> 99			84
98			94
> 99			95
> 99			91
95			94
80			
> 99	80	Li: 95, La: > 99	94

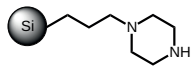
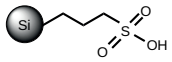
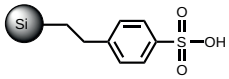
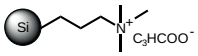
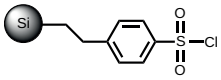
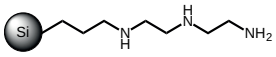
Scavenging > 99 %	Scavenging 95 - 99 %	Scavenging 90 - 94 %	Scavenging 80 - 89 %

Silia*Bond* Organic Scavengers Portfolio

Silia*Bond* Organic Scavengers Technical Information

Scavengers	Structure	Nature	Molecules Removed	Typical Characteristics [1, 2]
Silia*Bond* Amine **PN: R52030B** Loading: ≥ 1.20 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.700 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic Phenols	
Silia*Bond* Carbonate **PN: R66030B** Loading: ≥ 0.46 mmol/g Endcapping: Yes		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids, Acidic Phenols & Boronic Acids	Color: Off-white Density: 0.608 g/mL Solvent Compatibility: 3 Prolonged Storage: 1 Shelf Life: 1 Years
Silia*Bond* Carboxylic Acid **PN: R70030B** Loading: ≥ 0.92 mmol/g Endcapping: Yes		Scavenger for Bases (*Ionic Bonding*) Catch & Release	Primary / Secondary Amines & Anilines	Color: Off-white Density: 0.687 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*MetS* DEAM **PN: R54430B** Loading: ≥ 0.85 mmol/g Endcapping: Yes		Scavenger for Electrophiles & Lewis Acids (*Covalent & Ionic Bonding*) Catch & Release	Boronic Acids	Color: Off-white Density: 0.691 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*MetS* Diamine **PN: R49030B** Loading: ≥ 1.28 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.728 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic phenols	
Silia*Bond* Diol **PN: R35030B** Loading: ≥ 0.97 mmol/g Endcapping: No		Scavenger for Electrophiles & Lewis Acids (*Covalent & Ionic Bonding*) Catch & Release	Boronic Acids	Color: Off-white Density: 0.687 g/mL Solvent Compatibility: 2 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* DMAP **PN: R75630B** Loading: ≥ 0.53 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides & Sulfonyl Chlorides	Color: Light brown to brown Density: 0.674 g/mL Solvent Compatibility: 1 Prolonged Storage: 3 Shelf Life: 1 Years
Silia*Bond* Guanidine **PN: R68230B** Loading: ≥ 0.80 mmol/g Endcapping: Yes		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids, Acidic Phenols & Boronic Acids	Color: Light yellow Density: 0.732 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
Silia*Bond* Isocyanate **PN: R50030B** Loading: ≥ 1.16 mmol/g Endcapping: Yes		Scavenger for Nucleophiles (*Covalent Bonding*)	Alcohols, Alkoxides, Amines, Anilines, Hydrazines, Organometallics, Thiols & Thiolates	Color: Off-white Density: 0.741 g/mL Solvent Compatibility: 3 Prolonged Storage: 2 Shelf Life: 2 Years
Silia*Bond* Maleimide **PN: R71030B** Loading: ≥ 0.64 mmol/g Endcapping: Yes		Scavenger for Nucleophiles (*Covalent Bonding*)	Thiols & Thiolates	Color: Off-white Density: 0.644 g/mL Solvent Compatibility: 5 Prolonged Storage: 3 Shelf Life: 2 Years

SiliaBond Organic Scavengers Technical Information

Scavengers	Structure	Nature	Molecules Removed	Typical Characteristics [2, 3]
PGI-S SiliaBond Piperazine **PN: R60030B** Loading: ≥ 0.83 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.671 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic Phenols	
PGI-S SiliaBond Propylsulfonic Acid **PN: R51230B** Loading: ≥ 0.63 mmol/g Endcapping: Yes		Scavenger for Bases (*Ionic Bonding*) Catch & Release	Amines & Anilines	Color: Off-white Density: 0.728 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
PGI-S SiliaBond Tosic Acid **PN: R60530B** Loading: ≥ 0.54 meq/g Endcapping: Yes				Color: Off-white Density: 0.698 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
SiliaBond TMA Acetate **PN: R66430B** Loading: ≥ 0.71 mmol/g Endcapping: No		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Carboxylic Acids	Color: Off-white Density: 0.665 g/mL Solvent Compatibility: 1 Prolonged Storage: 1 Shelf Life: 2 Years
SiliaBond Tosyl Chloride **PN: R44030B** Loading: ≥ 0.63 mmol/g Endcapping: Yes		Scavenger for Nucleophiles (*Covalent Bonding*)	Alcohols, Alkoxides, Amines, Anilines, Hydrazines, Organometallics, Thiols & Thiolates	Color: Off-white Density: 0.761 g/mL Solvent Compatibility: 4 Prolonged Storage: 3 Shelf Life: 6 months
PGI-S SiliaMetS Triamine **PN: R48030B** Loading: ≥ 1.11 mmol/g Endcapping: Yes		Scavenger for Electrophiles (*Covalent Bonding*)	Acyl Chlorides, Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones & Sulfonyl Chlorides	Color: Off-white Density: 0.736 g/mL Solvent Compatibility: 1 Prolonged Storage: 2 Shelf Life: 2 Years
		Scavenger for Acids (*Ionic Bonding*) Catch & Release	Acids & Acidic Phenols	

[1] **Solvent Compatibility**:
1- All solvents, aqueous and organic
2- All organic solvents
3- Anhydrous aprotic solvents
4- Anhydrous aprotic solvents, unstable in DMF
5- Polar solvents (*DMF, MeOH, H_2O*)

[2] **Prolonged Storage**:
1- Keep dry
2- Keep cool (< *8°C*) and dry
3- Keep cool (< *8°C*), dry and under inert atmosphere

PGI-S *Potentially Genotoxic Impurities (PGI) Scavenger*
Contact Us for More Information

Scavenging Solutions

SiliaBond Organic Scavengers Selection Table

SiliaBond Organic Scavengers can help you purify your API. Functional group is bound to silica, that will specifically react with a given product. Use the double-entry chart below to choose the best match between the impurity you are dealing with or the scavenger your already have in hand.

Electrophile scavenger (*Covalent Bonding*): ◆ **| Nucleophile scavenger (*Covalent Bonding*):** ▼

Ionic bonding: ● **| Catch & release:** ⬢

SiliaBond Organic Scavengers Selection Table

Scavenger	SiliaBond Amine (*Si-WAX*) PN: R52030B	SiliaMetS Diamine (*Si-DIA*) PN: R49030B	SiliaMetS Triamine (*Si-TRI*) PN: R48030B	SiliaBond Carbonate (*Si-CO3*) PN: R66030B	SiliaBond Carboxylic Acid (*Si-WCX*) PN: R70030B	SiliaMetS DEAM (*Si-DEAM*) PN: R54430B	SiliaBond Diol (*Si-Diol*) PN: R35030B	SiliaBond DMAP (*Si-DMAP*) PN: R75630B
Loading (*mmol/g*)	≥ 1.20	≥ 1.28	≥ 1.11	≥ 0.46	≥ 0.92	≥ 0.85	≥ 0.97	≥ 0.53
Typical Tap Density (*g/mL*)	0.700	0.728	0.736	0.608	0.687	0.691	0.687	0.674
Electrophiles & Nucleophiles to be scavenged								
Acid *Carboxylic acid*		● ⬢		● ⬢				
Acyl chloride		◆						◆
Acidic phenol		● ⬢		● ⬢				
Alcohol								
Aldehyde		◆						
Alkoxide								
Amine					● ⬢			
Anhydride		◆						
Aniline					● ⬢			
Boronic acid				● ⬢		◆ ⬢	◆ ⬢	
Chloroformate		◆						
Hydrazine								
Isocyanate		◆						
Ketone		◆						
Organometallic								
Sulfonyl chloride		◆						◆
Thiol / Thiolate								

SiliaBond Organic Scavengers Selection Table

SiliaBond Guanidine (Si-GUA) PN: R68230B	SiliaBond Isocyanate (Si-ISO) PN: R50030B	SiliaBond Maleimide (Si-MAL) PN: R71030B	SiliaBond Piperazine (Si-PPZ) PN: R60030B	SiliaBond Propylsulfonic Acid (Si-SCX-2) PN: R51230B Tosic Acid (Si-SCX) PN: R60530B	SiliaBond TMA Acetate (Si-SAX-2) PN: R66430B	SiliaBond Tosyl Chloride (Si-TsCl) PN: R44030B	Scavenger	
≥ 0.80	≥ 1.16	≥ 0.64	≥ 0.83	SCX-2: ≥ 0.63 SCX: ≥ 0.54 meq/g	≥ 0.71	≥ 0.63	Loading (*mmol/g*)	
0.732	0.741	0.644	0.671	SCX-2: 0.728 SCX: 0.698	0.665	0.761	Typical Tap Density (*g/mL*)	
● ⬢			● ⬢		● ⬢		Acid *Carboxylic acid*	Electrophiles & Nucleophiles to be scavenged
			◆				Acyl chloride	
● ⬢			● ⬢				Acidic phenol	
	▼					▼	Alcohol	
			◆				Aldehyde	
	▼					▼	Alkoxide	
	▼			● ⬢		▼	Amine	
			◆				Anhydride	
	▼			● ⬢		▼	Aniline	
● ⬢							Boronic acid	
			◆				Chloroformate	
	▼					▼	Hydrazine	
			◆				Isocyanate	
			◆				Ketone	
	▼					▼	Organometallic	
			◆				Sulfonyl chloride	
	▼	▼				▼	Thiol / Thiolate	

Scavenging Solutions

Beyond the Basics

This section is a step-by-step guide for all technical questions you might have:

How much scavenger should be used?

How long should the reaction last?

How do we know when the scavenging process is completed?

And if it doesn't, which parameters can be adjusted?

You will also be able to choose which format we offer best suits your needs. Because all matrices are unique and that small differences can influence the scavenging efficiency, we recommend to screen our scavenger kits, especially if you are new to this technology.

Steric hindrance of the catalyst, electronic effects and solvent solubility, all factors that can influence the removal of your impurity.

We have many kits, all designed for specific scavenging needs. Let us help you take the plunge and switch to this powerful technology for your everyday purification routine!

Typical Experimental Procedures in Batch Mode Reactor (*Bulk*)

STEP	For Silia*MetS* Metal Scavengers	For Silia*Bond* Organic Scavengers
	For initial screening, start with 4 - 8 molar equivalents of Silia***MetS*** in respect to the residual metal concentration.	For initial test, start with 2 - 4 molar equivalents of Silia***Bond*** in respect to the impurity.
1	Dissolve the crude product to be treated in a suitable solvent (*or directly use the crude reaction mixture*) and prepare vials containing the same solution volume. Directly add your chosen Silia*MetS* / Silia*Bond* to these vials. ***Note***: *no pre-wetting / pre-activation is required.*	
2	For initial tests, stir the solution for at least one hour at room temperature.	
3	Scavenging progress can be followed by normal analytical techniques. The scavenging progress can also be estimated by looking at the color of the solution, as depicted herein:  When the scavenging is almost complete, the solution is less colored and Silia*MetS* becomes colored. In some occasional cases, if all the samples are still colored, try one or all of the following: let them react for a longer period of time; add more equivalents of the Silia*MetS*; increase the temperature of the reaction. Keep in mind that colors can come from other factors unrelated to the impurities.	Scavenging progress can be followed by normal analytical techniques. If scavenging seems incomplete or very slow, reaction time or temperature can be increased, or more equivalents of the scavenger can be added.
4	At the end of the scavenging, filter off the scavenger using a fritted funnel or filtration device.	
5	Wash the Silia*MetS* with additional solvent for total recovery of the API (*or compound of interest*) and concentrate the solution under vacuum.	Wash thoroughly with solvent to afford impurity-free solution. Concentrate under vaccum.
6	Analyze the residual metal or organic impurity concentration of each vial to identify the most efficient scavenger.	
7	Direct scale-up is now possible. Otherwise, scavenging optimization can be examined.	

Please keep in mind that the above procedures are standard and introductory, but optimization of conditions is key to optimal scavenging efficiency.

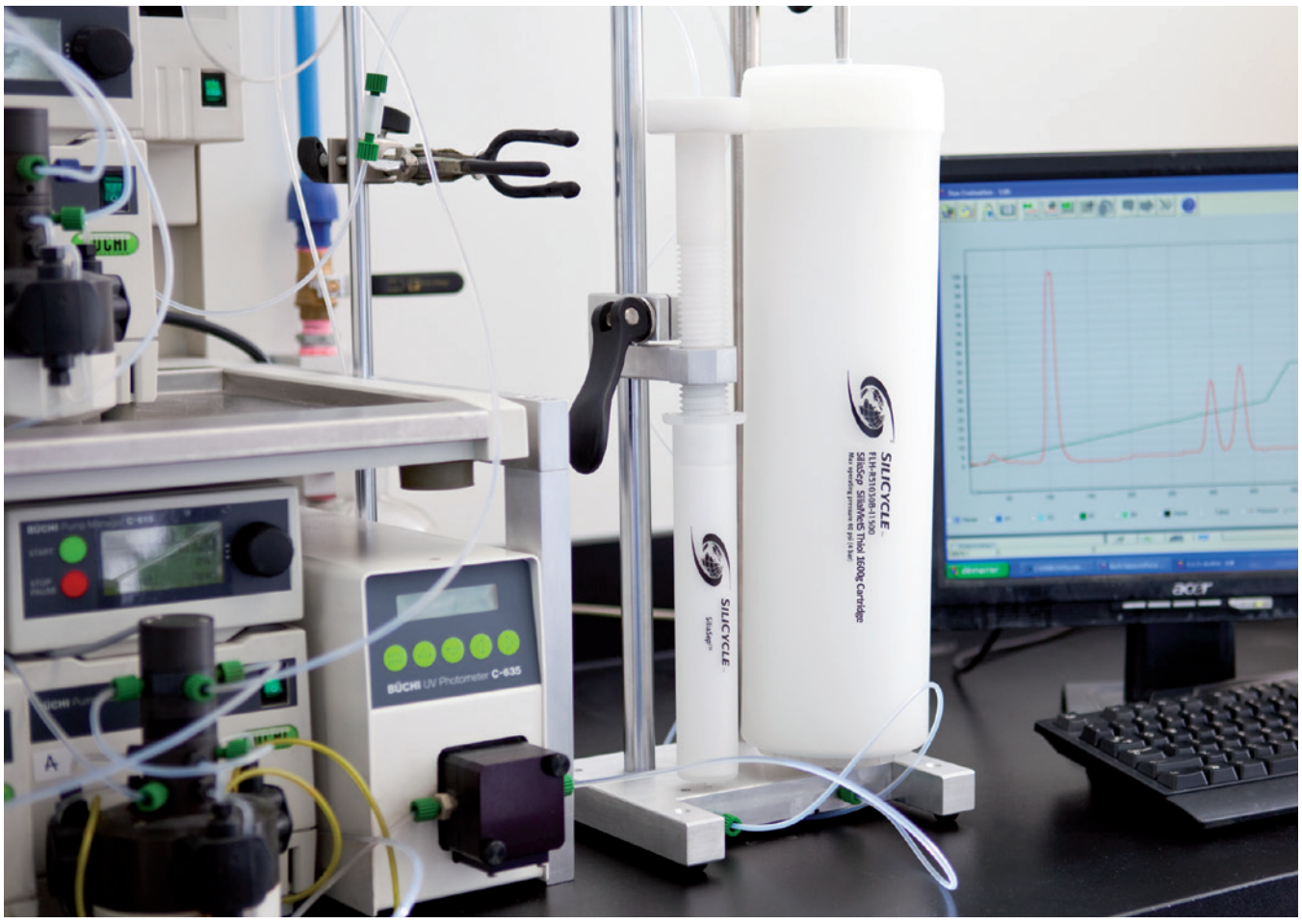
Due to it's ease of operation & how swiftly it can handle different sets of conditions, we use the SiliCycle MiniBlock to run our scavenging screenings & optimisations.

Typical Experimental Procedures in Fixed-Bed Mode (*SPE or Flash cartridges*)

Fixed-bed formats are a great alternative for metal or organic removal and are directly scalable.

We suggest initial screening investigations to be done using Silia*Prep* 2 g / 6 mL SPE cartridges.

Typical Experimental Procecures	
STEP	**Description**
1	Condition the cartridge with 3 - 4 column volumes using the same solvent as the solution to be treated.
2	Add the solution containing the API and the metal or organic impurity to the top of the cartridge and let it pass through the cartridge under gravity. ***Note***: if needed, a slight positive pressure on the top of the cartridge or a light vacuum at the bottom can be applied to speed up the flow rate.
3	For most Silia*MetS* metal scavengers, a dark colored band will be observed on the top of the silica bed (*right*). ***Note****: if the residual solution is still colored, multiple passes through the same cartridge can be done.*
4	Once the scavenging is completed, wash the cartridge using at least three column volumes of solvent to ensure total API recovery.



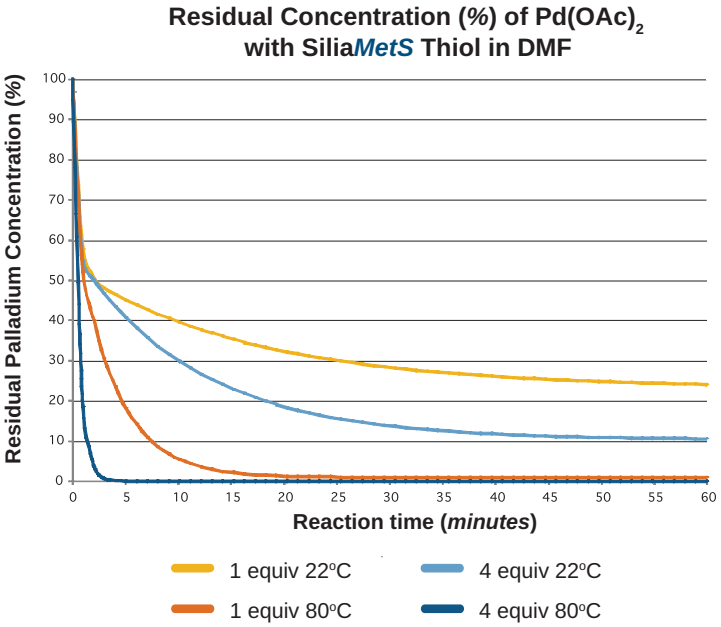
Experimental Optimization for Scavengers

If the scavenging is incomplete or if you wish to optimize the reaction, you can try the steps below. Various parameters can be changed one at a time or simultaneously to improve removal efficiency.

***Note**: you can mix multiple scavengers to get superior efficiency for example when multiple species are suspected or when there's more than one catalyst present.*

Number of Silia*MetS* or Silia*Bond* Equivalents

For initial screening experiments we suggest using 4 - 8 molar equivalents for Silia*MetS* and 2 - 4 molar equivalents for Silia*Bond* relative to the residual impurities concentration. Once the preferred scavenger is identified, further optimization can be done to reduce the number of equivalents used (*typically down to 2 - 4 equivalents, although some cases might require a higher ratio*).



Subsequent Treatments

In some cases (*equilibrium process or the presence of multiple species*), multiple treatments with our scavengers are desirable over a single treatment with a larger amount.

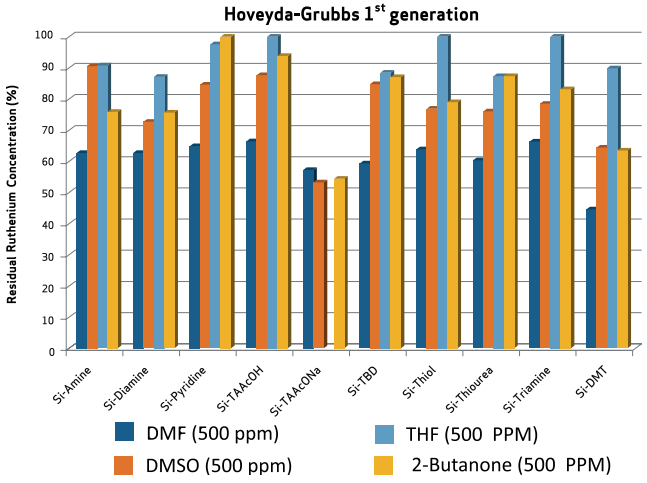
For optimal results, filtration between each treatment can enable higher scavenging efficiency.

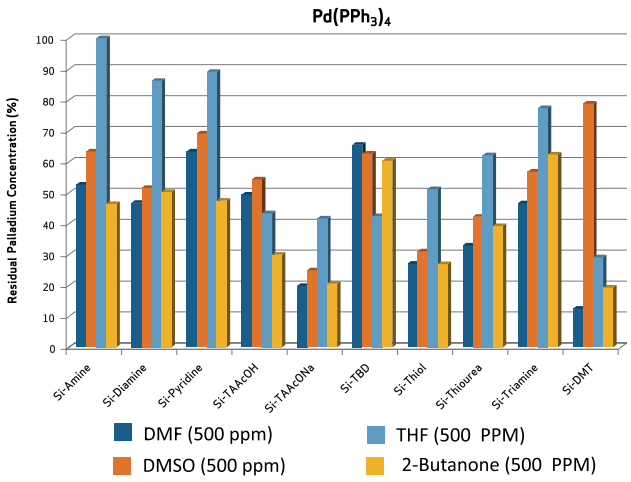
Temperature

In initial screening, we suggest the scavenging experiments be run at room temperature. Usually, scavenging is completed after one to four hours. However, when shorter scavenging times are required, higher scavenging rates can be achieved by increasing the temperature. Silia*MetS* and Silia*Bond* can be safely used at elevated temperature without degradation and can be added either at room temperature or directly to a warm solution.

Solvent

Silia*MetS* and Silia*Bond* can safely be used in a wide range of organic and aqueous solvents commonly used in laboratory and in process, such as DMF, DMSO, THF, 2-butanone, alcohols, ethers, chlorinated solvent, etc. As demonstrated in figures below, the nature of the solvent does sometimes influence scavenging efficiency. If scavenging or kinetics are too slow, changing solvent or adding a co-solvent should be considered.





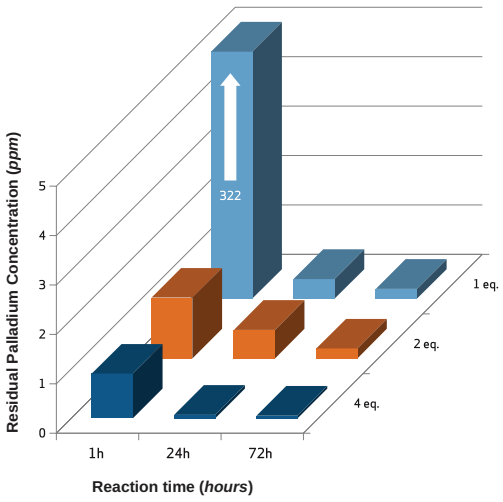
Mixing Rate

Our scavengers are mechanically stable and offer excellent scavenging efficiency in batch processes agitated by overhead stirrers as well as orbital shaking under low to moderate agitation rates.

If required, mixing rates can be increased to get better scavenging results. With faster stirring, scavenger dispersion in solution is improved.

Reaction Time

In some cases, where increasing the temperature is impossible, longer contact time with the scavenger can allow higher scavenging efficiency.



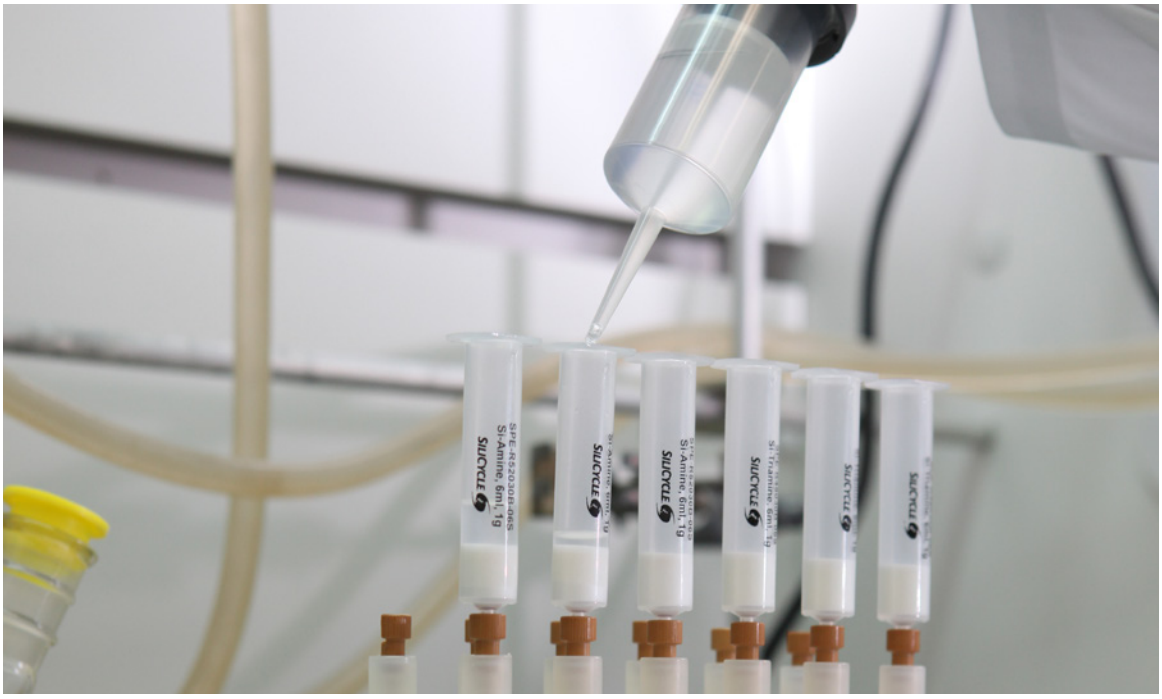
Conditions: $Pd(OAc)_2$, THF, Silia*MetS* Thiol, r.t.
Initial concentration: 1,000 ppm

pH of the Aqueous Solution

When the scavenging is done in aqueous solutions, it is possible to use our scavengers in a pH range of 2 to 12. Depending on the nature of the scavenging agent, pH can modify the functional groups present on the scavengers by charging them, scavenging might be affected (*e.g.: amine groups in acidic conditions*).

Silia*MetS* or Silia*Bond* Format (*Mode Used*)

One advantage of our scavengers is their compatibility with various technologies. They can be used in batch, in fixed-bed (*SPE or Flash cartridges*), in flow chemistry or in microwave. Scavenging efficiency can be improved by changing the mode used.



Determining the Optimal Amount of Scavenger to be Used

From Residual Metal Concentration

Example: knowing that the palladium (*Pd*) concentration in 800 g of material is 500 ppm (*the oxidation state does not affect the calculation*).

Data needed:

- Loading of the scavenger: e.g.: Silia*MetS* Thiol = 1.2 mmol/g
- Metal molecular weight: e.g.: Pd = 106.42 g/mol
- Amount of product to be treated: e.g.: 800 g
- Residual concentration of metal: e.g.: 500 ppm of Pd

1. Determine the amount of palladium to be scavenged

$$\text{Amount of Pd in mg} = \frac{\text{Residual metal concentration x Qty of product to be treated}}{1{,}000}$$

$$\text{Amount of Pd in mg} = \frac{500 \text{ ppm x } 800 \text{ g of product}}{1{,}000} = 400 \text{ mg of Pd in 800 g of product}$$

$$\text{Conversion in mmol of Pd} = \frac{\text{Amount of Pd in mg}}{\text{Metal molecular weight}}$$

$$\text{Conversion in mmol of Pd} = \frac{400 \text{ mg}}{106.42 \text{ g/mol}} = 3.76 \text{ mmol of Pd}$$

2. Calculate the amount of scavenger (*SiliaMetS Thiol*) to use (*1 equivalent*)

$$\text{Amount of Silia}\textit{MetS}\text{ Thiol to use} = \frac{\text{Number of mmol of metal concentration}}{\text{Silia}\textit{MetS}\text{ Thiol loading}}$$

$$\text{Amount of Silia}\textit{MetS}\text{ Thiol to use} = \frac{3.76 \text{ mmol of Pd}}{1.2 \text{ mmol/g}} = 3.13 \text{ g of Silia}\textit{MetS}\text{ Thiol for 1 equiv}$$

To scavenge 400 mg of palladium, 3.13 g of Silia*MetS* Thiol are needed if using only one equivalent. However, it is highly recommended that a minimum of four equivalents be used at first. In this case, the amount of Silia*MetS* Thiol will be four times higher (*4 x 3.13 g = 12.52 g*).

Sometimes, the metal residual concentration is unknown. In such case, the amount (*g*) of palladium to be scavenged can be replaced by the amount of metal catalyst used for the reaction.

If you have any doubt, please go to our online calculator to have all the work automatically done for you !
http://www.silicycle.com/web-tools/scavengers-calculator

From Amount of Metal Catalyst Used

Data needed:

Amount of metal catalyst used: e.g.: 10 g of $Pd(PPh_3)_4$

Metal catalyst molecular weight: $Pd(PPh_3)_4$ = 1,155.56 g/mol

Determine the amount of palladium to be scavenged

$$\text{Amount of Pd in mmol} = \frac{\text{Qty of catalyst used for the reaction x 1,000}}{\text{Metal catalyst molecular weight}}$$

$$\text{Amount of Pd in mmol} = \frac{10 \text{ g of } Pd(PPh_3)_4 \text{ x } 1{,}000}{1{,}155.56 \text{ g/mol}} = 8.65 \text{ mmol of Pd (}\textit{max to be scavenged}\text{)}$$

The amount of Silia*MetS* Thiol to be used can then be determined as stated above (*see point 2. above*). In this particular case, one equivalent of Silia*MetS* Thiol corresponds to 7.20 g.

From Residual Organic Residue Concentration

Data needed:

Loading of organic scavenger: e.g.: Silia*Bond* Guanidine = 0.74 mmol/g

Estimated amount of impurity to be removed (*in mmol*): e.g.: 5 mmol

Calculate the amount of scavenger (*SiliaBond Guanidine*) to use (*1 equivalent*)

$$\text{Amount of Silia}\textit{Bond}\text{ Guanidine to use} = \frac{\text{Number of mmol of impurity}}{\text{Silia}\textit{Bond}\text{ Guanidine loading}}$$

$$\text{Amount of Silia}\textit{Bond}\text{ Guanidine to use} = \frac{5\text{ mmol}}{0.74\text{ mmol/g}} = 6.76\text{ g of Silia}\textit{Bond}\text{ Guanidine for 1 equiv}$$

To scavenge 5 mmol of impurity, 6.76 g of Silia*Bond* Guanidine are needed if using only one equivalent. However, keep in mind that it is highly recommended that a minimum of two equivalents be used at first.

In this case, the amount (*g*) of Silia*Bond* Guanidine will be two times higher (*2 x 6.76 g = 13.52 g*).

Silia*MetS* / Silia*Bond* Stability & Leaching Studies

Because our Metal and Organic Scavengers are being used by many pharmaceutical companies, each Silia*MetS* and Silia*Bond* manufactured by SiliCycle is submitted to an extensive washing procedure to ensure the product exhibits extremely low levels of extractables and leachables.

SiliCycle has implemented a quality control procedure that includes loading and reactivity determination, as well as leachables and extractables analysis. The solution must be free of contaminants for the product to successfully pass the rigorous quality control tests.

Chemical Resistance In Acidic Medium

Silia*MetS* Thiol (*0.4 g*) was added to several acidic solutions for chemical resistance testing (*4 mL*). Methanol (*0.4 mL*) was added to each vial in order to ensure the silica was well impregnated with the aqueous medium. The solution was stirred mechanically for 1 to 16 hours at 22°C, and 1 hour at 60°C. Si-Thiol was then filtered and rinsed thoroughly with water and methanol, dried and subjected to CNS analysis.

Chemical Resistance of Silia*MetS* Thiol in Acidic Media

Experimental Conditions	1 M, 1h 22°C	5 M, 1h 22°C	5 M, 16h 22°C	5 M, 1h 60°C	5 M, 16h 60°C
H_3PO_4 (*phosphoric acid*)					
H_2SO_4 (*sulfuric acid*)					
HCl (*hydrochloric acid*)				[1]	
HNO_3 (*nitric acid*)					
AcOH (*acetic acid*)					
TFA (*trifluoroacetic acid*)					
HCO_2H (*formic acid*)	N/A	N/A			

[1]: reaction was stirred at 40°C.

Chemical Resistance In Basic Medium

Silia*MetS* Thiol (*0.4 g*) was added to several basic media in water, methanol or dichloromethane (*4 mL*). In the case where water was the solvent, methanol (*0.4 mL*) was added to each vial in order to ensure the silica was well impregnated with the aqueous medium. The solution was stirred mechanically for 1 to 16 hours at 22°C. Si-Thiol was then filtered and rinsed thoroughly with water and methanol, dried and subjected to CNS analysis.

Chemical Resistance of Silia*MetS* Thiol in Basic Media

Experimental Conditions	1 M, 1h, 22°C *in protic solvent (water)*	5 M, 1h, 22°C *in protic solvent (water)*	5 M, 16h, 22°C *in protic solvent (methanol)*	5 M, 1h, 22°C *in aprotic solvent (dichloromethane)*
NaOH (*sodium hydroxide*)			N/A	
NH_4OH (*ammonium hydroxide*)				
Na_2CO_3 (*sodium carbonate*)				
$NaHCO_3$ (*sodium bicarbonate*)				
TEA (*triethylamine*)				
DEA (*diethanolamine*)				
Pyridine				
NH_3 (*ammonia*)	N/A			

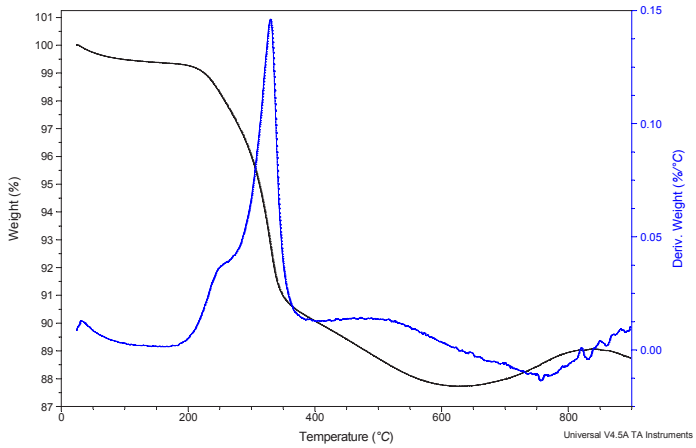
No Significant Change (*0 - 0.7 % difference*)
Light Loss (*0.8 - 1.0 % difference*)
Fair Loss (*1.0 - 1.5 % difference*)
Substantial Loss (*> 1.5 % difference*)
Silica was dissolved

No change in color was observed in the supernatant after filtration and washing steps.
Silia*MetS* Thiol is resistant to most basic and acidic conditions.

Thermal Stability

Thermogravimetric analysis, or TGA, is our method to determine any mass loss on Si-Thiol due to decomposition, oxidation, or loss of volatiles (*such as moisture*).
Based on TGA Analysis, Silia*MetS* Thiol is considered to be stable up to 220°C, but we suggest not to go over 150°C.

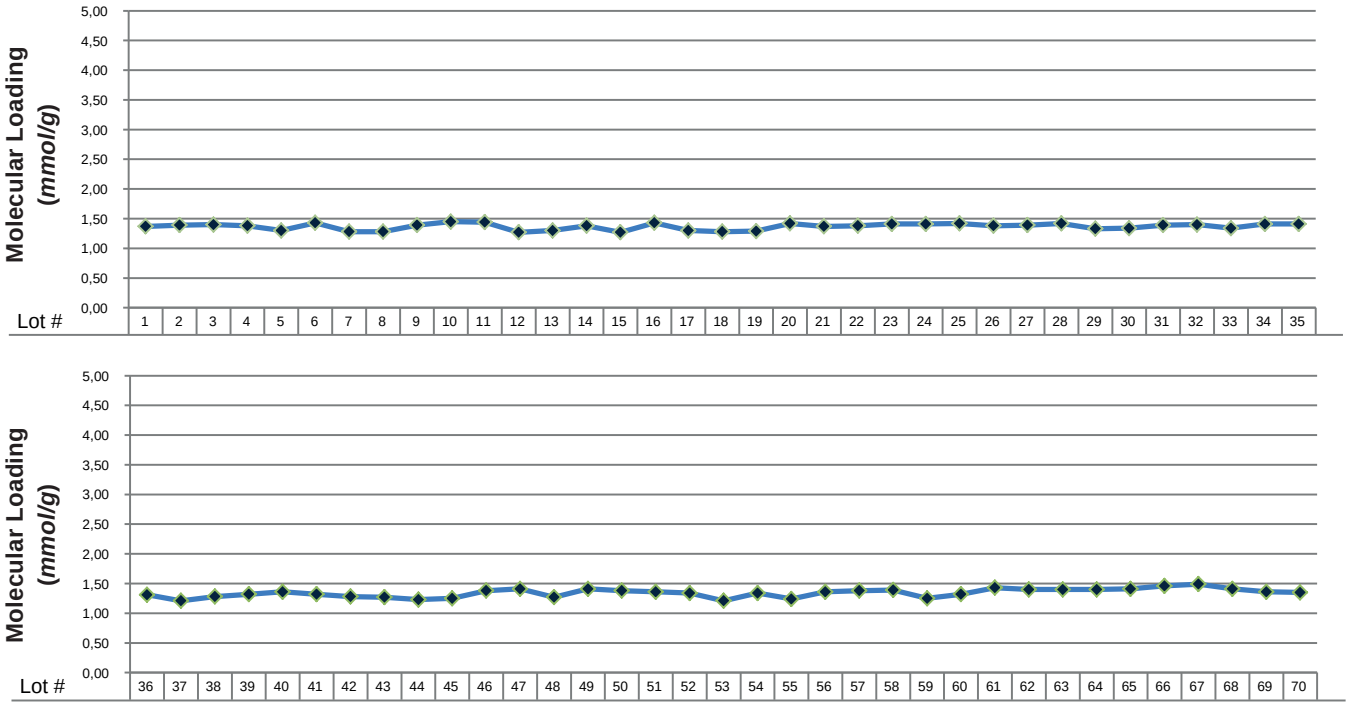
Zoom on important mass loss
(*TGA from 0 - 400°C*)



Silia*MetS* Thiol Batch History - Lot-to-lot Reproducibility

The manufacture of functionalized silica gels is both a complex and controlled process. SiliCycle maintains extensive records of each batch manufactured, and retains these for a minimum of 7 years. Such records contain the production history of finished and released products. They provide objective evidence that the functionalized gels were manufactured in accordance to our quality standards and minimal requirements, and act as a record of traceability information for all units or lots.

SiliCycle's loadings of functionalized gels are always extremely constant from batch-to-batch. As an example, here is an overview of lot-to-lot reproducibility over seventy consecutive lots of Silia*MetS* Thiol of same batch size manufactured.



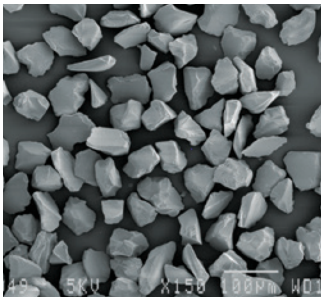
Scavenging Solutions

Mechanical Stability

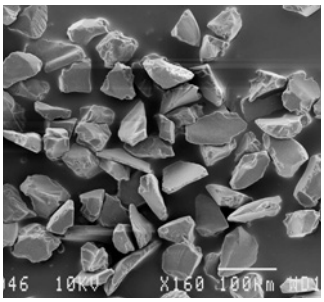
The mechanical resistance of silica gel is roughly 10,000 psi. This value depends on pore diameter and particle size.

In the following experiment, a comparison of mechanical resistance between silica gel and polymer was conducted:

SEM of Silia*MetS* Thiol

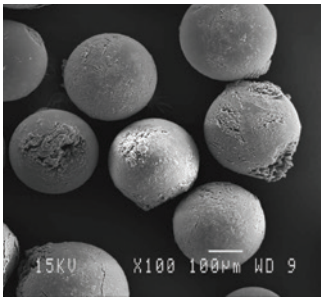


After 4 hours
under mechanical stirring

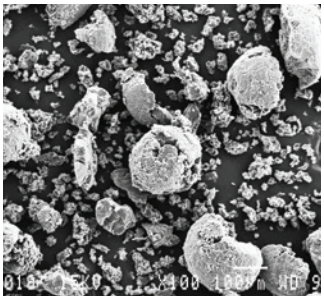


After 16 hours
under mechanical stirring

SEM of Polymer-Support



After 4 hours
under mechanical stirring

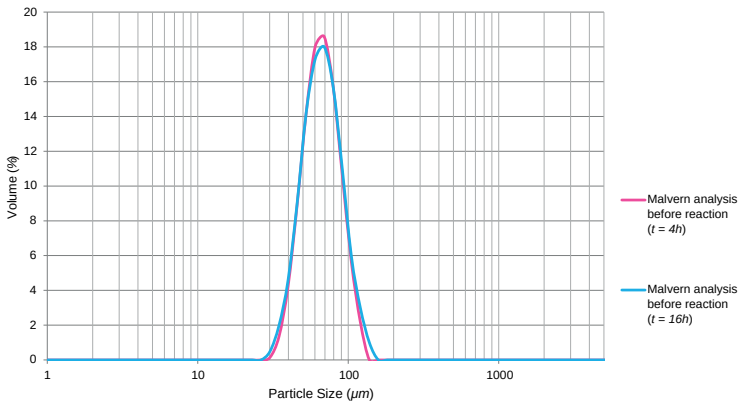


After 16 hours
under mechanical stirring

- Stirring speed: 500 RPM
- Solvent: DMF
- Temperature: 22°C

After 16 hours, there was hardly no difference in the silica particles on which our scavengers are functionalized. In comparison, the polymer support was completely destroyed.

SEM & Malvern Analysis are a safe and clear demonstration that almost no mechanical grinding nor crushing of the silica occurs after stirring, which is not the case for polymeric support, for which drastic grinding appears.



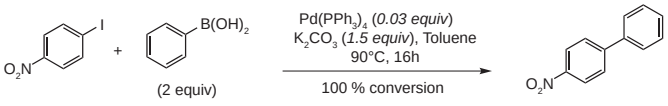
Mechanical Stirrer in Reactor

This picture was taken in one of SiliCycle's medium-sized reactors.

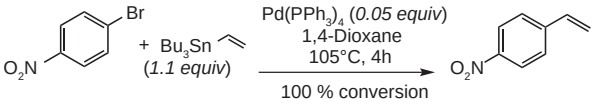
Silia*MetS* Thiol has been produced for more than 20 years in SiliCycle's reactors without any damage.

Leaching and Extractable Studies

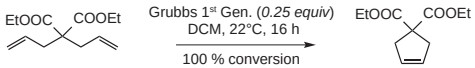
To address the concerns for potential leaching of impurities into reaction mixtures using Silia*MetS* Thiol & DMT, four typical metal-containing reactions were performed. Detection, identification and quantification of possible impurities resulting from the scavenging action was then performed.



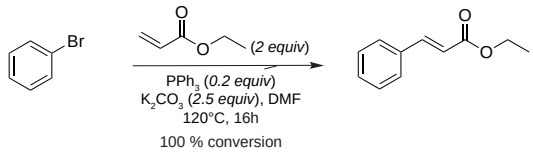
Suzuki Coupling



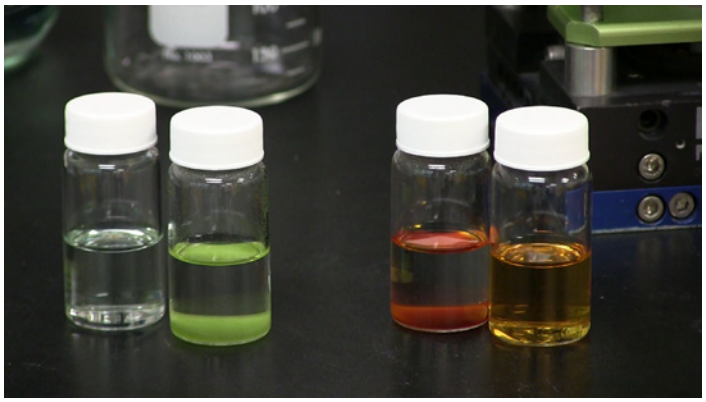
Stille Coupling



Grubbs Ring-Closing Metathesis



Heck Coupling



Experimental Procedure

Crude reaction mixtures (*8 mL*) were placed in a standard polypropylene tube equipped with a 20 µm frit, loaded with 1 g of the appropriate Silia*MetS* Metal Scavenger, and mixed for 4 h at either room temperature or 80°C. Solutions were then filtered through a 0.2 µm filter prior to analysis.

Leaching Analysis

Silane leaching was analyzed by Inductively-Coupled Plasma-Optical Emission Spectroscopy (*ICP-OES*) which has proven to be very sensitive for silicon quantification (*detection limit in solution is 0.125 ppm*).

Traces of non-silicon containing impurities were also analyzed by Gas Chromatography-Mass Spectrometry (*GC-MS*), Liquid chromatography-tandem mass spectrometry (*LC-MS*) and ^{1}H NMR Analysis.

Gel Purity Calculation

Here is an example of how gel purity can be calculated:

$$\text{Impurity \%} = \frac{\text{2 mg of silicon x 100}}{\text{1,000,000 mg of Silia}\textit{MetS}} \Rightarrow \text{0.0002 \% impurity}$$

Gel purity = 100 - (*Impurity %*) => 99.9998 % purity

Silane Leaching Analysis by ICP-OES

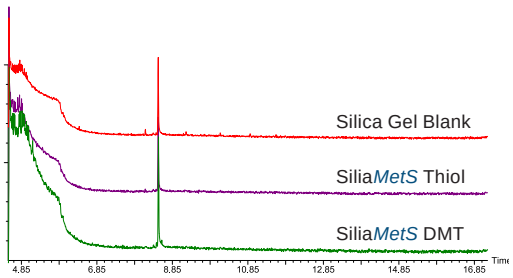
Results shown in the table below for Silia*MetS* Thiol & DMT confirm that minimal leaching occurs with SiliCycle Silia*MetS*.

Stability of Silia*MetS* in Suzuki, Stille, Heck and Grubbs Ring-Closing Metathesis Reactions

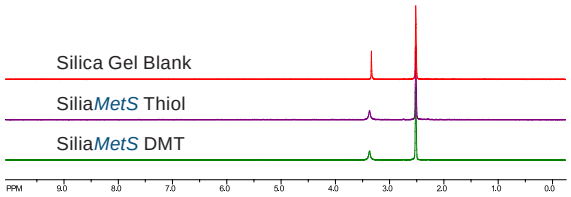
Reaction (*solvent*)	Temperature	Silia*MetS* Thiol		Silia*MetS* DMT	
		[*Silicon*]	Gel Purity (%)	[*Silicon*]	Gel Purity (%)
Suzuki (*Toluene*)	22°C	2 ppm	99.9998	1 ppm	99.9999
	80°C	2 ppm	99.9998	2 ppm	99.9998
Stille (*1,4-Dioxane*)	22°C	2 ppm	99.9998	1 ppm	99.9999
	80°C	1 ppm	99.9999	3 ppm	99.9997
Heck (*DMF*)	22°C	2 ppm	99.9998	1 ppm	99.9999
	80°C	1 ppm	99.9999	2 ppm	99.9998
Grubbs Ring-Closing Met. (*DCM*)	22°C	2 ppm	99.9998	2 ppm	99.9998

Non-Silicon Leaching Analysis

Each experiment was run on a 1 g aliquote of Silia*MetS* and was shaken for 1 hour at room temperature. Leaching examination was performed through both GC-MS and ^{1}H NMR analysis, comparing leaching profiles of bare silica, Silia*MetS* Thiol and Silia*MetS* DMT.



Gas Chromatography-Mass Spectrometry (*GC-MS*)



^{1}H NMR Analysis (d_6-*DMSO*)

Compared to the silica blank spectrum, neither experiment showed evidence of any impurities for either Silia*MetS* Thiol or DMT.

***Note**: in GC-MS spectrum, peak at 8.5 minutes is the internal standard (1-fluoronaphthalene, 100 ppm). In NMR spectrum, peaks at 2.4 and 3.4 ppm are, respectively, d_6-DMSO and water contained in deuterated solvent.*

Stability Study (*Shelf Life*)

SiliCycle certifies that Silia*MetS* Metal Scavengers stored under recommended conditions in an undamaged container are guaranteed to perform for two years from the manufacturing date without significant loss of performance.

Silia*MetS* Thiol after Two Years		
Lot #	**QC Date**	**Scavenging (%)**
11577	Year 0	> 99.9
	Year 1	99.5
	Year 2	99.6
12218	Year 0	99.9
	Year 1	99.5
	Year 2	99.1
64215	Year 0	99.2
	Year 1	99.3
	Year 2	99.5

Scavenging: 1,000 ppm of $Pd(OAc)_2$ in DMF.
Conditions: 2 equiv of Silia*MetS* Thiol, 1 h, 22°C.

Application Notes and Case Studies

We have selected a few applications to help understanding how our functionalized silicas can be introduced in your daily synthetic strategies.

Application Notes

You can skim read through our “Application Notes” section to learn more about different applications that were developed in our labs, but don’t take our word for granted and check out customers Case Studies.

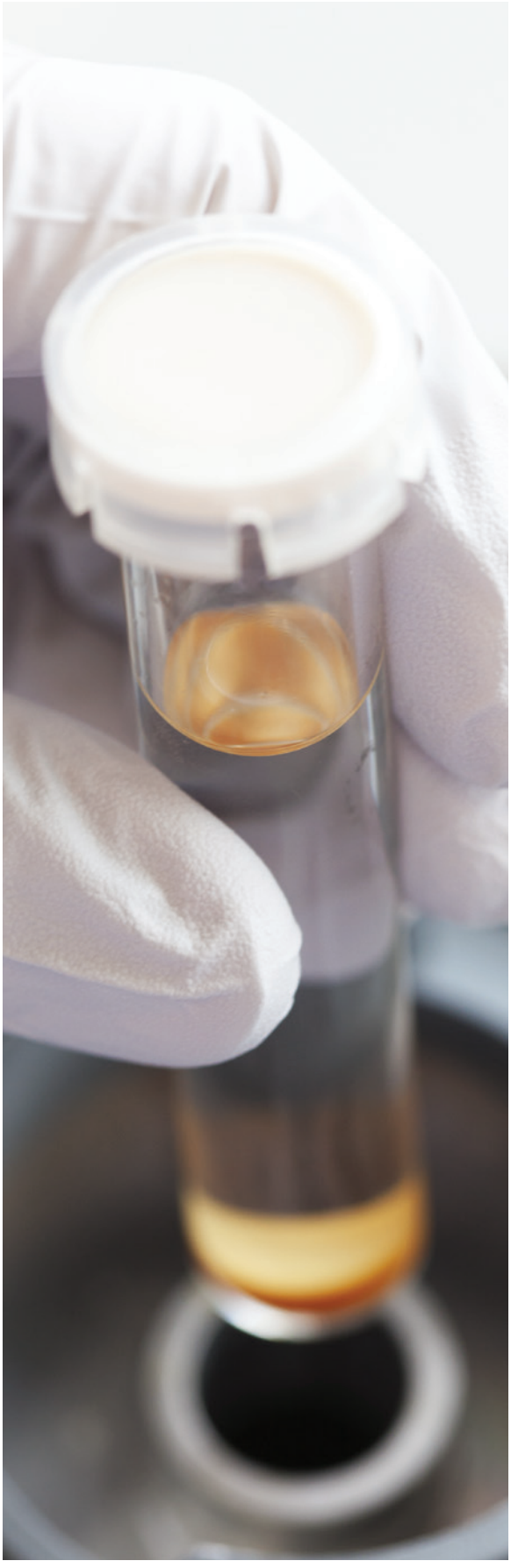
In the following section, application notes are identified by this logo:

Case Studies

Discover and learn what some of our customers are doing with our technology in the “Case Studies” section.

In the following section, customer case studies are identified by this logo:

Nothing speaks more than lab examples and real-life experiences!



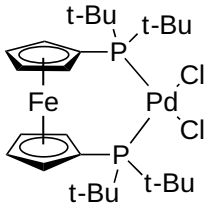
Silia*MetS* Metal Scavengers Application Examples & Case Studies

Scavenging of Pd-118 Using Silia*MetS* Metal Scavengers

(*More experimental details avalaible in Application Note #AN-001. Please check our Website*)

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

Pd-118, or Pd(d*t*bpf)Cl_2 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 our Silia*MetS* Metal Scavengers Toward this Specific Complex (*catalyst only in solvent*)

Scavengers	Scavenging Efficiency of Preliminary Screening (*in %*)									
	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
Silia*MetS* DMT	76	45	**97**	51	85	63	**97**	47	**96**	83
Silia*MetS* Diamine	76	27	54	18	51	25	80	0	38	29
Silia*MetS* Thiol	51	28	72	34	50	50	88	64	36	48
Silia*MetS* Cysteine	59	49	67	49	70	60	**93**	52	53	50
Silia*MetS* Tosic Acid	25	47	8	54	70	69	85	**83**	80	**78**

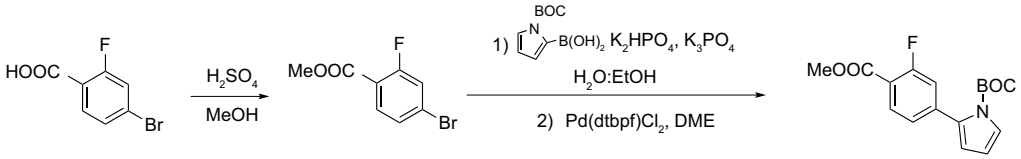
Conditions: Palladium complex solutions were made in DMF, methyl-THF and dichloromethane, and shaken with four molar equivalents of metal scavengers for four hours, at room temperature or 60°C.

Scavenging Conclusion

Silia*MetS* DMT and Cysteine proved to be the preferred scavengers for Palladium (*Pd*) in this application. As for Iron (*Fe*), Silia*Bond* Tosic Acid (*SCX*) was the best scavenger. Furthermore, very good removal of both metals could be achieved through a combination of scavengers.

Scavenging of Pd(d*t*bpf)Cl_2 in Suzuki Coupling for the Preparation of Arylpyrrolidines

Abbott Laboratories has recently used Pd(d*t*bpf)Cl_2 for the preparation of arylpyrrolidines resulting in a final mixture contaminated with Pd and Fe.



SiliCycle 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

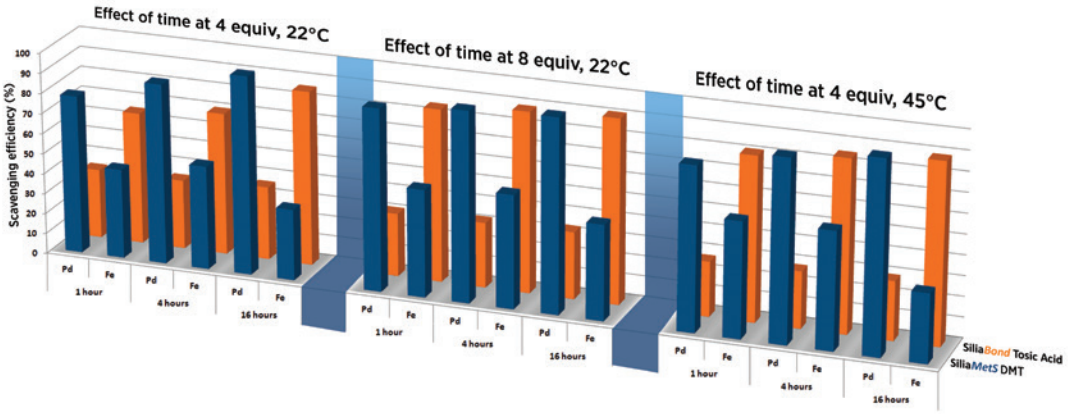
Effect of Time in the Scavenging Efficiency with 4 equiv at 22°C (*in %*)						
Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* DMT	78	44	**89**	51	**98**	35
Silia*Bond* Tosic Acid	34	65	34	70	36	**86**

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
Silia*MetS* DMT	**90**	53	**94**	56	**96**	47
Silia*Bond* Tosic Acid	31	**85**	32	**89**	33	**91**

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

Scavenging Conclusion

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

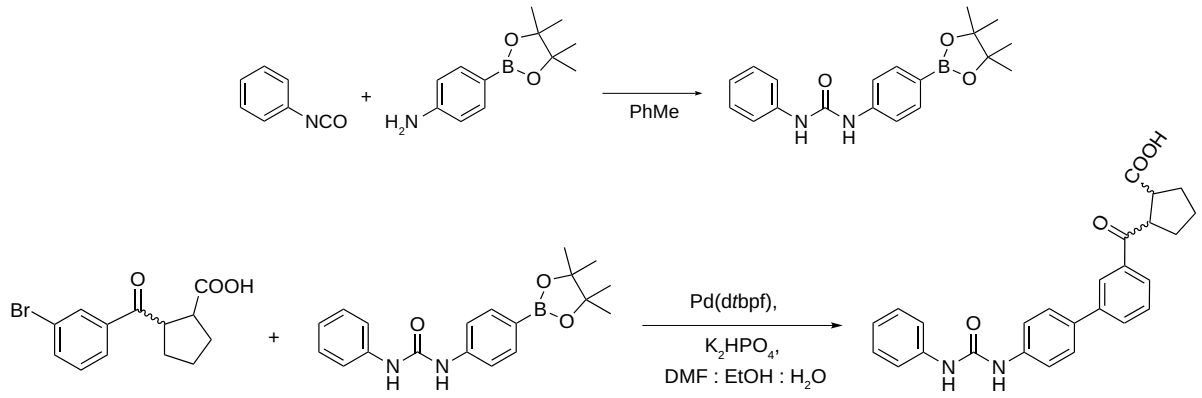


M. Ravn *et al.*, *Org. Proc. Res. Dev.*, **2010**, *14*, 417-424
D. Barnes *et al.*, *Org. Proc. Res. Dev.*, **2009**, *13*, 225-229
Abbott Laboratories, North Chicago, Illinois, United States

Scavenging of Pd(d*t*bpf)Cl_2 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 Equivalents at 22°C (*in %*)

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

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

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* Thiol	69	12	**86**	37	**96**	69
Silia*Bond* Tosic Acid	24	**91**	33	**91**	17	**92**

Effect of Time in the Scavenging Efficiency with 4 Equivalents at 45°C (*in %*)
Treatment with 2 Scavengers Simultaneously: Silia*MetS* Thiol & Silia*Bond* Tosic Acid

Scavengers / Conditions	1 h		4 h		16 h	
	Pd	Fe	Pd	Fe	Pd	Fe
Silia*MetS* Thiol & Silia*Bond* Tosic Acid	78	81	91	81	**96**	81

Conclusion

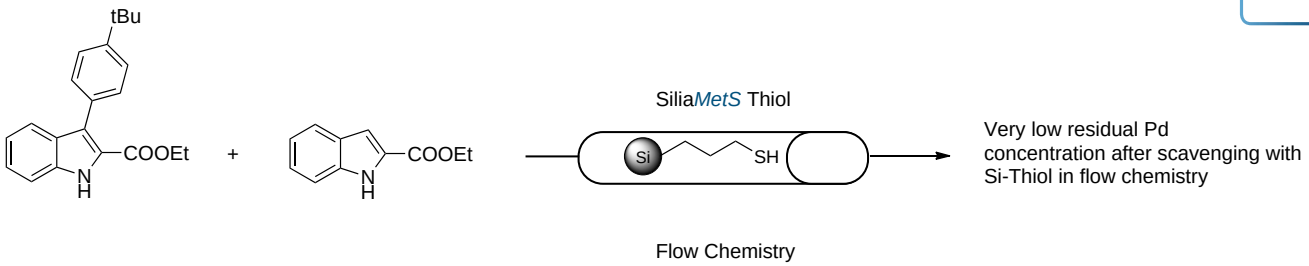
In this case again, it was Silia*MetS* Thiol that proved to be the preferred scavenger for palladium under any conditions. As for iron, Silia*Bond* Tosic Acid was, again and by far, the most effective.

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

Metal Scavenging in Flow Chemistry (*Preliminary Results in Suzuki Coupling Reaction*)

Silia*MetS* Metal Scavengers can also be used in flow chemistry. A crude reaction mixture purified using a Syrris ASIA® Flow Chemistry System is presented in the table below.



Silia*MetS* Thiol Scavenging Results in Flow Chemistry

Flow Rate	Solution Volume	Contact Time with Silia*MetS* Thiol	Time Needed to Treat the Solution	Scavenging Results (*in* %)
1.50 mL/min	100 mL	16 min	1h10	94
1.00 mL/min		24 min	1h40	94
0.75 mL/min	50 mL	32 min	1h10	94
0.50 mL/min		48 min	1h40	**95**

Initial Pd Concentration: 547 ppm in EtOAc

Experimental Conditions:

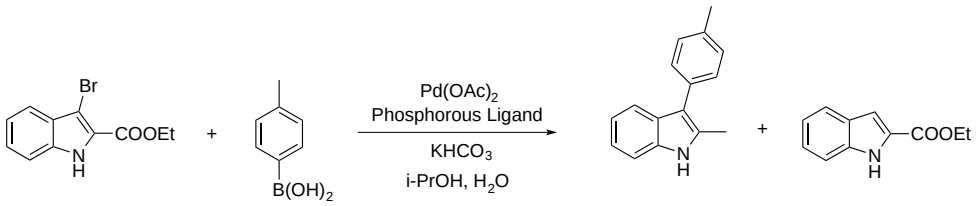
Scavenger Used: Silia*MetS* Thiol
Palladium Complex $Pd(OAc)_2/P(o\text{-}Tolyl)_3$ homogeneous catalyst
Nb. Equivalent: 13.5 equiv
Reactors: 2 x 12 mL Reactors in Series
Total Solution Volume: 50 or 100 mL
Purification Scale: 12.5 g
Temperature: 22°C

Conclusion

Although top scavenging result reached 95 % at a flow rate of 0.50 mL/min (*using a solution volume of 50 mL and with a contact time of 48 min*, *1h40 of treatment*), all flow conditions appeared to yield excellent level of scavenging.

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 ligands. For comparison purposes, scavenging screening was done by using the same two sets of conditions. No optimization was done to increase Silia*MetS* performance. By experience, using longer reaction times or higher temperatures will allow for better results.



Silia*MetS* Scavenging Results with Monodentate Ligands (*in* %) with 4 equiv, 4 h

Silia*MetS*	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
Silia*MetS* Thiol	70	**97**	87	**96**	26	85
Silia*MetS* Thiourea	55	86	54	82	18	41
Silia*MetS* Cysteine	69	76	77	**90**	17	44
Silia*MetS* DMT	**95**	**97**	**95**	**> 99**	36	87
Initial Pd Concentration:	27 ppm in EtOAc		84 ppm in EtOAc		90 ppm in EtOAc	

Silia*MetS* Scavenging Results with Bidentate Ligands (*in* %) with 4 equiv, 4 h

Silia*MetS*	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
Silia*MetS* Thiol	50	69	75	**90**	31	56
Silia*MetS* Thiourea	3	23	40	60	33	21
Silia*MetS* Cysteine	29	36	47	55	19	29
Silia*MetS* 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, Silia*MetS* 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, more basic phosphine ligands. The best conditions were using 4 equiv for 4 h, at 60°C.

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 Silia*MetS* 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 Silia*MetS* *(in %)*

Silia*MetS*	Grubbs 1st Gen.		Grubbs 2nd Gen.		Hoveyda-Grubbs 1st Gen.		Hoveyda-Grubbs 2nd Gen.	
	Toluene[1]	DMF[2]	Toluene[1]	DMF[2]	Toluene[1]	DMF[2]	Toluene[1]	DMF[2]
Silia*MetS* Thiol	90	**96**	-	**99**	**97**	93	-	-
Silia*MetS* Thiourea	-	**98**	-	**96**	**97**	**98**	-	-
Silia*MetS* DMT	**95**	**99**	**> 99**	**99**	**> 99**	**98**	**98**	**99**
Silia*Bond* Amine	**95**	**97**	92	-	-	-	-	-
Silia*MetS* Diamine	**99**	**99**	91	94	**> 99**	**98**	-	90
Silia*MetS* Triamine	-	**95**	-	-	93	**95**	-	**95**
Silia*MetS* TAAcOH	93	-	-	-	-	-	-	-
Silia*MetS* TAAcONa	**96**	-	**96**	-	**98**	-	-	-

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

Experimental Conditions:

Nb. Equivalent: [1] 8 equiv of Silia*MetS*, 16 h, 80°C
[2] 4 equiv of Silia*MetS*, 16 h, 80°C

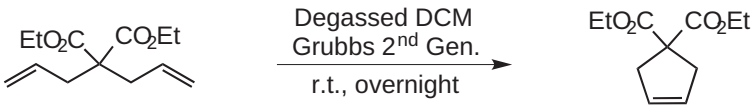
Initial Concentration: 500 ppm for all ruthenium-based catalysts.

Conclusion

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

Silia*MetS* vs Other Purification Methods

The use of Silia*MetS* 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.



quantitative yield

Scavenging Results for Various Purification Methods* (*in %*)						
Scavenging	Scavenger	Filtration over packed bed of ...[2]			Flash Purification	
	Silia*MetS* DMT[1]	Act. Carbon	Celite	Silica	Manual	Silia*Sep* Cart.
Ruthenium captation	**93**	73	24	58	70	73

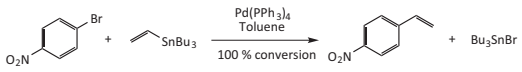
[1] Using 4 equiv, 16 h, 22°C. [2] Solution is passed directly on a packed bed of various adsorbents, which was then washed with the same quantity of solvent.

*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*).

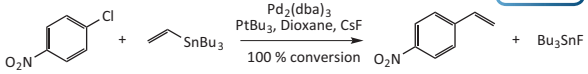
Tin Scavenging Using Silia*MetS* Cysteine & TAAcONa

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 particular compounds.

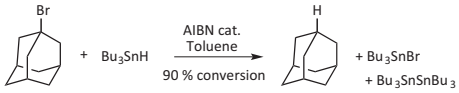
Both Silia*MetS* Cysteine & TAAcONa can be used to efficiently remove tin residues from organic mixtures, as demonstrated by the examples below.



Stille Coupling #1



Stille Coupling #2



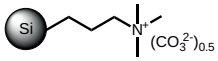
Radical Reduction

Tin Scavenging using Silia*MetS* Cysteine & TAAcONa (*in %*)						
Reactions	Initial Concentration	Silia*MetS* Cysteine		Silia*MetS* 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

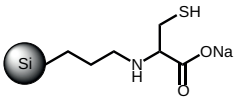
[1] Pd residues were completely removed after only one treatment with Silia*MetS* Cysteine.

Comparison of Tin Scavenging Using Silia*Bond* Carbonate vs Silia*MetS* Cysteine

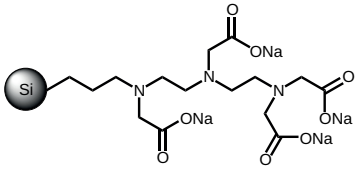
SiliCycle also provides a quaternary ammonium salt grafted on silica to which a carbonate group is ionically bounded. The latter has shown to be an excellent alternative for tin retrieval from organic mixtures.



Silia*Bond* Carbonate



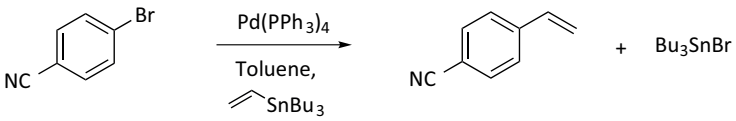
Silia*MetS* Cysteine



Silia*MetS* TAAcONa

Stille Reaction

Tin scavenging was demonstrated on a Stille coupling in which Bu_3SnBr 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 %*)				
	4 h, 8 equiv, 22°C	4 h, 16 equiv, 22°C	16 h, 8 equiv, 80°C	4 h, 8 equiv, 22°C [*2 treatments*]
Silia*Bond* Carbonate	91	**99**	**96**	**99**
Silia*MetS* Cysteine	77	**99**	84	94

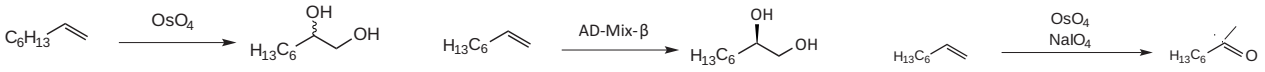
Conclusion

Scavenging yields were excellent with both scavengers. Hence, Silia*Bond* Carbonate was found to be of the same high efficiency as Silia*MetS* Cysteine to scavenge tin compounds of R_3SnX type.

Osmium Scavenging with Silia*MetS*

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 Silia*MetS* is highlighted in the following table.



Dihydroxylation Reaction
[OsO_4]

Sharpless Dihydroxylation
[*Potassium osmate* ($K_2OsO_2(OH)_4$)]

Lemieux-Johnson Oxidation
[$NaIO_4$, OsO_4]

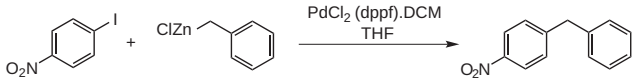
Osmium Scavenging using Silia*MetS* (*in %*) at 22°C					
Silia*MetS*	Dihydroxylation	Sharpless Dihydroxylation		Lemieux-Johnson Oxidation	
	4 equiv, 4 h	8 equiv, 4 h	8 equiv, 16 h	8 equiv, 4 h	8 equiv, 16 h
Silia*MetS* Thiol	87	**> 98**	**> 98**	87	92
Silia*MetS* Cysteine	89	**> 98**	**> 98**	87	91
Silia*MetS* DMT	92	**97**	**> 98**	87	91
Silia*MetS* 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, Silia*MetS* DMT was slightly more efficient.

Multiple Metal Scavenging

Silia*MetS* 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 Silia*MetS* can be used to simultaneously remove residual palladium, iron and zinc present after the reaction.

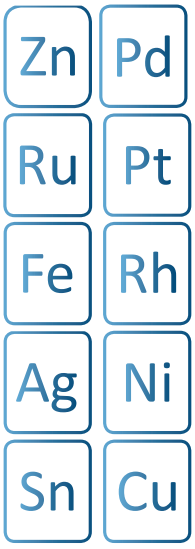
Multiple Removal Scavenging Results (*in %*)			
Silia*MetS*	Pd	Fe	Zn
Silia*MetS* Cysteine	**95**	**> 99**	**98**
Silia*MetS* DMT	83	93	**99**
Silia*MetS* Imidazole	84	91	**97**
Silia*MetS* TAAcONa	**97**	**> 99**	**> 99**
Initial Concentration (*in THF*)	188 ppm	110 ppm	6 ppm

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

For Zinc removal, all tested scavengers gave excellent results. Overall, for multiple removal scavenging results, Silia*MetS* Cysteine and TAacONa showed to be the most versatile scavengers.

Silia*MetS* in Aqueous Conditions

Along with growing importance of sustainable chemistry and catalysis, Silia*MetS* compatibility in aqueous conditions needed to be evaluated. As a preliminary exploration, palladium nitrate scavenging was tested at four (*4*) different pH in various acidic medias.



Scavenging (*in %*) of $Pd(NO_3)_2$ in Various Aqueous Conditions, 4 equiv at 22°C, 4 h				
Scavengers	**H_2SO_4 (*1 M*)**	**HNO_3 (*1 M*)**	**AcOH (*1 M*)**	**H_2O**
Silia*MetS* Cysteine	**> 99**	**> 99**	**> 99**	76
Silia*MetS* Diamine	43	23	**> 99**	5
Silia*MetS* DMT	**> 99**	**> 99**	**> 99**	15
Silia*MetS* Imidazole	**> 99**	**> 99**	**> 99**	36
Silia*MetS* TAAcOH	**98**	**98**	**98**	**98**
Silia*MetS* Thiol	**> 99**	**> 99**	**> 99**	77
Silia*MetS* Thiourea	**> 99**	**> 99**	**> 99**	35
Silia*Bond* Tosic Acid	19	6	76	28
Silia*MetS* Triamine	55	49	**96**	10

Experimental Conditions: an aqueous 250 ppm solution of $Pd(NO_3)_3$ 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.

In purely aqueous conditions, Silia*MetS* TAAcOH was the most compatible and efficient scavenger. However, in acidic conditions, apart from Silia*Bond* Tosic Acid, all scavengers showed good to excellent removal capability.

Scavenging activity can either be driven by H_3O^+ concentration (*pH*), or its counter-ion. Results illustrate well that the counter-anion (*and counter-cation*) plays a determinant role in the affinity of the resin toward palladium.

Other complexes were tested using the same method described as above for scavenging of $Pd(NO_3)_3$.

Various Metallic Complexes Scavenging (*in %*) & Concentrations in Aqueous Conditions, 4 Equiv at 22°C, 4 h					
Scavenger	**$RuCl_3$ [*150 ppm*]**	**K_3PtCl_6 [*250 ppm*]**	**$FeCl_3$ [*250 ppm*]**	**$RhCl_3$ [*250 ppm*]**	**$Pd(NO_3)_2$ [*250 ppm*]**
Silia*MetS* Cysteine	**94**	**96**	**> 99**	14	76
Silia*MetS* Diamine	11	71	25	94	5
Silia*MetS* DMT	0	**97**	6	68	15
Silia*MetS* Imidazole	0	91	6	59	36
Silia*MetS* TAAcOH	63	0	**> 99**	5	**98**
Silia*MetS* TAAcONa	47	87	**98**	7	77
Silia*MetS* Thiol	0	57	7	0	35
Silia*MetS* Thiourea	0	92	9	34	28
Silia*Bond* Tosic Acid	52	87	**> 99**	**98**	**99**
Silia*MetS* Triamine	14	61	13	92	10

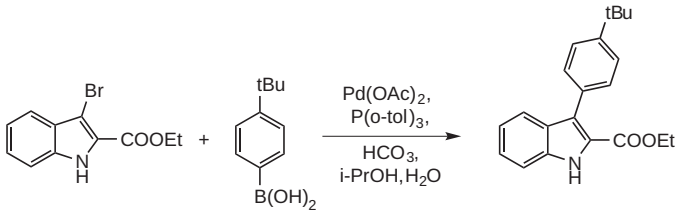
Various Metallic Complexes Scavenging (*in %*) & Concentrations in Aqueous Conditions, 4 Equiv at 22°C, 4 h					
Scavenger	$AgNO_3$ *[250 ppm]*	$Ni(NO_3)_2$ *[250 ppm]*	$Sn(OTf)_2$ *[250 ppm]*	$CuSO_4$ *[250 ppm]*	$ZnSO_4$ *[250 ppm]*
Silia*MetS* Cysteine	92	70	**97**	**97**	**98**
Silia*MetS* Diamine	74	43	47	93	58
Silia*MetS* DMT	**> 99**	40	60	86	51
Silia*MetS* Imidazole	90	25	39	64	39
Silia*MetS* TAAcOH	**> 99**	84	93	**99**	86
Silia*MetS* TAAcONa	**97**	**96**	73	94	**95**
Silia*MetS* Thiol	**96**	6	6	0	0
Silia*MetS* Thiourea	79	1	17	14	3
Silia*Bond* Tosic Acid	86	90	**95**	88	81
Silia*MetS* Triamine	76	33	58	44	58

Conclusion

Scavengers such as Silia*MetS* Cysteine and Silia*MetS* TAAcONa were shown to have very good scavenging efficiency in aqueous media. Silia*MetS* TAAcOH and Silia*Bond* Tosic Acid were also efficient. Generally speaking, many metal scavengers have demonstrated excellent performance in aqueous environment, even when bearing hydrophobic moieties.

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 Silia*MetS* in different formats, scavenging kinetics, intermediate recovery and purity.



Scavenging Efficiency, Recovery & Purity

Small-Scale Scavenging (*Synthesis Scale ~ 5 g*)

The table below shows the most efficient Silia*MetS* 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*).

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

Scavenging Conclusion

Addition of 5 equivalents of Silia*MetS* products for 4 hours 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 sequestrated by Silia*MetS* products. No impurities were released.

Larger Scale Scavenging (*Synthesis Scale ~ 55 g*)

Silia*MetS* Metal Scavengers in pre-packed Silia*Sep* 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.

Silia*Sep* Scavenging Results (*in %*)	
Run #	Scavenging
1	**97**
2	**99**
3	**> 99**

Initial Pd Concentration: 700 ppm in AcOEt

Experimental Conditions:

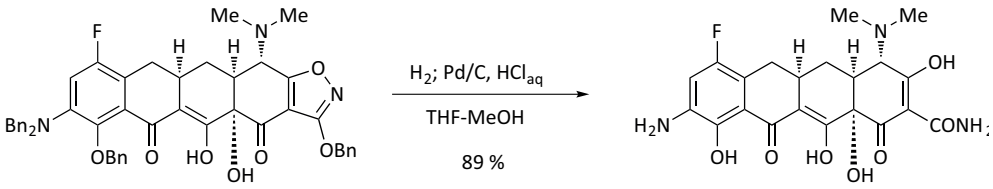
Scavenger Used: Silia*MetS* Thiol
Cartridge Size: 120 g
Nb. Equivalent: 25 equiv
Solution Volume: 1 L
Flow Rate: 40 mL/min

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

A Tetraphase Case Study: Palladium Scavenging in the Development of the First Fully Synthetic Fluorocycline Using Silia*MetS* 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.**

Silia*MetS* 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_2O (*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 % Silia*MetS* DMT in MeOH for 2 - 3 h, residual levels were consistently below 1.5 ppm.

Another strategy to avoid subsequent purification by Silia*MetS* DMT can be to use an heterogeneous palladium-based catalyst, namely Silia*Cat* DPP-Pd. See p. 18-19 for more information on our catalysts.

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

A Genentech Case Study: Palladium and Ruthenium Removal in the Synthesis of Akt Inhibitor Ipatasertib using Silia*MetS* Thiol (*Multi-kilogram Scale*)

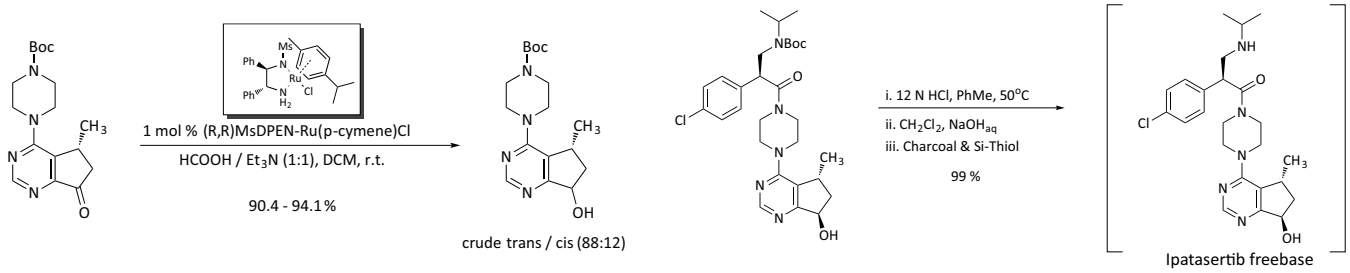
The first-generation process to manufacture Akt inhibitor Ipatasertib through a late-stage convergent coupling of two challenging chiral components on a multi-kilogram scale was reported by Array BioPharma.

A carbonylative esterification and subsequent Dieckmann cyclization sequence was developed to forge a cyclopentane ring in the target. A second key chiral component, a β^2-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.

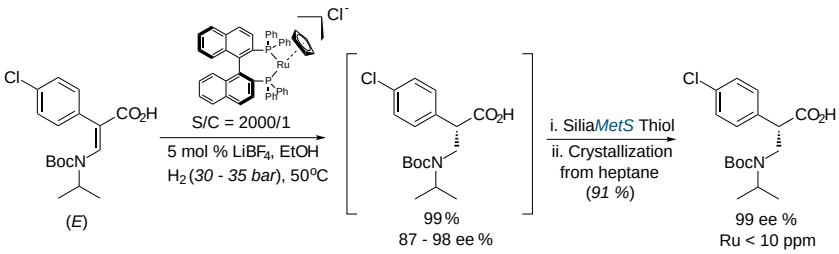
The aqueous layer was then basified to pH ≥ 12 with aqueous NaOH in order to extract the Ipatasertib free-base with DCM. The DCM solution was subsequently treated with charcoal and Silia*MetS* Thiol to remove colored impurities and trace heavy metals resulting from previous synthetic steps.

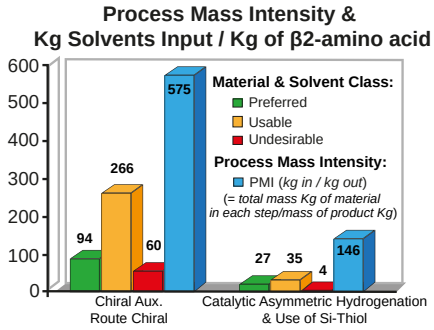
These metals consisted in Palladium (*Pd/C catalyst in a Noyori Asymetric Transfer Hydrogenation of ketone*), Ruthenium [*(R,R) MsDPEN-Ru(p-cymene)Cl) catalyst for asymmetric ketone reduction*] and Titanium ($TiCl_4$ *catalyst in asymmetric Aldol addition*).



In Akt inhibitor synthesis, Genentech describes a scalable catalytic asymmetric hydrogenation process for the multi-kilogram scale production of a β^2-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 Silia*MetS* 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*).

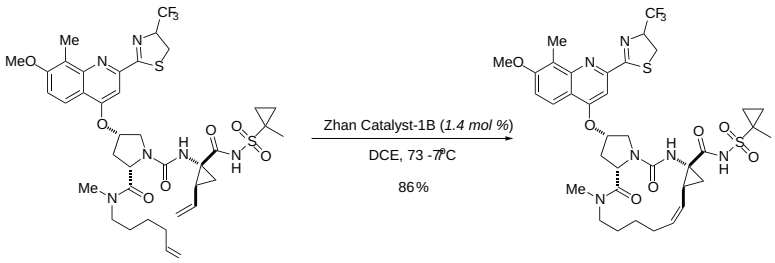
J. Lane, T. Remarchuk *et al.*, *Org. Proc. Res. Dev.*, **2014**, *18*, 1641-1651
Small Molecule Process Chemistry, Genentech, Inc., a member of the Roche Group, California, United States
Array BioPharma Inc., Colorado, United States

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 Idenix Case Study: Ruthenium Removal in the Macrocyclization of Dienyl-ureas Via RCM, using Silia*MetS* 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 dienyl-urea 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 mercaptonicotinic acid (*MNA*) and washing with aqueous $NaHCO_3$, and the use of supercritical fluid extraction. Resulting Ru levels of those methods vs Silia*MetS* 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 (*initial*)	-
		1st MeOH trituration	12	63
		2nd MeOH trituration	7.5	58
2	250 mL/g diene 4.9 mM 1.5 wt % catalyst	charcoal ; silica gel filtration	120 (*initial*)	-
		1st MeOH trituration	34	81
		2nd MeOH trituration	20	75
3	250 mL/g diene 4.9 mM 1.5 wt % catalyst	charcoal ; silica gel filtration	120 (*initial*)	-
		1st 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 (*initial*)	-
		1st 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 (*initial*)	-
		1st 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	Silia*MetS* DMT 16 h treatment + filtration	380 (*initial*)	-
			66	75
7	160 mL/g diene 7.6 mM 1.25 wt % catalyst		200 (*initial*)	-
			3.6	86
8	250 mL/g diene 4.9 mM 1.25 wt % catalyst		180 (*initial*)	-
			7.7	89

Conclusion

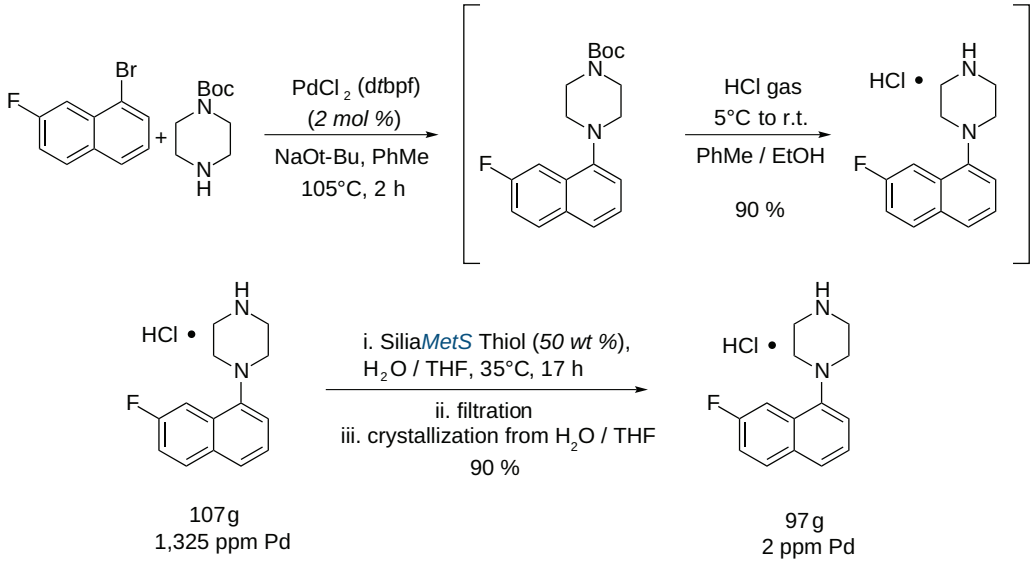
As one can easily note, treatment with Silia*MetS* DMT gave a much lower Ru residual content conjointly with the highest final yields. Hence, low yield losses (*11 - 14 %*) and high purities (*98 %*) were achieved, together with excellent Ru levels observed (*as low as 3.6 ppm*), indicating the strong 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

A Pfizer Case Study: Palladium Removal Using Silia*MetS* Thiol After a Buchwald-Hartwig Amination

Silia*MetS* 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 Silia*MetS* Thiol (*50 wt %*) at 35°C for 17 h and, following crystallization from water / THF.



107 g
1,325 ppm Pd

97 g
2 ppm Pd

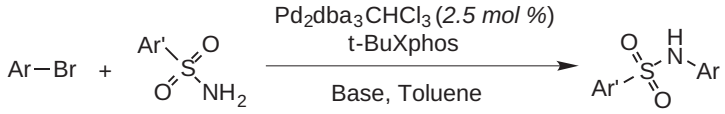
Conclusion

The HCl salt was obtained with a 90 % yield and 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

An Amgen Case Study: Palladium Removal using Various Resins

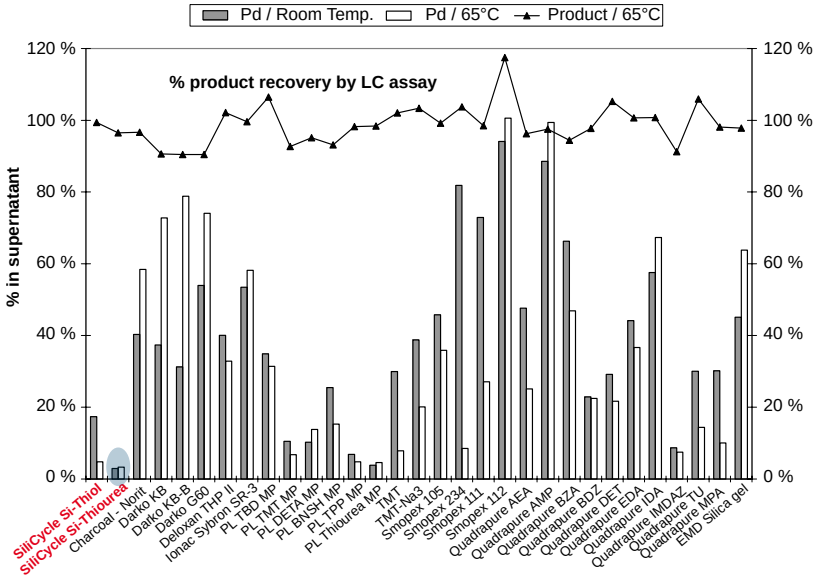
In 2009, Amgen published a chapter in "C*atalysis of Organic Reactions*" related to the use of scavengers for the removal of palladium in small to multi-kilogram production scales. In this study, several parameters were evaluated, such as scavenging efficiency, influence of the scavenger loading and 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.



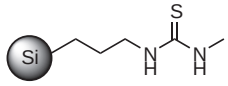
Amgen Scavenger Screening Results

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 Silia*MetS* Thiourea providing the lowest Pd content (*residual palladium concentration: 3 % or < 14 ppm*) without product sequestration. They mentioned that Silia*MetS* Thiourea was used extensively in early process development work.



SiliaMetS Thiourea was the BEST!

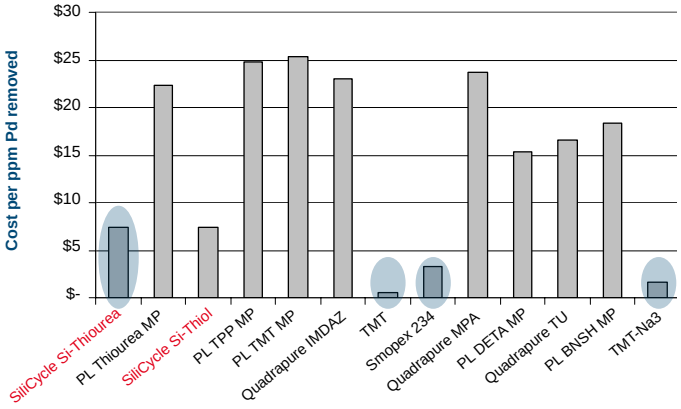


Silia*MetS* Thiourea

Cost Comparison for Most Efficient Scavengers (≥ *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 Silia*MetS* Thiourea, followed by TMT, TMT-Na_3 and Smopex 234.



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

Top 4 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. Silia*MetS* Thiourea was chosen for the large scale purification.

Screening Validation Results on Top 4 Scavengers

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 (*not effective with base-sensitive groups*) 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)*.

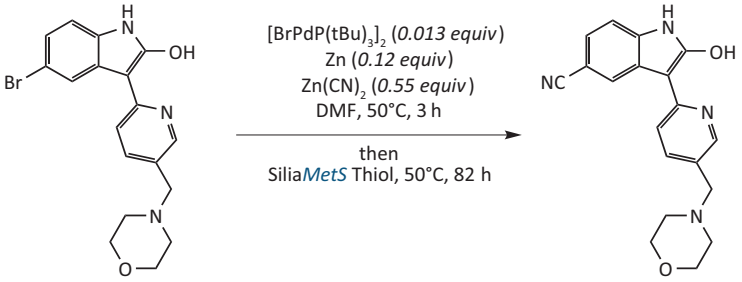
Amgen's Conclusion

"*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.*, *Catalysis of Organic Reactions*, Chapter 5. Application of Scavengers for the Removal of Palladiumin Small Lot Manufacturing, Amgen Inc., Thousand Oaks, California

An AstraZeneca Case Study: Palladium Removal using Silia*MetS* Thiol

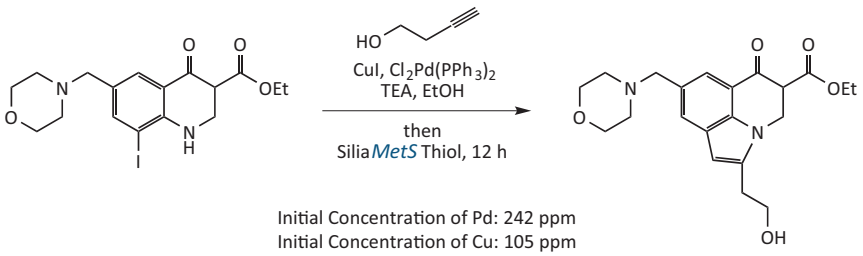
In 2008, AstraZeneca published a paper on removal of palladium impurities in a pilot-scale process. The work-up method found to work the best was a treatment with Silia*MetS* Thiol (*25 % w/w or ~1.4 kg*) at 50°C to purify more than 6.7 kg of material. Final residual palladium concentration was as low as 1 - 2 ppm.



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

A Pfizer Global R&D Case Study: Palladium and Copper Removal on a Large Scale Batch using Silia*MetS* Thiol

In 2006, Pfizer published a paper on removal of palladium & copper impurities in a 20 kg pilot-plant batch. They made two subsequent treatments using Silia*MetS* Thiol (*20 % + 7 % w/w*) at room temperature for 12 hours. After scavenging with Silia*MetS* Thiol, the desired product was obtained with a yield of 76 % containing only 17 ppm Pd and 1 ppm Cu.



Initial Concentration of Pd: 242 ppm
Initial Concentration of Cu: 105 ppm

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 Silia*MetS* and the yield was lower.

Screening Validation Results on Top 4 Scavengers			
Scavengers	Residual Metal Concentration (*ppm*)		Yield (%)
	Pd	Cu	
Degussa Deloxan THP	20	2	60 - 70
SiliCycle SIlia*MetS* Thiol	**17**	**1**	**76**

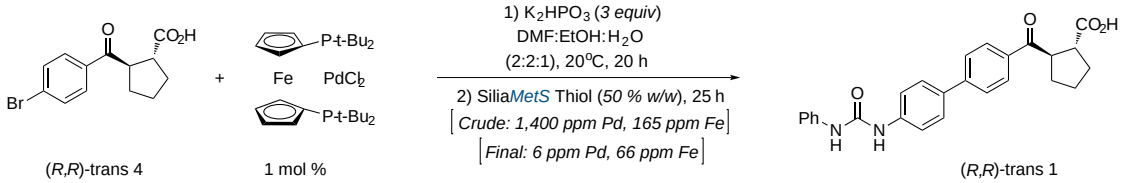
Silia*MetS* allows lower residual metal concentration & higher yield with fewer manipulations!

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

An Abbott Laboratories Case Study: Palladium and Iron Removal using Silia*MetS* Thiol

In 2010, Abbott Laboratories published a paper on removal of palladium and iron impurities using Silia*MetS* 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 ben achieved by optimizing the purification experimental conditions.

Refer to Abbott's publication for more details.

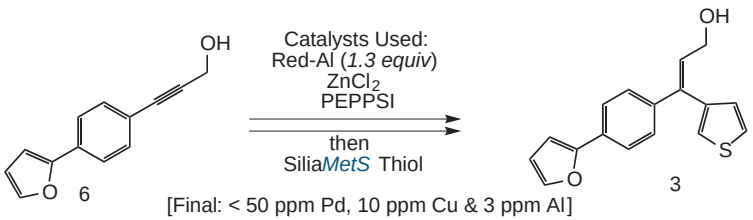


(*R*,*R*)-trans 4 — 1 mol % — (*R*,*R*)-trans 1

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

In 2009, Johnson & Johnson, in collaboration with Solvias, published a paper in which a mild Sonogashira reaction was developed using various metal catalysts. Treatment with Silia*MetS* Thiol simultaneously removed Pd, Cu & Al. Residual concentrations were below 50, 10 and 3 ppm respectively, in the isolated product 3.



[Final: < 50 ppm Pd, 10 ppm Cu & 3 ppm Al]

Note: copper comes from a previous synthesis step.

Refer to J&J's publication for more details.

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

Silia*Bond* Organic Scavengers Application Examples & Case Studies

Nucleophilic Scavenging of Boronic Acids with Silia*Bond* Diol, Carbonate and Silia*MetS* DEAM

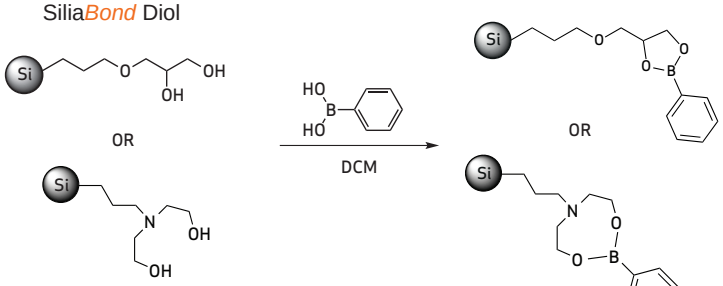
Boronic acids and their derivatives are one of the most widespread intermediates and reagents in organic and medicinal synthesis. On-the-market drugs have even been adding boron atoms to enhance compatibility, selectivity and potency to their target molecules.

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.

Please see our White Paper for more details on our website.

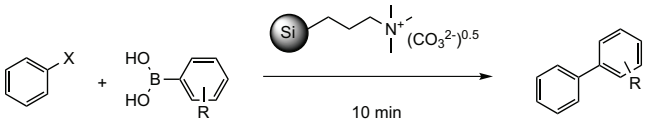
Silia*Bond* Diol



Silia*Bond* DEAM

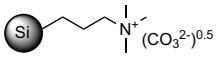
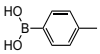
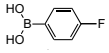
Scavenging Boronic Acids Results

Scavengers	Equivalent	Time	Efficiency (%)
Silia*MetS* DEAM	4	1 h	**> 99**
Silia*Bond* Diol	4	1 h	**> 99**



50 to 99 % Yield

Scavenging Boronic Acids Results

Scavengers	Boronic Acid	Time	Efficiency (%)
 Silia*Bond* Carbonate		10 min	**> 99**
			**> 99**
			**> 99**
			**> 99**

All % scavenged determined by GC-MS

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

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

Scavenging via Silia*Bond* Scavengers vs Functionalized Polymers

Electrophilic Scavenging of Benzylamines with Silia*Bond* Isocyanate

A comparative study between SiliCycle's silica-based Isocyanate and polystyrene-based Isocyanate was performed, using the scavenging of benzylamine as the control reaction. For each scavenger, the experimental conditions were strictly identical.

Scavenging Benzylamine Results (*in %*)				
Scavenger	**DCE**	**THF**	**DCM**	**ACN**
Silia*Bond* Isocyanate	**> 99**	**98**	**98**	**95**
PS-Isocyanate (*supplier A*)	**> 99**	**98**	**98**	79
PS-Isocyanate (*supplier B*)	**> 99**	**98**	**98**	88

Conditions: 3 equiv relative to benzylamine, 1 h at room temperature in solvent
% scavenged determined by GC-MS

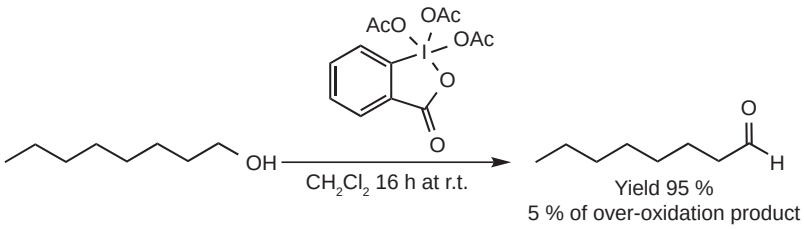
All three scavengers showed to be excellent, albeit Silia*Bond* Isocyanate was the most versatile and unaffected by the polarity of solvents.

Scavenging in two different formats: bulk vs SPE

Ionic Scavenging of 2-Iodobenzoic Acid with Silia*Bond* TMA Acetate and 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 $Na_2S_2O_3$ (*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 Silia*Bond* 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 succesfully scavenged using all products and formats.

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

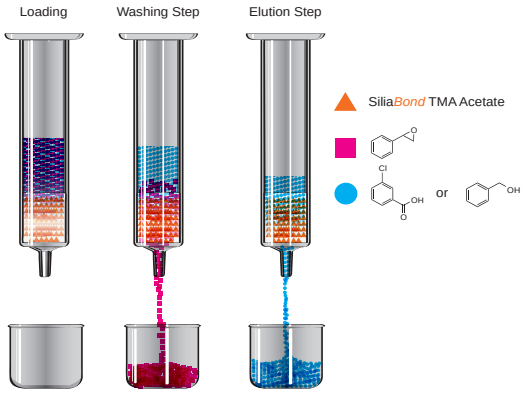
Catch and Release of the API

Carboxylic Acids Purification with Silia*Bond* TMA Acetate

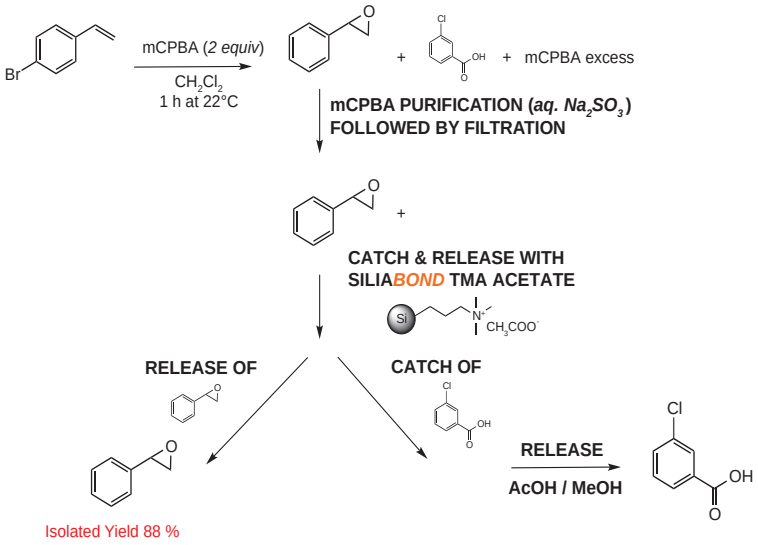
Silia*Bond* TMA Acetate is an ion exchange media useful to extract organic anions from organic or inorganic matrices. It is less selective than Silia*Bond* TMA Chloride. The acetate anion being more labile than the chloride, it therefore retains more easily acidic compounds with pK_a in the range of 4 - 5, such as carboxylic acids.
12 mL cartridges were filled with 2 or 4 g of Silia*Bond* 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

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

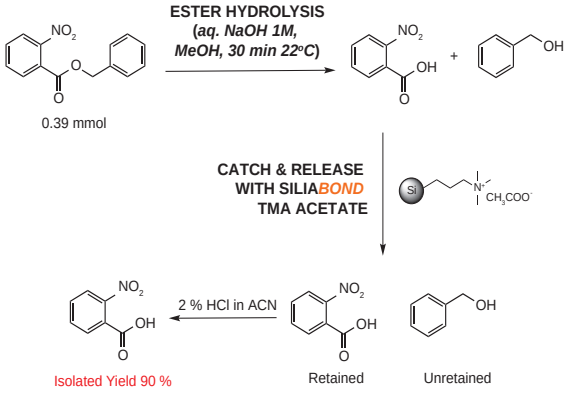


3-CHLOROBENZOIC ACID PURIFICATION VIA CATCH & RELEASE



Isolated Yield 88 %

ESTER HYDROLYSIS PURIFICATION VIA CATCH & RELEASE



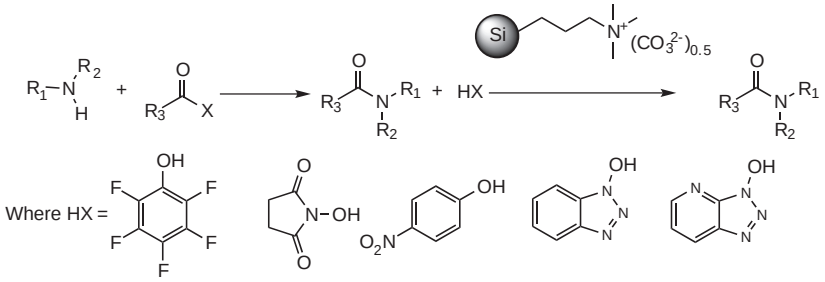
Isolated Yield 90 %

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, Silia*Bond* 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.

Ionic Scavenging of Phenols and Acids with Silia*Bond* Carbonate

The efficiency of Silia*Bond* 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.



HX	Silia*Bond* 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

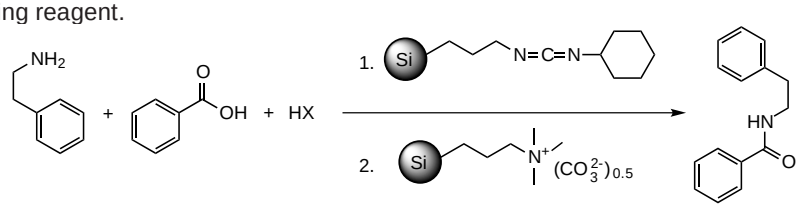
Phenol Scavenging Results (*in %*)

Initial concentration: 5,000 ppm - 3 equiv of Silia*Bond* Carbonate. Analyzed by UV. [1] Analyzed by GC-MS, [2] in THF

Conclusion

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

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



HX	Yield	Purity
No Catalyst	35	**95**
N-Hydroxysuccinimide[1]	67	**98**
1-Hydroxybenzotriazole[2]	**99**	**98**
1-Hydroxy-7-azabenzotriazole[2]	**100**	**99**

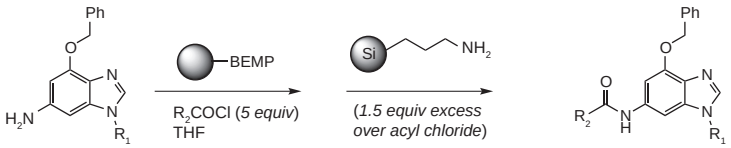
Benzoic Acid Scavenging Results (*in %*)

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

For experimental details using a silica-bound heterogeneous DCC coupling reagent, please see p. 96

A Roche Case Study: Nucleophilic Scavenging of Acyl Chlorides with Silia*Bond* 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. Silia*Bond* Amine was used to sequester the excess acyl chloride instead of using polystyrene-based trisamine resins.



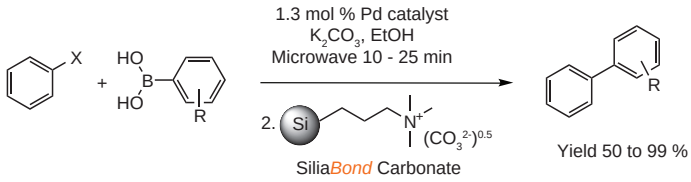
General Procedure

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

An Abbott Case Study: Ionic Scavenging of Boronic Acids with Silia*Bond* Carbonate

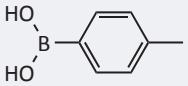
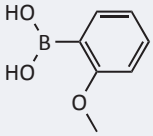
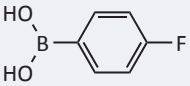
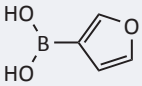
An efficient Suzuki coupling protocol was developed and excess boronic acids were rapidly removed using solid-phase extraction and Silia*Bond* Carbonate to yield clean product.



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 K_2CO_3 was added followed by the Pd catalyst. The reaction vessel was sealed and heated to 110°C for 600 seconds under microwave irradiation. After cooling, the reaction mixture was transferred to a pre-packed column of Silia*Bond* Carbonate which had been conditioned with MeOH / CH_2Cl_2 (*1:1*), and the eluent was collected via gravity filtration. The column was then washed with MeOH / CH_2Cl_2 (*1:1*) (*3 × 3 mL*).

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

Scavenging Boronic Acids Results (*in %*)				
# of Equivalents				
10	**> 97**	**> 97**	**> 97**	**> 97**

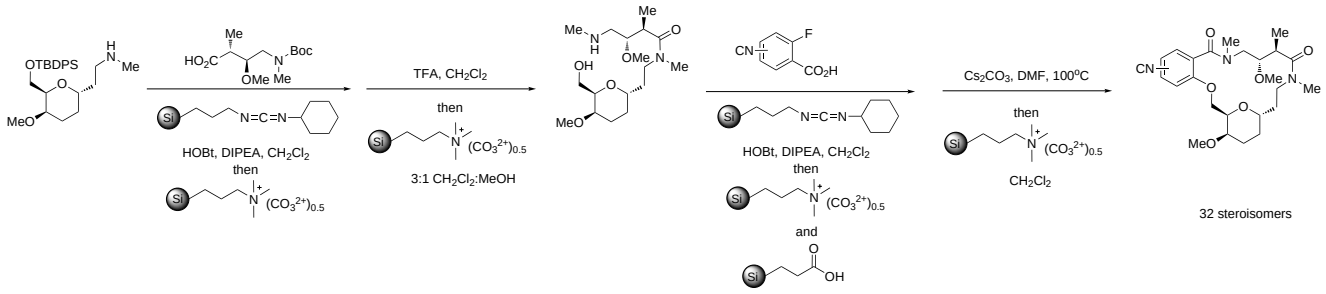
Y. Wang, D. R. Sauer *et al.*, *Org. Lett.*, **2004**, *6*, 2793-2796
High-Throughput Organic Synthesis Group, Global Pharmaceutical R&D, Abbott Laboratories, Illinois, United States

A Broad Institute Case Study: Ionic Scavenging of Acids with Silia*Bond* Carbonate & Electrophilic Scavenging of Amines with Silia*Bond* Carboxylic Acid

In the context of the synthesis of a library of highly complex macrocycles with a pyran core, Silia*Bond* Carbonate (*Si-CO_3*) and Silia*Bond* Carboxylic Acid (*Si-WCX*) were used in the purification process.

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

All reactions were carried out using SiliCycle MiniBlock and MiniBlock XT for parallel synthesis.
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*), Silia*Bond* 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-CO_3 (*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.

S_NAr Macrocyclization: All crude products from above were dissolved in DMF (*4.0 mL*) and heated at 110°C with Cs_2CO_3 (*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-CO_3 (*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.

Please see p. 112 to learn more about the acylation reaction using Silia*Bond* Carbodiimide.

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

Control & Removal of Potential Genotoxic Impurities (*PGI*)

Potential Genotoxic Impurities (*PGI*) have gained considerable attention due to their carcinogenic character to induce genetic mutations and / or chromosomal rearrangements. These compounds cause DNA damage by various mechanisms such as alkylation or other interactions and lead to mutation of the genetic code.

In situations where formation of PGIs cannot be avoided, an ideal solution would be to perform complete removal of PGIs after the synthesis is completed. For example, recrystallization, preparative chromatography or other downstream processing approaches might be considered. Many disadvantages of using such approaches include: potential yield loss, high solvent consumption, additional time and resources required for process development.

If you are concerned about such impurity regulations, here are regularly updated websites and work of reference you may rely on:

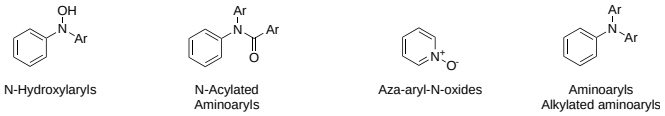
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
http://www.ich.org

The European Medicines Agency
http://www.ema.europa.eu/

References and On-Going Updates from Regulatory Authorities and Industry Practices Related to Genotoxic Impurities
http://www.labcompliance.com/info/links/impurities/genotoxins

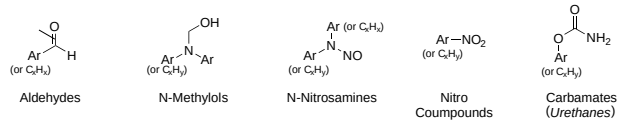
Alerting Structures Examples (*ICH*)

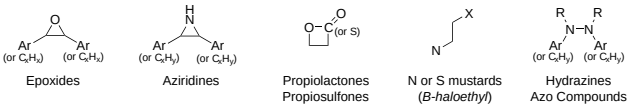
GROUP 1: Aromatic Groups



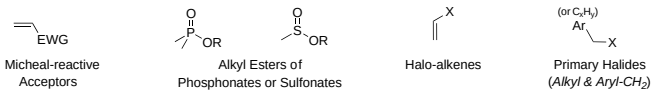
Purines or Pyrimidines, intercalators, PNAs or PNAHs

GROUP 2: Alkyl & Aryl Groups





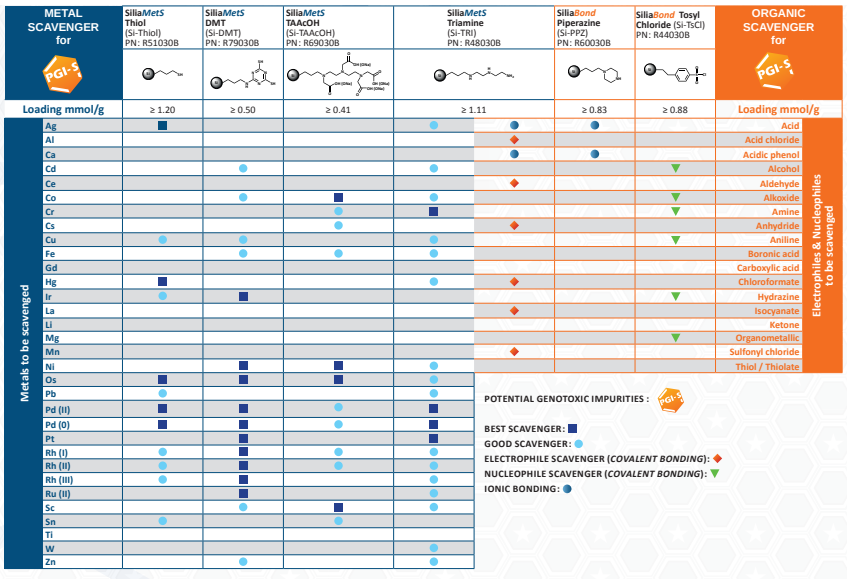
GROUP 3: Heteroatomic Groups



Whatever the nature of the impurity you might encounter, you can rely on our family of genotoxic impurity scavengers in order to eliminate tedious post-reaction purifications.

Also available:

- Silia*MetS* DOTA
- Silia*MetS* Tosic acid
- Silia*MetS* DEAM
- Silia*MetS* Propylsulfonic acid



Scavenging Solutions

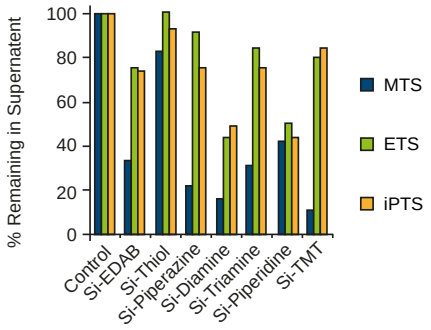
A Merck Case Study: Removal of Electrophilic Potential Impurities Using Silica-Based Nucleophilic Scavengers

Merck & Co. has reported a rapid approach to remove electrophilic PGIs from APIs. Solutions of methyl, ethyl and isopropyl *p*-toluenesulfonate were treated with different nucleophilic functionalized-silicas for 30 min.

The graph below shows screening results for removal of *p*-TSA methyl (*MTS*), ethyl (*ETS*) and isopropyl (i*PTS*) esters by the different resins. One milliliter of 1 µg/mL *pT*SA ester solution in MeOH was added to 100 mg of each of the functionalized silicas. The solutions were sonicated for 30 min, filtered through a 0.45 µm filter and assayed by LC/MS.

Several scavengers showed extensive removal of methyl *p*-toluenesulfonate, with multiple thiol- or amine-containing Silia*Bond* affording greater than 80 % impurity removal under these conditions.

These same resins were less effective in removal of the ethyl and isopropyl esters, presumably owing to the increased steric bulk of the ethyl and isopropyl esters versus the methyl ester.



R. Helmy, M. A. Al-Sayah *et al.*, *Org. Proc. Res. Dev.*, **2010**, *14*, 1021-1026
Merck & Co. Inc., New Jersey, United States

In the same vein, eleven compounds containing structurally alerting functional groups were studied in SiliCycle labs, and scavenged by at least one of our grafted silica: **Best scavenger: ■ | Good scavenger: ●**

Scavenging Affinity for Various Potentially Genotoxic Impurities

Alerting Functional Groups	Acetamide	Pyridine N-oxide	Aniline	Phenyl-hydroxylamine	Benzaldehyde	Octaldehyde
Silia*MetS* DMT					●	●
Silia*MetS* Thiourea						
Silia*MetS* Triamine					■	■
Silia*MetS* TAAcOH		●				
Silia*MetS* TAAcONa						
Silia*Bond* Tosic Acid	■	■	■	■		
Silia*Bond* Tosyl Hydrazine					■	■
Silia*Bond* Tosyl Chloride	●	■	●	●		

Scavenging Affinity for Various Potentially Genotoxic Impurities

Alerting Functional Groups	Methyl methane sulfonate	Propiolactone	Benzyl bromide	Allyl bromide	1,2-epoxyoctane
Silia*MetS* DMT	■	■	■	■	
Silia*MetS* Thiourea		●	●	●	
Silia*MetS* Triamine	●	■			
Silia*MetS* TAAcOH					
Silia*MetS* TAAcONa	●	■			
Silia*Bond* Tosic Acid					■
Silia*Bond* Tosyl Hydrazine		■			
Silia*Bond* Tosyl Chloride					■

Silia*MetS* & Silia*Bond* Ordering Information

Many of our customers are pleasantly surprised when they discover how flexible the use of scavengers can be. No matter what your favorite purification technique might be or which one you are most familiar with, scavengers come in various formats for all preferences.

Bulk, SPE cartridges, flash cartridges and even guard cartridges to protect your expensive HPLC columns, all are formats that are frequently used in order to take full advantage of SiliCycle scavengers' strength.

Purity will never be an issue again!

Ordering Information for Batch Reactor Mode (*Bulk*)

All Scavengers are available in the following sizes: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc. Up to multi-ton scale!

All Particle Size and Pore Size are respectively 40 - 63 µm and 60 Å. Other matrices are available upon request.

Silia*MetS* Metal Scavengers	
Scavenger Name	Scavenger Product Number
Silia*MetS* AMPA	R85130B
Silia*Bond* Amine (*WAX*)	R52030B
Silia*MetS* Cysteine	R80530B
Silia*MetS* DEAM	R54430B
Silia*MetS* DOTA	R91030B
Silia*MetS* DMT	R79030B
Silia*MetS* Diamine	R49030B
Silia*MetS* Imidazole	R79230B
Silia*MetS* TAAcOH *nec*	R69030B
Silia*MetS* TAAcONa *nec*	R69230B
Silia*MetS* Thiol	R51030B
Silia*MetS* Thiourea	R69530B
Silia*Bond* Tosic Acid (*SCX*)	R60530B
Silia*MetS* Triamine	R48030B

Silia*Bond* Organic Scavengers	
Scavenger Name	Scavenger Product Number
Silia*Bond* Amine (*WAX*)	R52030B
Silia*Bond* Carbonate	R66030B
Silia*Bond* Carboxylic Acid (*WCX*)	R70030B
Silia*MetS* DEAM	R54430B
Silia*Bond* DMAP	R75630B
Silia*MetS* Diamine	R49030B
Silia*Bond* Diol	R35030B
Silia*Bond* Guanidine	R68230B
Silia*Bond* Isocyanate	R50030B
Silia*Bond* Maleimide	R71030B
Silia*Bond* Piperazine	R60030B
Silia*Bond* Propylsulfonic Acid (*SCX-2*)	R51230B
Silia*Bond* TMA Acetate *nec*	R66430B
Silia*Bond* Tosic Acid (*SCX*)	R60530B
Silia*Bond* Tosyl Chloride	R44030B
Silia*MetS* Triamine	R48030B

Ordering Information: Available Kits

Because all matrices are unique, and that small differences can influence scavenging efficiency, we recommend first trying one of our Scavenger Kit for screening purposes, especially if you are new to this technology. Steric hindrance of the catalyst, electronic effects, solubility in solvents, all are factors that can influence the removal of your impurity.
These kits are available in 5 g, 10 g, 25 g, 50 g and 100 g formats (*custom formats are also available, contact us for more details*).

How to order

Simply note the **Product Number** which starts with "**K**", add a dash mark and your choice of format, e.g.: **K30730B-10G** to obtain **10G** of each one of the scavengers listed in the kit.

All following kits have been designed for definite needs:

Silia*MetS* Metal Scavenger Kits

Kit Name	Kit PN	Composition
Silia*MetS* Novel Scavenger Kit	K34530B	AMPA, DEAM, DOTA, DMT, Guanidine & Thiol
Silia*MetS* Tin Metal Scavenger Kit	K34730B	Carbonate, Cysteine, DEAM, DMT, TAAcOH, TAAcONa, Thiourea & Thiol

Silia*MetS* Metal Scavenger Kits (*Con't*)

Kit Name	Kit PN	Composition
Silia*MetS* Universal Metal Scavenger Kit	K30730B	Cysteine, DMT, Imidazole, TAAcOH, TAAcONa Thiol, Thiourea & Triamine
Silia*MetS* Palladium Metal Scavenger Kit	K34630B	DMT, Diamine, Thiol, Thiourea Imidazole & Triamine

Silia*Bond* Scavenger Kits

Kit Name	Kit PN	Composition
Silia*Bond* Electrophile Introductory Scavenger Kit	K34230B	Amine, DMAP, Diamine, Tosyl Hydrazine, Piperazine & Triamine

Silia*Bond* Scavenger Kits (*Con't*)

Kit Name	Kit PN	Composition
Silia*Bond* Electrophile Complete Scavenger Kit	K35230B	Amine, DEAM, Diol, DMAP, TMA Acetate & Triamine
Silia*Bond* Nucleophile Complete Scavenger Kit	K32630B	Carbonate, Isocyanate, Maleimide & Tosyl Chloride

Ordering Information for Fixed-Bed Mode Formats (*SPE or Flash Cartridges*)

Silia*Prep*™ SPE Cartridges and Silia*Sep*™ Flash Cartridges

To build your SPE Cartridge Product Number, simply start with the code SPE, followed by the Product Number of the scavenger you wish your cartridge to be packed with, followed by the code of the desired format.

Example: **Silia*Prep* Thiourea, 6 mL, 500 mg = SPE-R69530B-06P**

Formats available:

Silia*Prep* SPE Scavenger Cartridges					
Formats available	**3 mL / 200 mg**	**3 mL / 500 mg**	**6 mL / 500 mg**	**6 mL / 1 g**	**6 mL / 2 g**
Associated code	03G	03P	06P	06S	06U
Units / Box	50	50	50	50	50

Silia*Sep*™ Flash Cartridges

To build your Flash Cartridge Product Number, simply start with the code FLH, followed by the Product Number of the scavenger you wish your cartridge to be packed with, followed by the code of the desired format.

Example: **Silia*Sep* Open-Top TAAcONa, 70 mL, 10 g = FLH-R69230B-70Y**
Silia*Sep* TAAcONa, 4 g = FLH-R69230B-ISO4

Formats available:

Silia*Sep* OT Scavenger Cartridges					
Formats available	**12 mL / 200 g**	**25 mL / 5 g**	**70 mL / 10 g**	**70 mL / 15 g**	**70 mL / 20 g**
Associated code	12U	20X	70Y	70i	70Z
Units / Box	20	20	16	16	16
Formats available	**150 mL / 25 g**	**150 mL / 50 g**	**150 mL / 70 g**	**276 mL / 100 g**	
Associated code	95K	95M	95N	276F	
Units / Box	10	10	10	12	

Silia*Sep* Scavenger Flash Cartridges					
Formats available	**4 g**	**12 g**	**25 g**	**40 g**	**80 g**
Associated code	ISO4	ISO12	ISO25	ISO40	ISO80
Units / Box	2	1	1	1	1
Formats available	**120 g**	**220 g**	**330 g**	**800 g**	**1,600 g**
Associated code	IS120	IS220	IS330	IS750	I1500
Units / Box	1	1	1	1	1

Silia*Sep* Scavenger Flash Cartridges for Industrial Scale				
Formats available	**2.5 kg**	**5 kg**	**20 kg**	**41 kg**
Associated code	150iM	150iL	400iM	400iL
Units / Box	1	1	1	1

Ordering Information for HPLC Guard Cartridges

Silia*Chrom* Guard Cartridges

Silia*Chrom* HPLC Guard Columns are designed to effectively protect both analytical and preparative HPLC columns. The usage of this shorter column is highly recommended to prolong column lifetime and does not alter the results.
Silia*Chrom* Guard Columns are cost effective and easy to use as a pre-filter to remove contaminants prior to injection. In liquid chromatography, contaminants introduced into the column can cause:

- Higher backpressure
- Resolution loss
- Baseline noise or drift
- Peak shape changes
- Irreversible damages (*column + system*)

Silia*Chrom* Guard Columns Dimensions

Silia*Chrom* Guard Columns are available in lengths of 10 - 20 mm and three internal diameters (*ID: 4.0, 10 and 21.2 mm*). You can check the most suitable dimension combinations on page 158 in our Analytical Catalog, or our website.

The Guard Column internal diameter should be the same as the HPLC column or one size smaller. Never use a guard column with a larger ID than that of the HPLC column (*risk of efficiency loss*).

Silia*Chrom* Guard Columns Packings & Dimensions

Silia*Chrom* Metal & Organic Scavenger Guard Columns		
Guard Cartridges Name	**Palladium's Favorite Metal Guard Cartridge**	**Universal Metal Guard Cartridge**
Scavenger Packing #	K346	K307

To build your Part Number, simply start with the code HPLG, followed by the PN of the scavenger packing you wish your cartridge to be filled with, followed by the code of the desired format.

Example: **Silia*Chrom* Plus Guard Cartridge** for **Pd removal**, **5 µm**, **4.6 x 20 mm** = **HPLG-K34605E-A-N020**

Available formats:

Silia*Chrom* Scavenger Guard Column Formats				
Particle Size of Sorbent (*µm*)	**Formats Available (*internal diameter x length in mm*)**			
	4.0 x 10	**4.0 x 20**	**10 x 10**	**21.2 x 10**
5	05E-A-N010	05E-A-N020	05E-A-Q010	05E-A-T010
10	07E-A-N010	07E-A-N020	07E-A-Q010	07E-A-T010

Silia*Chrom* Guard Cartridges Package Information:

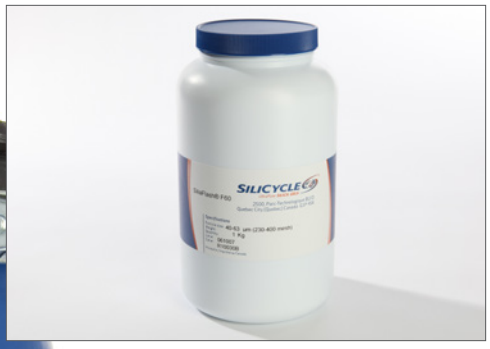
- 4.0 mm ID Guard Cartridges are sold in pack of 4 cartridges
- 10 mm ID Guard Cartridges are sold in pack of 2 cartridges
- 21.2 mm ID Guard Cartridges are sold in pack of 1 cartridge

Silia*Chrom* Guard Holder information:

- **HPH-N010** (*for 4.0 x 10 mm Guard Cartridges*)
- **HPH-N020** (*for 4.0 x 20 mm Guard Cartridges*)
- **HPH-Q010** (*for 10 x 10 mm Guard Cartridges*)
- **HPH-T010** (*for 21.2 x 10 mm Guard Cartridges*)

*Other dimensions and particle sizes could be available on a custom basis. Contact us.

Chromatography & Drying Applications



Bulk Silica Gels

SiliaFlash® Irregular Silica Gels
SiliaSphere™ PC Spherical Silica Gels

Chromatography at SiliCycle

SiliCycle is your partner of choice for your purification and chromatography needs.

Recognized as a leader with an outstanding quality silica gel, SiliCycle offers one of the largest selection on the market.

They are available in two different shapes:

- **Silia*Flash*®** Irregular silicas
- **Silia*Sphere*™** PC Spherical silicas

Get unbeatable performance with our products.

SiliCycle: Silica Expert

With pore diameters ranging from 30 to 1,000 Ångström (*Å*) and particle sizes up to 1,000 microns (*µm*), SiliCycle offers products to meet all your requirements. We offer one of the most reliable portfolios for flash and gravity grades for low to medium-high pressure. Our silica gels are ideal for preparative chromatography, from laboratory to pilot-plant processes and production scale.

Features and Benefits of Silia*Flash* & Silia*Sphere* PC

Features	Benefits
High purity silica gels	No contamination, consistency, reliability, reproducibility
Lowest level of fines on the market	No contamination, lower back-pressure, superior separation
Exceptional narrow particle and pore size distributions	Optimal separation and resolution
Batch-to-batch, year-to-year consistency	Reliable chromatography
Neutral pH	Wide range of products can be purified, even acid sensitive ones
Low metal content & controlled water content	Symmetrical peaks without tailing
High mechanical stability	Can be used under high pressures without surface abrasion
High surface area and density	Greater loading capacity, enabling more silica for the same volume Solvent economy (*smaller dead volume*)
Availability in bulk quantities	Always in stock with on-time delivery

Together, all these benefits mean optimal and reproducible separation power, saving you time and money.

SiliCycle, the Silica Supplier for Every Need

Each year, SiliCycle manufactures hundreds of tons of silica for a broad range of chromatography applications. All our products are manufactured under tightly controlled manufacturing processes and a stringent quality control ensures the highest quality.

Be confident in scaling-up your processes with our silica gels.

With SiliCycle, No Scale-up Limitations

Scaling-up from laboratory to production scale

Two Shapes Available From SiliCycle: Irregular & Spherical

The quality of a silica gel is extremely important when you are using it for chromatography purposes, particularly when dealing with difficult separations of valuable compounds. You need to be confident about your recoveries.

In chromatography, there are at least three physical properties that will influence your separation and that you need to consider when choosing your silica gel:

- Particle shape (*irregular or spherical*)
- Particle size distribution (*tight or large*)
- Pore diameter (*surface area*)

These caracteristics will directly influence crucial parameters involved in a successful chromatography:

- Resolution (*efficiency of separation & final purity*)
- Retention (*which allows separation*)
- Capacity (*maximal sample quantity and final recovery / yield*)
- Back-pressure (*speed and pumps related issues*)

At SiliCycle, we ensure **consistency**, **reliability** & **reproducibility**.

Our expertise and strong knowledge has been developed over many years of helping our customers find the best solutions to their particular needs.

How to Choose Between Silia*Flash* Irregular or Silia*Sphere* PC Spherical Gels?

Irregular silica gels are traditional in flash or gravity chromatography and have always been a spontaneous choice for preparative chromatography. Nowadays, spherical particles are now used increasingly.

Cost is very important in preparative and process chromatography, and the use of monodisperse spherical particles with narrow particle size distribution is more expensive. It is possible in this case to use irregular silica but the separation may not provide the desired results. For these situations, SiliCycle has developed a more affordable class of spherical particles for preparative chromatography: Silia*Sphere* PC.

The advantage of using Silia*Sphere* PC materials over standard silica gels includes the following:

- Increased efficiency of the eluent's flow characteristics
- Higher resolution
- Ease of packing / better packing reproducibility
- Higher mechanical stability

Silia*Sphere* PC: Truly Spherical

Silica gel quality varies greatly between manufacturers. Even when advertised as being "spherical" this may not be the case. Please discover on next page a quick comparison of Scanning Electron Microscopy (*SEM*) pictures between SiliCycle Silia*Sphere* PC and the competition.

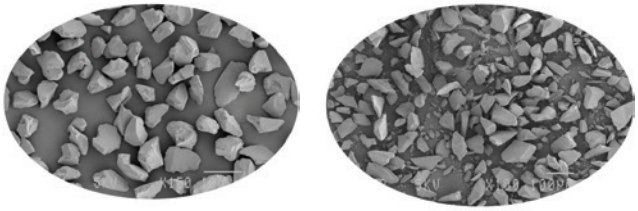
Silia*Flash* & Silia*Sphere* PC Exceptional Characteristics

Tight Particle and Pore Size Distributions

The importance of the particle and pore size distributions varies depending on the type of chromatography being done. For instance, it is very important when using HPLC that the particle size distribution of the spherical particles being used remain very narrow.

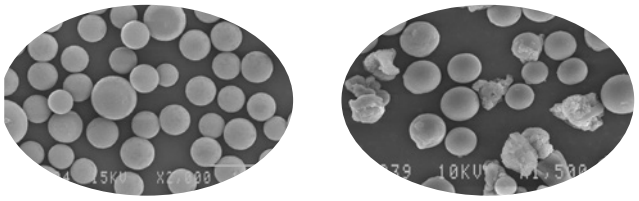
Importance of Tight Distributions in Chromatography	
Tight Particle Size Distribution	**Tight Pore Size Distribution**
Greater column performance and separation	Surface area (*Presence of bigger pore size leads to lower surface availability*)
Tighter peaks and better peak shape	Optimal peak shape (*Presence of smaller pore size leads to peak tailing*)
Better column packing, easier to pack	No molecule sequestration due to fluid diffusion inside pores
No preferential pathways (*channeling*)	
Faster flow rate with lower back-pressure	
Time and solvent savings	

Scanning Electron Microscopy (*SEM*) comparison of two IRREGULAR silica gels 40 - 63 µm, 60 Å



SiliCycle | Competitor

Scanning Electron Microscopy (*SEM*) comparison of two SPHERICAL silica gels 50 µm, 60 Å

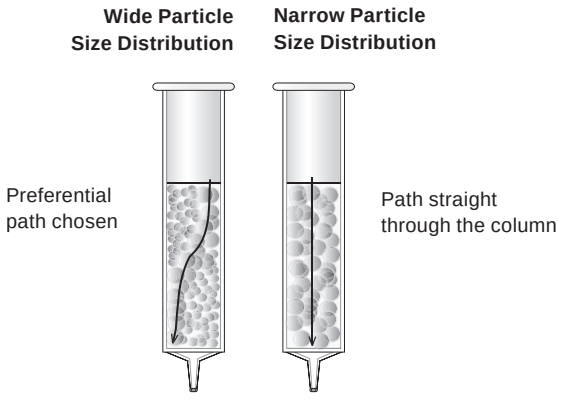


SiliCycle | Competitor

Effects of Homogeneous vs Uneven Packing

The connection between particle size distribution and column performance is very simple. When the distribution is broad, the packing is uneven. Some parts are composed of only large particles where the solvent will flow fast and meet little resistance, and there are sections composed of small particles where the solvent flows slowly and meets great resistance. As a result, the solvent will take the path of least resistance through the column and flow around the pockets of small particles instead of straight through the column. This uneven flow greatly affects the separation because the compounds will have different retention times depending on their flow path. As they exit the column, the compounds will give broad and poorly separated peaks.

The figure on the right illustrates the effect of a wide particle size distribution versus a narrow one. Narrower distribution gives a more homogenous packing and thus more concentrated fractions. And, by reducing solvent consumption, the process will be more cost-efficient.



Silia*Flash*
Silia*Sphere* PC

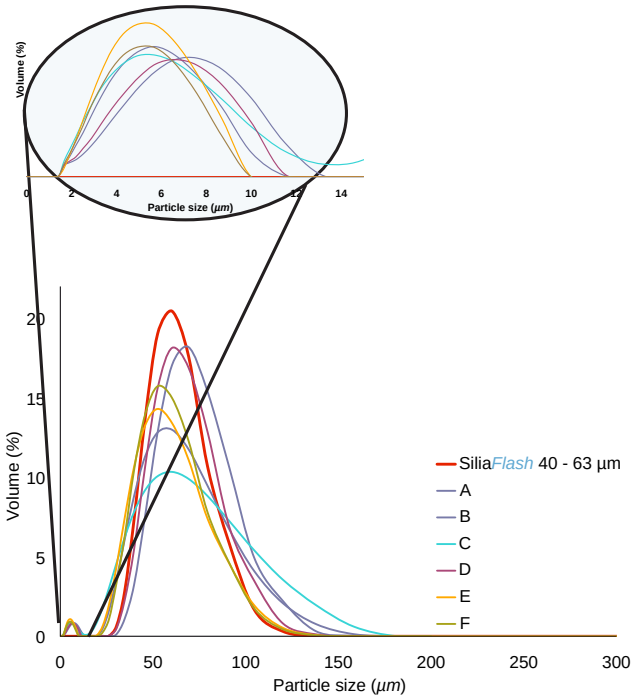
Silia*Flash*, one of the Tightest Particle Size Distribution on the Market

Of particle size distributions' disparity

When selecting a silica gel, chemists need to take into account that not all 40 - 63 µm gels are the same.

In this example, the figure on the right shows the distribution curves of SiliCycle's Silia*Flash* gel (*PN: R10030B*) compared to other manufacturers of flash silica gels of same particle sizes. ***All products were sold as 40 - 63 µm 60 Å gels.***

As you can observe, SiliCycle's gel has a mean of 90 % of the particles in the nominal range compared to maximum 80 % for the competitor gels. The higher the curve, the tighter the particle size distribution.



Of the importance of the absence of fines

In chromatography, fine particles (*small particles under 10 microns*) increase back-pressure and can result in clogging, which is particularly dangerous when using glass columns. Fines can also pass through filters and contaminate final products. The lack of fines gives a more regular, stable and reproducible chromatography bed and a faster and more even flow rate for better separation.

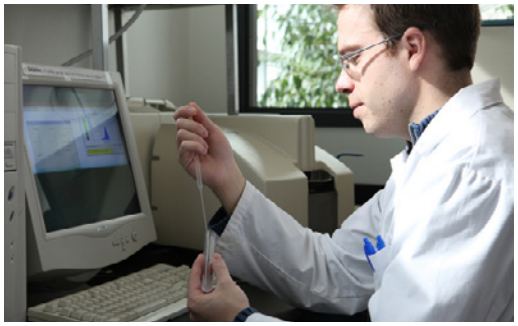
The zoomed part of the figure shows that our most popular silica gel, Silia*Flash* 40 - 63 microns 60 Å, has total absence of fines unlike the six competitor gels analyzed.

***SiliCycle has the lowest level of fines on the market for both* Silia*Flash* & Silia*Sphere* PC**.

Particle Size Analysis Methods

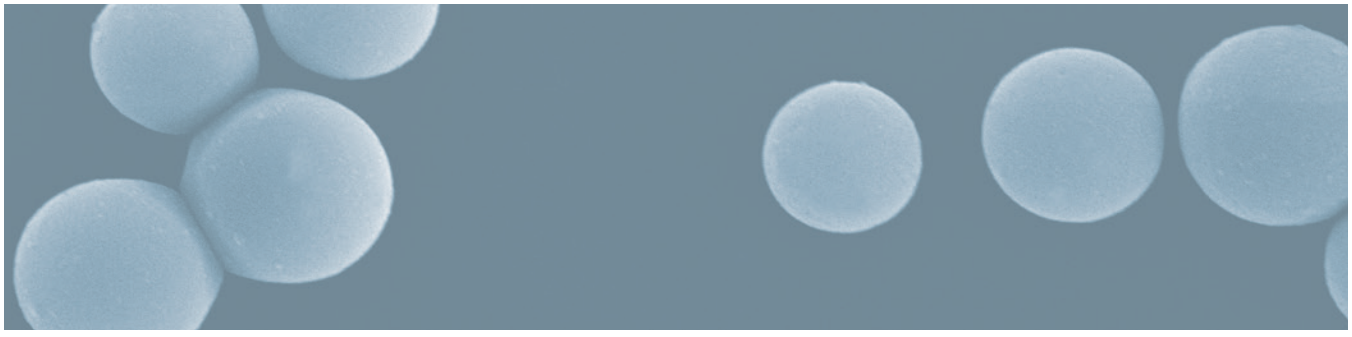
Laser Diffraction (*Malvern Analysis*)

Typically used for particle sizes below 40 microns. Particle size distribution is reported in term of D10, D50 (*average, mean*) and D90. Some manufacturers also mention the ratio of D90/D10.



Sieving

Usually for particle sizes over 40 microns. Particle size distribution is reported in percentage of undersized and oversized.



High Purity Silica Gels

You can be sure of the outstanding quality of SiliCycle's silica gels because of the closely controlled manufacturing conditions. Our tight control of every manufacturing process step allows reproducible results (*chemical, physical and structural*) as well as ensuring the same chromatographic selectivity. Hence, Silia*Flash* and Silia*Sphere* PC are suitable for validated chromatographic processes.

Our stringent Quality Control and Quality Assurance ensures high performance with no scale-up limitations. Every product meets our quality specifications and is shipped with a Certificate of Analysis (*CofA*). Individual data sheets are also available directly from our website.

Every day, SiliCycle's silica gels are being used by thousands of satisfied scientists for their purifications. They know that Silia*Flash* and Silia*Sphere* PC are synonymous of quality and that they can expect reproducible results every time.

Stable Water Level Content

Water level of silica gel affects the selectivity of the silica. Silia*Flash* and Silia*Sphere* PC have generally a water content between 2 to 6 %. This is advantageous for you since other products have a water variation from 2 to 15 % depending on the manufacturer. SiliCycle can also adjust the water level upon request.

Neutral pH

Our silicas are pH-adjusted between 6 and 8 to be safely used in the separation of a wide range of products (*a neutral pH is needed to separate pH-sensitive compounds*). Once again, this is advantageous when compared to many gels on the market that are much more acidic.

Low Trace Metal Content

Silica, depending on its method of manufacturing, contains a certain amount of various metals. This can, in turn, affect the quality of the separation. Aluminum, iron and lead are particularly problematic because they cause peak tailing. SiliCycle's proprietary technology generates a silica gel with the lowest trace metal content on the market. This ensures you will get optimal performance from your chromatography. Tight control of metals in every batch also improves your reproducibility and reduces risks of interaction between metals and desired compounds.

Typical Metal Content Comparison for 40 - 63 µm, 60 Å Silica Gels

Metals		SiliCycle F60 R10030B	Manufacturer A	Manufacturer B
Metal (*mg/kg*)				
Aluminum	**Al**	33	262	280
Barium	**Ba**	9	60	33
Calcium	**Ca**	336	1,150	502
Iron	**Fe**	32	75	41
Magnesium	**Mg**	61	149	104
Sodium	**Na**	466	945	585
Titanium	**Ti**	147	250	179
Zirconium	**Zr**	32	75	56

Silia*Flash* Irregular Silica Gels

Two Different Grades for Different Needs

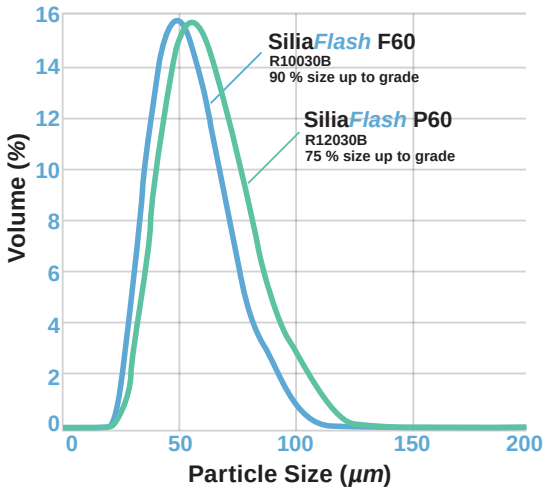
Over the years, SiliCycle has developed two different grades for the two most popular irregular gels used in the industry:
1) *40 - 63 µm, 60 Å*
2) 60 - 200 µm, 60 Å

Those two grades of each gel are available to address all our customers requirements, depending on their applications, areas of research, budgets and so on.

40 - 63 µm, 60 Å Gels: Silia*Flash* F60 (*R10030B*) VS Silia*Flash* P60 (*R12030B*)

Both compare favorably with the overall industry average of a 40 - 63 µm distribution, and each grade offers its own particle size distribution profile.

Two Different Grades of 40 - 63 µm, 60 Å Gels		
Characteristics	**F60 (*R10030B*)**	**P60 (*R12030B*)**
Particle Size (*µm*)	40 - 63	40 - 63
Pore Diameter (*Å*)	60	60
Particularities	• Extra step to reduce metal content to minimum level • Tighter particle size distribution • Fines have been removed	• Fines have been removed • Lower price



The figure on the right shows F60 tighter particle size distribution and the absence of fines for both gels.

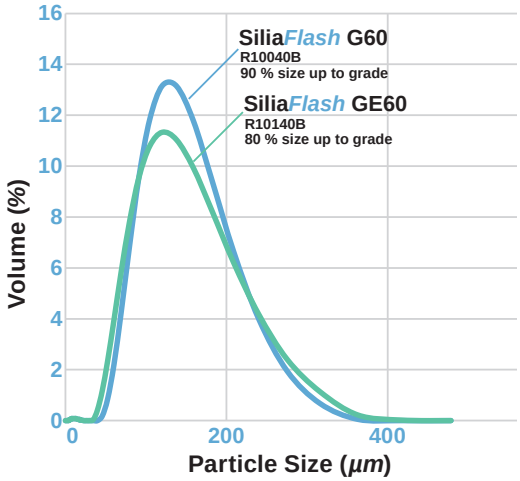
Acid washed silica gel for extra purity (*R10530B*)

SiliCycle also manufactures an acid washed Silia*Flash* 40 - 63 µm, 60 Å Silica Gel.
SiliCycle's acid washed gel has been developed to ensure a pH-controlled media with even lower levels of trace metal contaminants for maximal purity. Please refer to the table next page for metal content details.

60 - 200 µm, 60 Å Gels: Silia*Flash* G60 (*R10040B*) VS Silia*Flash* GE60 (*R10140B*)

Each grade offers its own particle size distribution profile.

Two Different Grades of 60 - 200 µm, 60 Å Gels		
Characteristics	**G60 (*R10040B*)**	**GE60 (*R10140B*)**
Particle Size (*µm*)	60 - 200	60 - 200
Pore Diameter (*Å*)	60	60
Particularities	• Extra step to reduce metal content to minimum level • Tighter particle size distribution • Fines have been reduced to minimal level	• Fines have been reduced to minimal level • Lower price



The figure on the right shows G60 tighter particle size distribution.

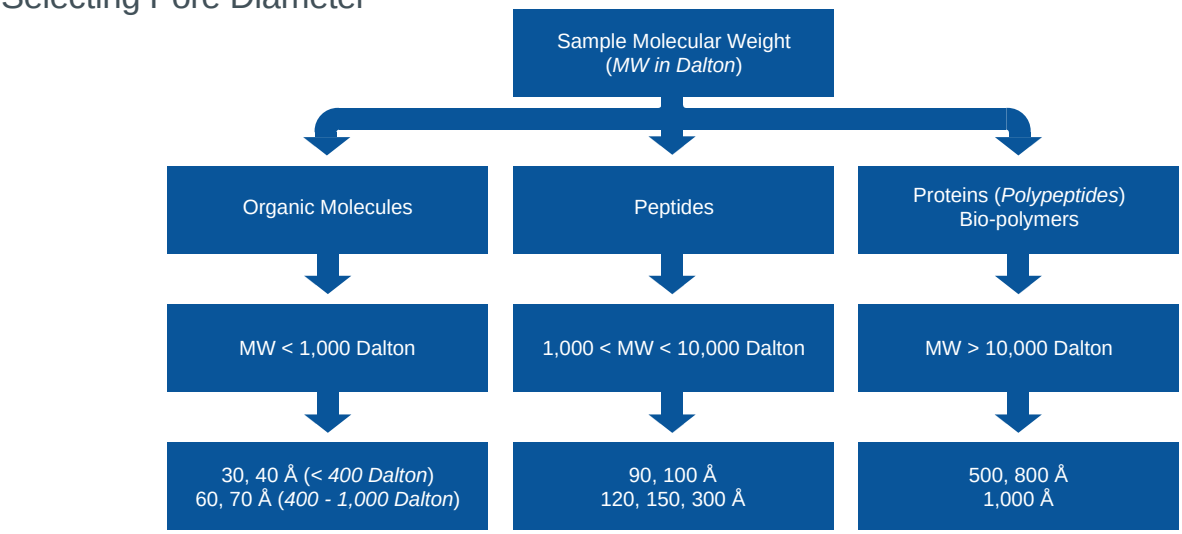
Typical metal content comparison between SiliCycle's five most popular gels

Typical Metal Content of Most Popular Irregular Silicas						
Product Number		**F60 (*R10030B*)**	**P60 (*R12030B*)**	**Acid Washed (*R10530B*)**	**G60 (*R10040B*)**	**GE60 (*R10140B*)**
Particle Size	µm	40 - 63			60 - 200	
Pore Diameter	Å	60			60	
Metal (*mg/kg*)						
Aluminum	**Al**	**< 200**	**< 1,000**	**< 70**	**< 350**	**< 900**
Antimony	Sb	< 0.2			< 0.2	
Arsenic	Ar	< 1			< 1	
Barium	**Ba**	**< 40**	**< 40**	**< 5**	**< 40**	
Beryllium	Be	< 0.1			< 0.1	
Bismuth	Bi	< 1			< 1	
Cadmium	Cd	< 0.01			< 0.01	
Calcium	**Ca**	**< 200**	**< 500**	**< 10**	**< 250**	**< 500**
Chromium	Cr	< 1			< 1	
Cobalt	Co	< 0.1			< 0.1	
Copper	Cu	< 1			< 1	
Iron	**Fe**	**< 75**	**< 350**	**< 10**	**< 75**	**< 350**
Lead	Pb	< 1			< 1	
Lithium	Li	< 0.1			< 0.1	
Magnesium	**Mg**	**< 150**	**< 250**	**< 10**	**< 100**	**< 150**
Manganese	Mn	< 1	< 2	< 1	< 1	
Molybdenum	Mo	< 0.1			< 0.1	
Nickel	Ni	< 1			< 1	
Potassium	**K**	**< 500**	**< 30**	**< 2**	**< 750**	**< 30**
Rubidium	Rb	< 0.2			< 0.2	
Selenium	Se	< 1			< 1	
Silver	Ag	< 0.1			< 0.1	
Sodium	**Na**	**< 150**	**< 1,500**	**< 15**	**< 150**	**< 1,500**
Strontium	**Sr**	**< 4**	**< 15**	**< 1**	**< 4**	**< 15**
Tellurium	Te	< 0.1			< 0.1	
Thallium	Tl	< 0.1			< 0.1	
Tin	Sn	< 0.4	< 0.4	< 0.2	< 0.4	
Titanium	**Ti**	**< 200**	**< 250**	**< 90**	**< 250**	
Uranium	U	< 0.1			< 0.1	
Vanadium	V	< 1			< 1	
Zinc	Zn	< 1			< 1	

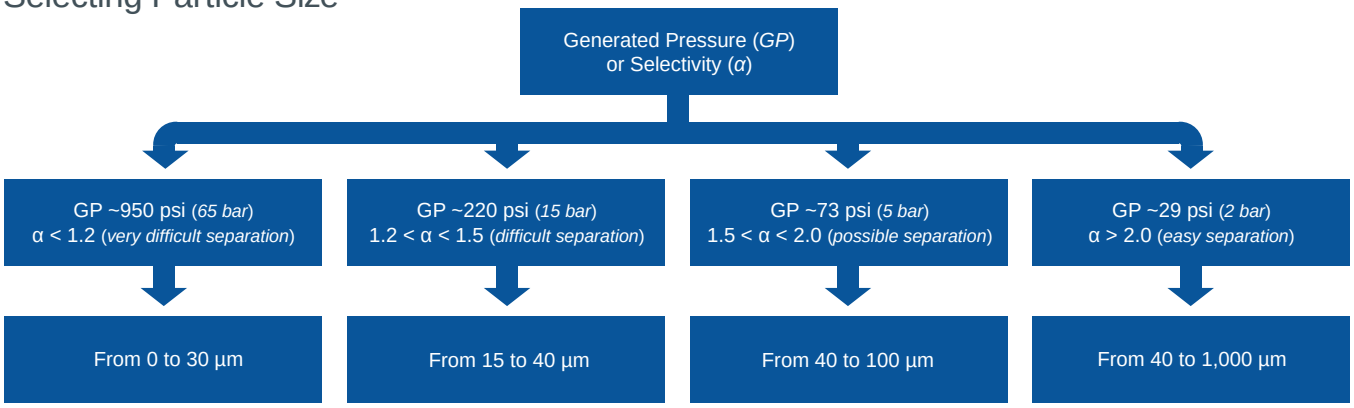
Silica Selection Guide

Selecting the most appropriate sorbent for any given application can be difficult. To help you choose the right pore diameter and particle size, simply follow the two pathways to select the most suitable sorbent.

Selecting Pore Diameter



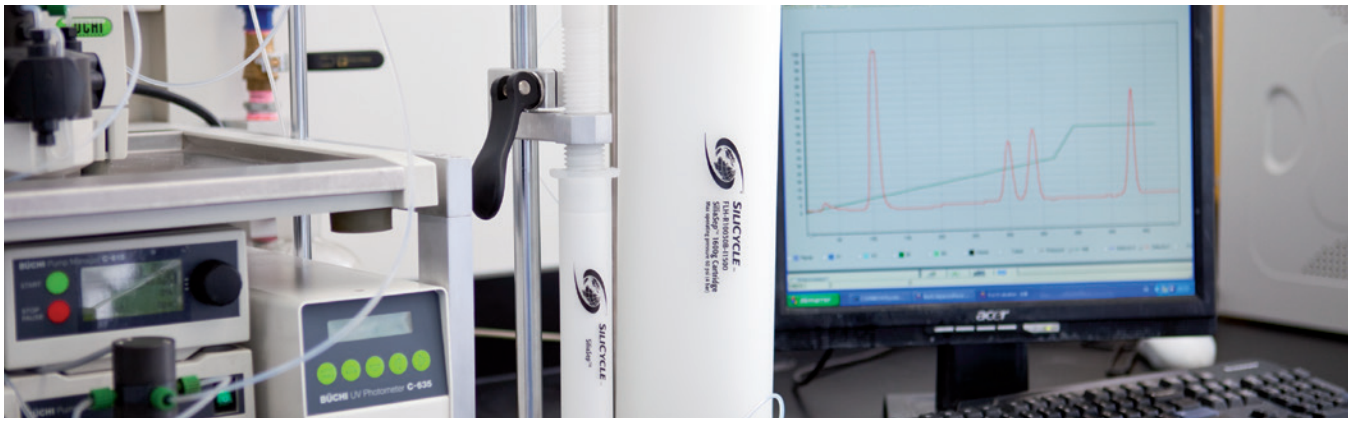
Selecting Particle Size



Selectivity (α) is measured by the retention factor ratio between two similar compounds: $\alpha = \frac{Tr_1 - T_0}{Tr_2 - T_0}$

A Particle Size for Each Application

Most Popular Particle Size Applications		
Particle Size Distribution		Applications
Irregular Particles	Spherical Particles	
Particles for Preparative TLC Plates		
From 0 to 20 µm	-	• Contains neither binder (*organic or inorganic*) nor UV indicator (F_{254}) • Can also be used in flash chromatography if higher resolution is required (*higher back-pressure*)
Particles for Difficult Separations		
From 10 to 45 µm	From 15 to 45 µm	• High-resolution silica for difficult separations (*similar polarities*)
Particles for Flash Chromatography		
40 - 63 µm	From 40 to 75 µm	• Chromatography types: high-resolution flash chromatography & low to medium-pressure preparative chromatography • Narrow particle size distribution • Easier to pack and more uniform packing • Superior resolution • Suitable for use with complex matrices MOST POPULAR PARTICLE SIZE DISTRIBUTION
60 - 120 µm	From 60 to 150 µm	• Alternative to 40 - 63 µm silica for faster flow rate with lower pressure
Particles for Column (*or Gravity*) Chromatography		
From 60 to 200 µm	From 75 to 250 µm	• Most economical silica for open column chromatography (*gravity*) • Suitable for very dirty purification • Easier to handle
From 120 to 200 µm	From 100 to 200 µm	• Silica for standard open column chromatography • Narrow particle size distribution enables uniform packing • Suitable for mass overload purification
Other Application		
From 200 to 1,000 µm	From 200 to 500 µm	• Silica for plugs



Silia*Flash* & Silia*Sphere* PC Ordering Information

This is only an overview of gels we can provide. Please contact us if you are looking for a different product.

Silia*Flash* Ordering Information			
Product Number	Particle Size (*µm*)	Particle Size (*mesh*)	Pore Diameter (*Å*)
R10037L	75 - 150	100 - 200	30
R10130A	40 - 63	230 - 400	40
R10150A	60 - 120	325 - 625	
R10140A	60 - 200	70 - 250	
R10160A	120 - 200	70 - 125	
R10170A	200 - 500	35 - 70	
R10180A	500 - 1,000	18 - 35	
R10110B	0 - 20	*	60
R10019B	10 - 30	*	
R10017B	15 - 40	400 - 800	
R10023B	20 - 45	*	
R10030B (*F60*)	40 - 63	230 - 400	
R12030B (*P60*)			
R10530B (*acid washed*)			
R10150B	60 - 120	325 - 625	
R10040B (*G60*)	60 - 200	70 - 230	
R10140B (*GE60*)			
R10137B	75 - 150	100 - 200	
R10057B	105 - 175	86 - 140	
R10160B	120 - 200	70 - 125	
R10160B	150 - 175	80 - 100	
R10160B	150 - 250	60 - 100	
R10170B	200 - 500	35 - 70	
R10180B	500 - 1,000	18 - 35	
R10130D	40 - 63	230 - 400	90
R10140D	60 - 200	70 - 250	
R10157D	105 - 175	86 - 140	
R10170D	200 - 500	35 - 70	
R10180D	500 - 1,000	18 - 35	
R10181D	800 - 1,200	16 - 22	
R10130H	40 - 63	230 - 400	150
R10150H	60 - 120	325 - 625	
R10140H	60 - 200	70 - 250	
R10157H	105 - 175	86 - 140	
R10160H	120 - 200	70 - 125	
R10170H	200 - 500	35 - 70	
R10072H	250 - 500	35 - 60	
R10180H	500 - 1,000	18 - 35	
R10181H	800 - 1,200	16 - 22	
R10130M	40 - 63	230 - 400	300
R10140M	60 - 200	70 - 250	
R10170M	200 - 500	35 - 70	

Silia*Sphere* PC Ordering Information			
Product Number	Particle Size (*µm*)	Particle Size (*mesh*)	Pore Diameter (*Å*)
S10030B-A	50	300	60
S10027B-A	60	250	
S10034B-A	75	200	
S10040B-A	100	150	
S10063B-A	150	100	
S10066B-A	200	70	
S10068B-A	300	50	
S10020C	20 - 45	-	70
S10040C	75 - 200	70 - 200	
S10030C	200 - 375	45 - 70	
S10070C	200 - 500	35 - 70	
S10095D-A	25	-	90
S10009E-A	20	-	100
S10020E	20 - 45	-	
S10030E	40 - 75	200 - 400	
S10040E	75 - 200	70 - 200	
S10065E	150 - 250	60 - 100	
S10070E	200 - 500	35 - 70	
S10009G-A	20	*	120
S10030G-A	50	300	
S10034G-A	75	200	
S10040G-A	100	150	
S10063G-A	150	100	
S10020M	20 - 45	*	300
S10030M	40 - 75	200 - 400	
S10040M	75 - 200	70 - 200	
S10064M	150 - 200	70 - 100	
S10070M	200 - 500	35 - 70	
S10020P	20 - 45	*	500
S10030P	40 - 75	200 - 400	
S10040P	75 - 200	70 - 200	
S10070P	200 - 500	35 - 70	
S10020S	20 - 45	*	800
S10030S	40 - 75	200 - 400	
S10040S	75 - 200	70 - 200	
S10070S	200 - 500	35 - 70	
S10020T	20 - 45	*	1,000
S10030T	40 - 75	200 - 400	
S10040T	75 - 200	70 - 200	
S10070T	200 - 500	35 - 70	

Formats: 1 kg, 5 kg, 10 kg, 25 kg, etc. Up to multi-ton scale.
* Mesh equivalent too small to exist as real screen size.

Low Pressure Chromatography

SiliaBond® Chromatographic Phases
SiliaSep™ Flash Cartridges

Solutions for Low Pressure Chromatography

SiliCycle offers a large range of silica-based solutions for low pressure chromatography

- Available in bulk (*SiliaBond*) and in pre-packed flash cartridges (*SiliaSep*)
- Non Polar Phases: C1 to C18, Phenyl, PFP, Cyclohexyl
- Polar Phases: Silica, Amino, Cyano, Diol, Silver Nitrate
- Ion Exchange Phases: SAX, WAX, SCX and WCX
- Alumina
- Florisil

Low Pressure Chromatography

Silica is the most widely used media in chromatography. These bare and bonded supports possess great properties for use as stationary phases and are particularly appreciated for their high mechanical resistance. In chromatography, there are two phases: the stationary phase packed in a column and the mobile phase that will be eluted through the stationary phase. If the analyte has a strong affinity for the mobile phase, there will be no retention. If the analyte interacts strongly with the stationary phase, there will be little or no migration. In a mixture, the interactions between the two phases will generate the separation. So depending on the analyte's polarity, the appropriate stationary phase has to be chosen and the mobile phase's polarity has to be optimized.

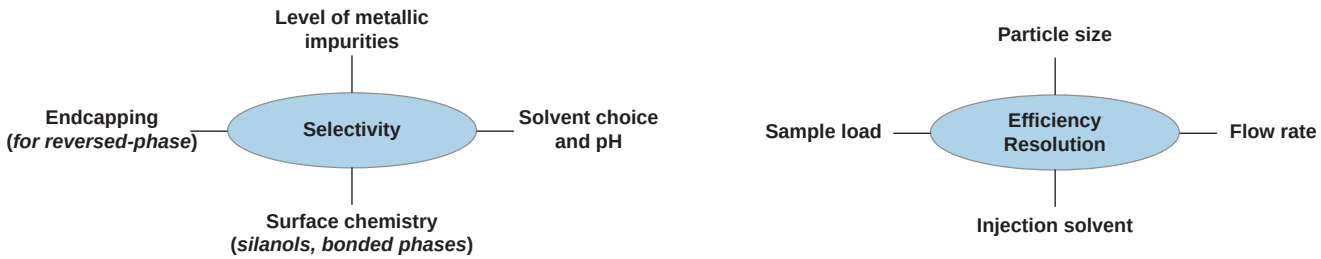
SiliCycle offers you two solutions: pack your own columns using Silia*Bond* / Silia*Flash* or use our pre-packed flash cartridges Silia*Sep*. The enhanced mechanical stability of our silica, which means no fines are created during the packing of the media, guarantees good column performance and lifetime.

Important Separation Parameters

Selectivity: Refers to the ability to retain or release certain types of compounds.

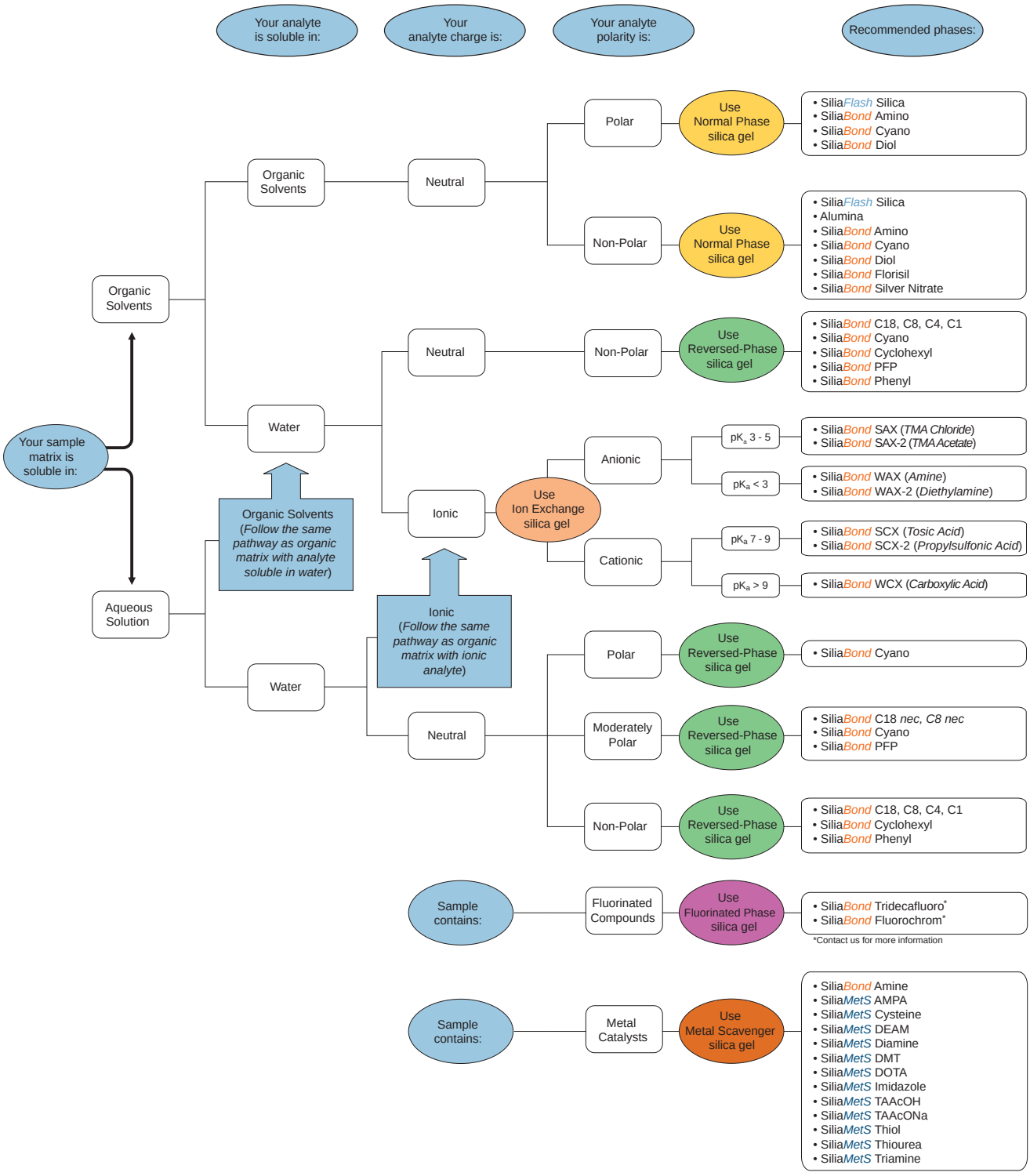
Efficiency & Resolution: The performance of flash cartridges can be measured by different parameters including plate count (*N*) and symmetry (*SI*). The higher (*N*), the better the separation.

Influencing Factors



Sorbent Selection Chart

SiliCycle offers a wide range of Silia*Bond* & Silia*Sep* sorbents to cover many kinds of purification. The following chart is designed to serve as a guide for the selection of the appropriated sorbent based on the characteristics of the sample to be purified.



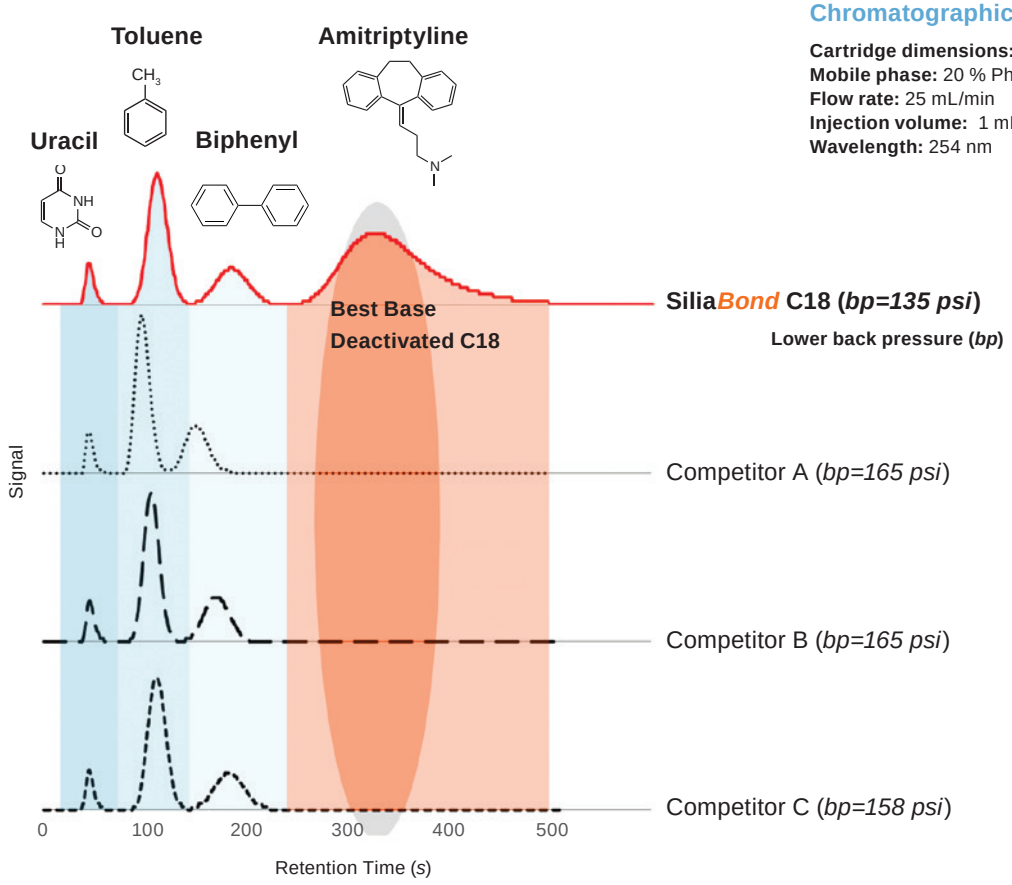
Note: for Metal Scavengers, see page 137 for more information.

Reversed-Phases

In reversed-phase chromatography, the packing material is always non-polar (*hydrophobic*) while the mobile phase is polar to non-polar. An important parameter affecting chromatographic efficiency is the hydrophobicity of the sorbent. As a general rule, stationary phase hydrophobicity increases with the alkyl chain length.

SiliCycle developed a C18 chromatographic phase (*PN: R33230B*) characterized by a homogeneous coverage of the alkyl chains on the surface. Consequently, the endcapping step is more controlled, which leads better separations and inhibition of the non-specific interactions with silanol groups (*highly deactivated silanol phase*).

Compared to competitive products, this endcapped C18 phase with 17 % carbon load exhibits high hydrophobicity and base deactivated properties. We have compared this high-performance chromatographic phase to similar C18 phases on the market (*20 % carbon load*). The comparison was done on a mixture of compounds to evaluate the dead volume (*uracil*), the hydrophobicity (*toluene and biphenyl*) and the silanol activity (*amitriptyline*). The test was done in isocratic conditions, with a mobile phase composed of 80/20 methanol / buffer (*20 nM potassium phosphate pH = 7*).



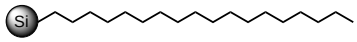
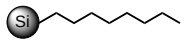
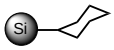
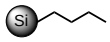
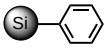
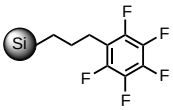
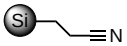
Chromatographic Conditions

Cartridge dimensions: 12 x 150 mm
Mobile phase: 20 % Phosphate buffer in Methanol
Flow rate: 25 mL/min
Injection volume: 1 mL
Wavelength: 254 nm

The basic product, amitriptyline, interacts with residual silanol groups and is retained more than 500 seconds on all the competitor phases, but not on the Silia*Bond* C18. Our C18 phase presents a better separation property thanks to a better endcapped surface. Also, the Silia*Bond* C18 presents lower back pressure compared to the competition.

Reversed-Phases Portfolio

Low Pressure Chromatography Reversed-Phases Characteristics

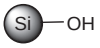
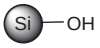
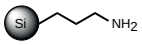
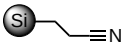
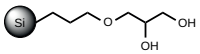
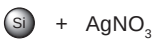
Sorbent & Sorbent Code	Structure	Characteristics*	Typical Applications
C18 R33230B		Endcapping: Yes % C: ≥ 16 % Density: 0.639 g/mL	Indicated for the purification of **low to high polarity compounds**. Provides reproducible purification without the complexity and cost of preparative HPLC.
C18 *nec* R33330B		Endcapping: No % C: 15.5 % Density: 0.640 g/mL	
C8 R30830B		Endcapping: Yes % C: 11.0 % Density: 0.586 g/mL	Presents less retention compared to C18. Typically used for **highly hydrophobic pesticides**, **small peptides** and **large molecule drugs**.
C8 *nec* R31130B		Endcapping: No % C: 11.6 % Density: 0.759 g/mL	
Cyclohexyl (*C6*) R61530B		Endcapping: Yes % C: 9.5 % Density: 0.662 g/mL	Presents less retention compared to C18 and C8, with additional **steric interaction**.
C4 R32030B		Endcapping: Yes % C ≥ 6.67 % Density: 0.656 g/mL	Presents less retention compared to C18 and C8. Widely used for **molecules with large hydrophobic regions**.
C4 *nec* R32130B		Endcapping: No % C ≥ 6.67 % Density: 0.692 g/mL	
C1 R33030B		Endcapping: No % C ≥ 4.17 % Density: 0.559 g/mL	Lower retention compared to other reversed-phases. Used for the purification of **polar and non-polar highly hydrophobic pharmaceutical products**.
Phenyl (*PHE*) R34030B		Endcapping: Yes % C: 8.0 % Density: 0.637 g/mL	Moderate non-polar sorbent with different selectivity for **aromatic compounds** compared to other non-polar sorbents.
Phenyl *nec* (*PHE*) R34130B		Endcapping: No % C: 8.0 % Density: 0.607 g/mL	
Pentafluorophenyl (*PFP*) R67530B		Endcapping: Yes % C: 9.0 % Density: 0.761 g/mL	For a new selectivity approach with aromatic ring interactions, or for the purification of **conjugated compounds (*isomers*)**.
Cyano (*CN*) R38030B		Endcapping: Yes % C: 7.0 % Density: 0.703 g/mL	Versatile sorbent that can be used either as normal or reversed-phase. Indicated for **products with intermediate to extreme polarity**. The slightly hydrophobic nature of the cyano group offers alternative selectivity.

* Typical values
For all sorbents, particle size is 40 - 63 µm and pore diameter is 60 Å.
In bold: most common phases for flash cartridges.
Other phases can be offered on a custom basis, contact us for more information.

Normal Phases Portfolio

Normal phase chromatography is used to separate polar compounds through polar interactions with the support. The interactions take place on the highly polar silanols of the silica gel surface, but there are also moderately polar interactions with the hydrogen bonds on Amino or Diol functions.

Low Pressure Chromatography Normal Phases Characteristics

Sorbent & Sorbent Code	Structure	Characteristics*	Typical Applications
Silica (*Si*) R10030B		Endcapping: No Density: 0.550 g/mL	Most popular sorbent for day-to-day use for the purification of **non-ionic polar organic compounds**.
Silica HP (*Si HP*) R10017B		Part. size: 15 - 40 µm Endcapping: No Density: 0.500 g/mL	High Performance sorbent for difficult separations (***isomers***). Higher loading capacity. Faster flow rate. Less solvent used.
Amine (NH_2) R52030B		Endcapping: Yes % N: ≥ 1.68 % Loading: 1.2 mmol/g Density: 0.700 g/mL	Good alternative for normal phase purification of **compounds with basic properties**. Useful for **monosaccharides** separation. ***Note**: imine formation can be seen with the purification of aldehydes and ketones.*
Amine *nec* (NH_2) R52130B		Endcapping: No % N: ≥ 1.68 % Loading: 1.2 mmol/g Density: 0.700 g/mL	
Cyano (*CN*) R38030B		Endcapping: Yes % N: ≥ 1.93 % Loading: 1.38 mmol/g Density: 0.703 g/mL	Versatile sorbent that can be used either as normal or reversed-phase. Less polar sorbent compared to silica. Used for the purification of **polar organic compounds**.
Cyano *nec* (*CN*) R38130B		Endcapping: No % N: ≥ 1.93 % Loading: 1.38 mmol/g Density: 0.703 g/mL	
Diol nec R35030B		Endcapping: No Loading: 0.97 mmol/g Density: 0.687 g/mL	Good alternative for difficult separation of low to medium polarity samples. Useful for **mono and polysaccharides** separation. Can be used in HILIC mode.
Neutral Alumina AUT-0054	Al_2O_3	Part. size: 75 - 150 µm Endcapping: No	Good retention of **aromatic compounds**, **aliphatic amines** and **compounds containing electronegative functions**.
Florisil AUT-0014	$SiMgO_3$	Part. size: 40 - 75 µm Pore size: 100 Å Endcapping: No	Mainly used for the separation of **chlorinated pesticides**, **polychlorinated biphenyl** (*PCBs*) and **polysaccharides**.
Silver Nitrate ($AgNO_3$) R23530B		Endcapping: No Loading: 10 % w/w Density: 0.604 g/mL	Mainly used for the separation of **cis / trans isomers of unsaturated compounds** such as alkenes, lipids, steroids and terpenes.

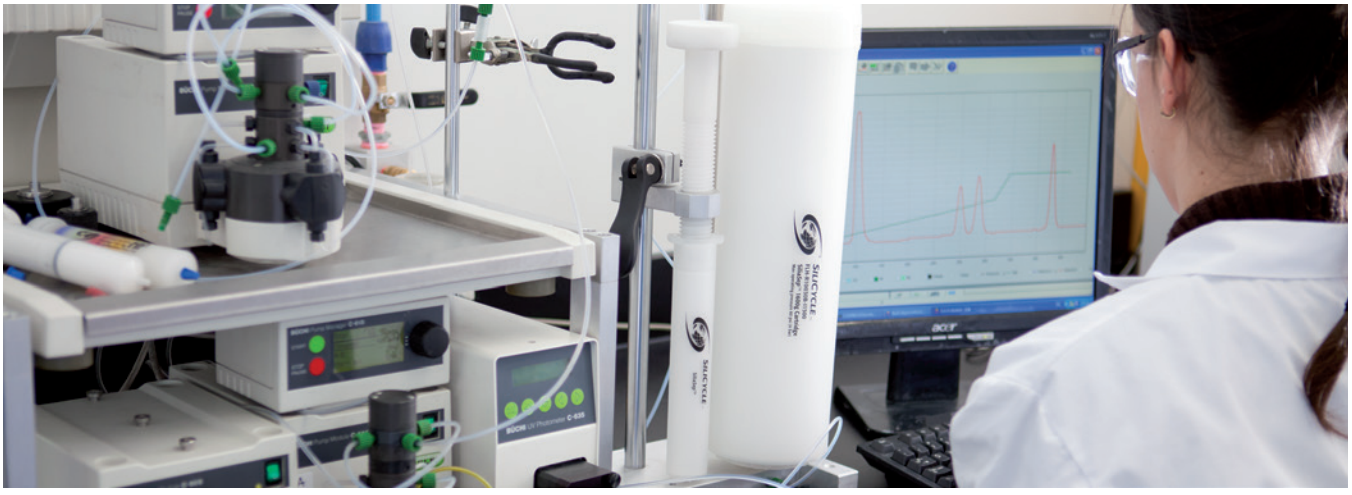
* Typical values
For all sorbents, particle size is 40 - 63 µm and pore diameter is 60 Å (*unless otherwise stated*).
In bold: most common phases for flash cartridges
Other phases can be offered on a custom basis, contact us for more information.

Typical Reversed and Normal Phases Applications

The table below will help you select the right media to purify your compounds of interest. All phases are available either in bulk or pre-packed cartridges.

Typical Applications Using Reversed and Normal Phases												
Analytes	**Examples**	**C18**	**C8**	**C6**	**C4**	**C1**	**PHE**	**PFP**	**CN**	**NH_2**	**Si**	**Diol**
Biomolecules	*Peptides, proteins*	x	x	x	x	x						x
Nucleotides	*Deoxyribonucleotides, ribonucleotides*	x								x		
Lipids	*Phospholipids*		x	x	x	x				x		
Carbohydrates	*Sugars*								x	x		x
Glycosides	*Glucosides, fructosides*								x	x		x
Oligosaccharides	*Malto-Oligosaccharides*									x		x
Pesticides	*Organophosphates*	x	x									
PCBs	-	x					x	x				
PAHs	*Anthracene, pyrene*	x	x				x	x				
Drugs	*Basic drugs, metabolites*	x	x	x					x	x	x	
Alkaloids	*Cocaine, morphine, nicotine, quinine*	x	x						x		x	
Analgesics	*Aspirin, acetaminophen, ibuprofen*	x	x					x	x			
Cyclosporine	-	x							x			
Conjugated Compounds	*Phenols, chloroanilines, steroids, caffeine*	x	x	x	x	x	x	x				
Natural Compounds	*Tannins, aflatoxins, flavonoids, carotenoids*	x	x	x	x	x	x	x				
Fat-Soluble Vitamins	*Vitamins A, D, E and K*	x	x									
Water-Soluble Vitamins	*Vitamins B and C*									x	x	
Heterocyclic Compounds	*Dioxins, Furans*	x										

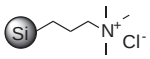
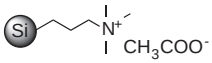
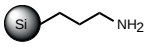
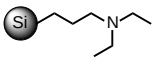
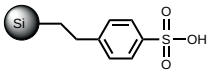
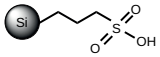
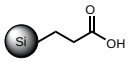
The $AgNO_3$ phase is particularly useful to separate isomers that present unsaturated groups.
The Neutral Alumina phase is used for the separation of aldehydes, ketones, quinines, esters, lactones and glucosides.
The Florisil phase will help analyze pesticides, PCBs and PAHs.



Ion Exchange Phases Portfolio

In ion exchange mode, the silica support is modified by a function carrying a charge with its counter-ion. This counter-ion is exchangeable with other ions in solution. If the immobilized phase is carrying an anion, the exchangeable species is a cation. Inversely, if the immobilized phase carries a cation, the ion exchangeable species will be an anion. Ion exchange phases are widely used in separation and purification.

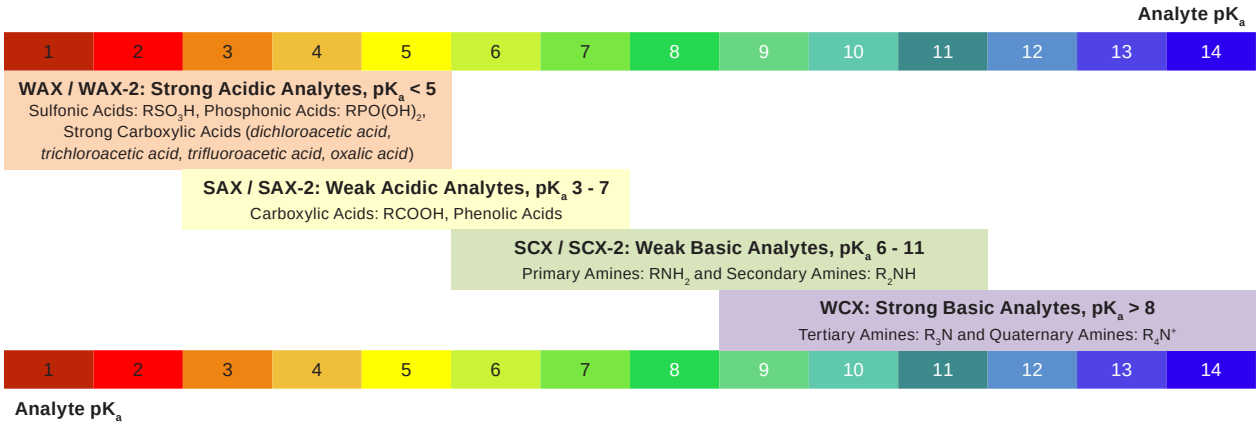
Low Pressure Chromatography Ion Exchange Phases Characteristics

Sorbent & Sorbent Code	Structure	Characteristics*	Typical Applications
SAX *nec* (*TMA Chloride*) R66530B		Endcapping: No Loading: 0.90 meq/g Density: 0.700 g/mL	The quaternary amine is permanently charged (*pH independant*). It is commonly used for the extraction of **weak anions** (*such as **carboxylic acids***) that may not bind strongly enough to weaker anion exchangers. Analysis of **acidic drugs and analgesics**, **biomolecules (*peptides and proteins*) and water-soluble vitamins (*vitamins B and C*)**.
SAX-2 *nec* (*TMA Acetate*) R66430B		Endcapping: No Loading: 0.71 mmol/g Density: 0.665 g/mL	The acetate counter-ion is easily exchangeable (*more than the chloride ion*) for compounds with pK_a < 5, such as carboxylic acids. This phase can be used in organic chemistry applications to **selectively purify acidic compounds** or **remove acidic impurities from reaction mixtures.**
WAX (*Amine*) R52030B		Endcapping: Yes Loading: 1.2 mmol/g Density: 0.700 g/mL	A weak anion exchanger with a pK_a of 9.8. At pH 7.8 or below, the functional groups are positively charged. It facilitates the rapid release of **very strong anions such as sulfonic acids** that may be too strongly retained on SAX.
WAX *nec* (*Amine*) R52130B		Endcapping: No Loading: 1.2 mmol/g Density: 0.700 g/mL	
WAX-2 (*Diethylamine*) R76530B		Endcapping: Yes Loading: 1.04 mmol/g Density: 0.761 g/mL	With a pK_a of 10.5, this phase is prefered over SAX when performing **catch and release purification of compounds bearing a permanent negative charge such as salts of sulfonic acids**. Using SAX in this case could make the release of the compound of interest difficult (*but not necessarily impossible*) due to the strong interaction between the two strong ions.
WAX-2 *nec* (*Diethylamine*) R76630B		Endcapping: No Loading: 1.04 mmol/g Density: 0.761 g/mL	
SCX (*Tosic Acid*) R60530B		Endcapping: Yes Loading: 0.54 meq/g Density: 0.698 g/mL	Due to the very low pK_a (< *1)* these functions are strong cation exchangers since they maintain a negative charge throughout the pH scale. The most common use is likely for **catch and release purification of weak cations (*for example basic drugs and analgesics*)**, **analysis of basic biomolecules (*peptides and proteins*) and water-soluble vitamins (*basic vitamins B and C*)**.
SCX *nec* (*Tosic Acid*) R60430B		Endcapping: No Loading: 0.54 meq/g Density: 0.698 g/mL	
SCX-2 (*Propylsulfonic Acid*) R51230B		Endcapping: Yes Loading: 0.63 mmol/g Density: 0.728 g/mL	
SCX-2 *nec* (*Propylsulfonic Acid*) R51430B		Endcapping: No Loading: 0.63 mmol/g Density: 0.728 g/mL	
WCX (*Carboxylic Acid*) R70030B		Endcapping: Yes Loading: 0.92 mmol/g Density: 0.687 g/mL	A weak cation exchanger with a pK_a of 4.8. A pH of 2.8 or below is needed to neutralize the phase and easily elute strong cationic analytes that are neutralized only at extreme basic conditions. This phase is commonly used for the extraction of **strong cationic species**, which would bind too strongly to strong cation exchangers.
WCX *nec* (*Carboxylic Acid*) R70130B		Endcapping: No Loading: 0.92 mmol/g Density: 0.687 g/mL	

* Typical values
For all sorbents, particle size is 40 - 63 µm and pore diameter is 60 Å.
In bold: most common phases for flash cartridges
Other phases can be offered on a custom basis, contact us for more information.

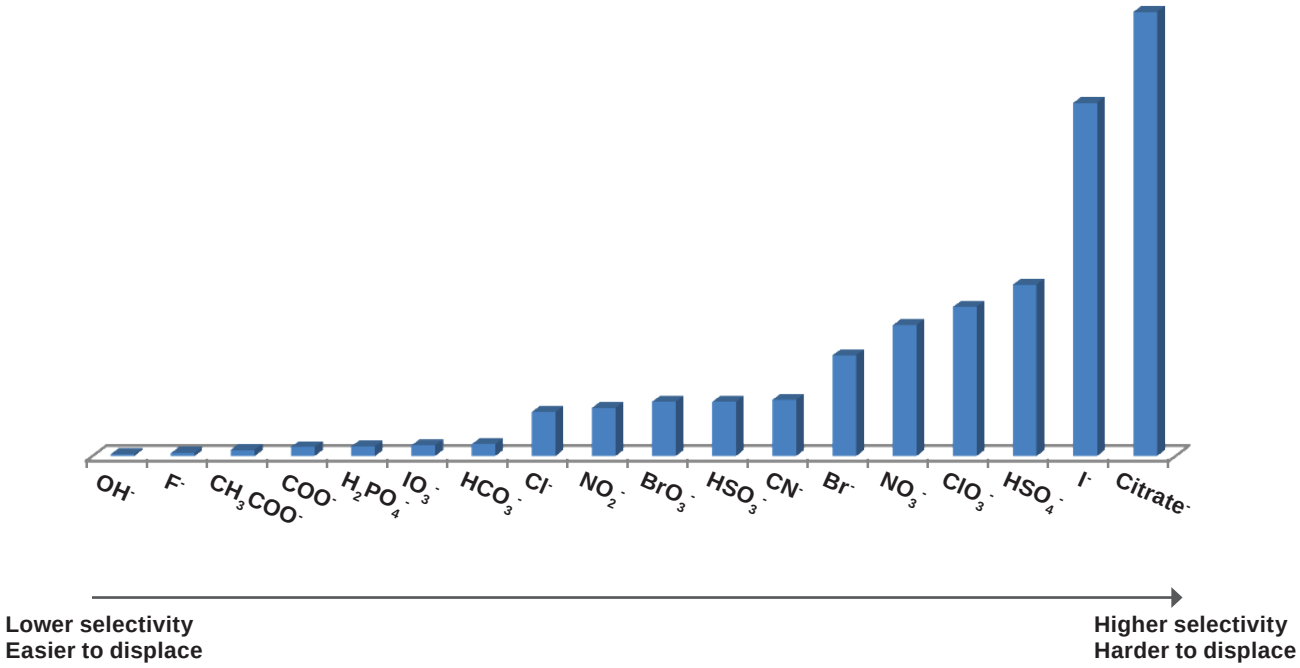
Ion Exchange Phases vs Analyte pK_a

The graph below will help you choose the right phase according to your analyte's pK_a.



Counter-Ion Selectivity in Ion Exchange Mode

SAX phases are always paired with a counter-ion to neutralize the quaternary amine charge. But counter-ions have different selectivites and some are more easily removed from the silica gel by the analyte. You will find below the relative selectivity of standard counter-ions, compared to the hydroxyl ion OH^- (*lowest selectivity*). Always choose a phase paired with a counter-ion less selective than the analyte.



Silia*Bond* Bulk Ordering Information

To build your own product number, just select the appropriate Sorbent Code (*see pages 229 - 232*) and add the quantity needed* at the end: [Sorbent Code] - [Format].
E.g.: 100 g of endcapped C18 => R33230B-100G (*for 60 Å and 40 - 63 µm silica gel*).

Silia*Bond* phases are also available on all irregular Silia*Flash* silicas (*R100-*) and on all spherical Silia*Sphere* PC silicas (*S100-*). You will find below the most common bare & bonded silica gels ordered in bulk.

Silia*Bond* Bulk Ordering Information					
Silica Type** (***Silica Code***)	60 Å, 40 - 63 µm (*30B*)	60 Å, 60 - 200 µm (*40B*)	60 Å, 200 - 500 µm (*70B*)	300 Å, 40 - 63 µm (*30M*)	Spherical 100 Å, 40 - 75 µm (*30E*)
Silia*Bond* Silica (*R100*)	R10030B	R10040B	R10070B	R10030M	S10030E
Silia*Bond* Amine (*R520*)	R52030B	R52040B	R52070B	R52030M	S52030E
Silia*Bond* Diol *nec* (*R350*)	R35030B	R35040B	R35070B	R35030M	S35030E
Silia*Bond* Cyano (*R380*)	R38030B	R38040B	R38070B	R38030M	S38030E
Silia*Bond* C18 (*17 %*) (*R332*)	R33230B	R33240B	R33270B	R33230M	S33230E
Silia*Bond* C8 (*R308*)	R30830B	R30840B	R30870B	R30830M	S30830E
Silia*Bond* Phenyl (*R340*)	R34030B	R34040B	R34070B	R34030M	S34030E
Silia*Bond* PFP (*R675*)	R67530B	R67540B	R67570B	R67530M	S67530E
Silia*Bond* SCX (*R605*)	R60530B	R60540B	R60570B	R60530M	S60530E
Silia*Bond* SCX-2 (*R512*)	R51230B	R51240B	R51270B	R51230M	S51230E
Silia*Bond* SAX *nec* (*R665*)	R66530B	R66540B	R66570B	R66530M	S66530E
Silia*Bond* SAX-2 *nec* (*R664*)	R66430B	R66440B	R66470B	R66430M	S66430E

* Available formats: from a few grams to multi-ton scale. 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 2 kg, 5 kg, etc.
** See page 223 for all available irregular Silia*Flash* & spherical Silia*Sphere* PC silica types and corresponding codes.
Please note product numbers begin by R- for irregular silicas and by S- for spherical silicas.
For Metal Scavengers bulk silicas, see page 206 for more information.

Silia*Sep* Flash Cartridges Features & Benefits

With a more tightly packed silica bed and a homogeneous packing, the use of pre-packed flash cartridges improves purification efficiency by offering superior reproducibility and productivity compared to conventional manual flash chromatography.

Today, various manufacturers offer pre-packed flash cartridges, but performance and quality varies. Silia*Sep* offers superior performances over competitive cartridges. With Silia*Sep*, you will benefit from the same quality that all our products are known for: speed, reliability & selectivity.

Features & Benefits of Silia*Sep*	
Features	**Benefits**
Highest silica gel quality, with lowest level of fines	No product contamination Homogeneous packing, no channelling (*no peak tailing*) High loading capacity (*high surface area*) Direct transfer from TLC to flash chromatography
Innovative packing technology	Consistent packing for reproducible high plate count (*N*) Superior performance & separation Higher resolution with improved band definition (*no tailing*) Greater compound purity & higher recovery
Versatility	Wide choice of cartridge sizes from 4 grams to 1.6 kg (*for bigger columns, consult the Process & Industrial Purification section page 247*) Purification scale-up from milligram to hundreds of grams Variety of sorbents to meet any separation need
Reproducibility, reliability & safety	Leak-free guaranteed by unique one-piece cartridge design Reproducible performance from lot-to-lot (*stringent quality control*) Excellent durability to withstand high pressures Universal luer fittings for compatibility with any flash system
Cost effectiveness	Excellent performance vs price ratio Readily available from stock inventory for many volumes

Silia*Sep* Flash Cartridge Design

Silia*Sep* Flash Cartridge Types Overview

Silia*Sep* Cartridges Characteristics						
Characteristics	**Units**	Silia*Sep* 4 g	Silia*Sep* 12 g	Silia*Sep* 25 g	Silia*Sep* 40 g	Silia*Sep* 80 g
Cartridge Code	-	ISO04	ISO12	ISO25	ISO40	ISO80
Silica Weight	g	Bare: 4 g Bonded: ≥ 5 g	Bare: 12 g Bonded: ≥ 15 g	Bare: 25 g Bonded: ≥ 30 g	Bare: 40 g Bonded: ≥ 45 g	Bare: 80 g Bonded: ≥ 90 g
Qty / Box	unit	Bare: 20 Bonded: 2	Bare: 20 Bonded: 1	Bare: 15 Bonded: 1	Bare: 15 Bonded: 1	Bare: 12 Bonded: 1
Dimension (*ID x Length*)	mm	12 x 98	21 x 117	21 x 165	27 x 169	31 x 237
Column Volume	mL	4.9	17	31	47	123
Recommended Flow Rate	mL/min	15 - 25	20 - 40	20 - 45	25 - 50	40 - 80
Loading Capacity (*Bare Silica*)	g	0.040 - 0.4	0.120 - 1.2	0.250 - 2.5	0.400 - 4.0	0.800 - 8.0
Max Operating Pressure	-	225 psi / 16 bar	225 psi / 16 bar	225 psi / 16 bar	225 psi / 16 bar	225 psi / 16 bar

How to build your own product number:
Product Number ➔ FLH - [Sorbent Code] - [Cartridge Code] E.g.: 4 g cartridge with endcapped C18 silica gel => FLH-R33230B-ISO04

Silia*Sep* Ordering Information

Silia*Sep* Cartridges Ordering Information					
Silia*Sep* Type	Silia*Sep* 4 g	Silia*Sep* 12 g	Silia*Sep* 25 g	Silia*Sep* 40 g	Silia*Sep* 80 g
Silia*Sep* Bare Phases					
Qty / Box	20	20	15	15	12
Silia*Sep* Silica	FLH-R10030B-ISO04	FLH-R10030B-ISO12	FLH-R10030B-ISO25	FLH-R10030B-ISO40	FLH-R10030B-ISO80
Silia*Sep* Silica HP	FLH-R10017B-ISO04	FLH-R10017B-ISO12	FLH-R10017B-ISO25	FLH-R10017B-ISO40	FLH-R10017B-ISO80
Silia*Sep* Bonded Phases					
Qty / Box*	2	1	1	1	1
Silia*Sep* Amine	FLH-R52030B-ISO04	FLH-R52030B-ISO12	FLH-R52030B-ISO25	FLH-R52030B-ISO40	FLH-R52030B-ISO80
Silia*Sep* Diol *nec*	FLH-R35030B-ISO04	FLH-R35030B-ISO12	FLH-R35030B-ISO25	FLH-R35030B-ISO40	FLH-R35030B-ISO80
Silia*Sep* Cyano	FLH-R38030B-ISO04	FLH-R38030B-ISO12	FLH-R38030B-ISO25	FLH-R38030B-ISO40	FLH-R38030B-ISO80
Silia*Sep* C18 (*17 %*)	FLH-R33230B-ISO04	FLH-R33230B-ISO12	FLH-R33230B-ISO25	FLH-R33230B-ISO40	FLH-R33230B-ISO80
Silia*Sep* C8	FLH-R30830B-ISO04	FLH-R30830B-ISO12	FLH-R30830B-ISO25	FLH-R30830B-ISO40	FLH-R30830B-ISO80
Silia*Sep* Phenyl	FLH-R34030B-ISO04	FLH-R34030B-ISO12	FLH-R34030B-ISO25	FLH-R34030B-ISO40	FLH-R34030B-ISO80
Silia*Sep* PFP	FLH-R67530B-ISO04	FLH-R67530B-ISO12	FLH-R67530B-ISO25	FLH-R67530B-ISO40	FLH-R67530B-ISO80
Silia*Sep* SCX	FLH-R60530B-ISO04	FLH-R60530B-ISO12	FLH-R60530B-ISO25	FLH-R60530B-ISO40	FLH-R60530B-ISO80
Silia*Sep* SCX-2	FLH-R51230B-ISO04	FLH-R51230B-ISO12	FLH-R51230B-ISO25	FLH-R51230B-ISO40	FLH-R51230B-ISO80
Silia*Sep* SAX *nec*	FLH-R66530B-ISO04	FLH-R66530B-ISO12	FLH-R66530B-ISO25	FLH-R66530B-ISO40	FLH-R66530B-ISO80
Silia*Sep* SAX-2 *nec*	FLH-R66430B-ISO04	FLH-R66430B-ISO12	FLH-R66430B-ISO25	FLH-R66430B-ISO40	FLH-R66430B-ISO80

* Bigger box sizes available, contact us for more information.
Other phases can be offered, contact us for details.
For Metal Scavengers Cartridges, see page 208 for more information.

SiliaSep Cartridges Characteristics						
SiliaSep 120 g	SiliaSep 220 g	SiliaSep 330 g	SiliaSep XL 800 g	SiliaSep XL 1,600 g	Units	Characteristics
IS120	IS220	IS330	IS750	I1500	-	Cartridge Code
Bare: 120 g Bonded: ≥ 130 g	Bare: 220 g Bonded: ≥ 230 g	Bare: 330 g Bonded: ≥ 360 g	Bare: 800 g Bonded: ≥ 870 g	Bare: 1,600 g Bonded: ≥ 1,700 g	g	Silica Weight
Bare: 10 Bonded: 1	Bare: 4 Bonded: 1	Bare: 4 Bonded: 1	Bare: 2 Bonded: 1	Bare: 2 Bonded: 1	unit	Qty / Box
36 x 256	60 x 195	60 x 268	78 x 382	104 x 429	mm	Dimension (*ID x Length*)
190	306	441	1,500	2,900	mL	Column Volume
60 - 120	60 - 180	80 - 180	200 - 300	300 - 450	mL/min	Recommended Flow Rate
1.2 - 12.0	2.2 - 22.0	3.3 - 33.0	8.0 - 80.0	16.0 - 160.0	g	Loading Capacity (*Bare Silica*)
205 psi / 13 bar	160 psi / 11 bar	160 psi / 11 bar	125 psi / 8 bar	100 psi / 7 bar	-	Max Operating Pressure

SiliaSep Cartridges Ordering Information					
SiliaSep 120 g	SiliaSep 220 g	SiliaSep 330 g	SiliaSep XL 800 g	SiliaSep XL 1,600 g	SiliaSep Type
					SiliaSep Bare Phases
10	4	4	2	2	Qty / Box
FLH-R10030B-IS120	FLH-R10030B-IS220	FLH-R10030B-IS330	FLH-R10030B-IS750	FLH-R10030B-I1500	SiliaSep Silica
FLH-R10017B-IS120	FLH-R10017B-IS220	FLH-R10017B-IS330	FLH-R10017B-IS750	FLH-R10017B-I1500	SiliaSep Silica HP
					SiliaSep Bonded Phases
1	1	1	1	1	Qty / Box*
FLH-R52030B-IS120	FLH-R52030B-IS220	FLH-R52030B-IS330	FLH-R52030B-IS750	FLH-R52030B-I1500	SiliaSep Amine
FLH-R35030B-IS120	FLH-R35030B-IS220	FLH-R35030B-IS330	FLH-R35030B-IS750	FLH-R35030B-I1500	SiliaSep Diol *nec*
FLH-R38030B-IS120	FLH-R38030B-IS220	FLH-R38030B-IS330	FLH-R38030B-IS750	FLH-R38030B-I1500	SiliaSep Cyano
FLH-R33230B-IS120	FLH-R33230B-IS220	FLH-R33230B-IS330	FLH-R33230B-IS750	FLH-R33230B-I1500	SiliaSep C18 (*17 %*)
FLH-R30830B-IS120	FLH-R30830B-IS220	FLH-R30830B-IS330	FLH-R30830B-IS750	FLH-R30830B-I1500	SiliaSep C8
FLH-R34030B-IS120	FLH-R34030B-IS220	FLH-R34030B-IS330	FLH-R34030B-IS750	FLH-R34030B-I1500	SiliaSep Phenyl
FLH-R67530B-IS120	FLH-R67530B-IS220	FLH-R67530B-IS330	FLH-R67530B-IS750	FLH-R67530B-I1500	SiliaSep PFP
FLH-R60530B-IS120	FLH-R60530B-IS220	FLH-R60530B-IS330	FLH-R60530B-IS750	FLH-R60530B-I1500	SiliaSep SCX
FLH-R51230B-IS120	FLH-R51230B-IS220	FLH-R51230B-IS330	FLH-R51230B-IS750	FLH-R51230B-I1500	SiliaSep SCX-2
FLH-R66530B-IS120	FLH-R66530B-IS220	FLH-R66530B-IS330	FLH-R66530B-IS750	FLH-R66530B-I1500	SiliaSep SAX *nec*
FLH-R66430B-IS120	FLH-R66430B-IS220	FLH-R66430B-IS330	FLH-R66430B-IS750	FLH-R66430B-I1500	SiliaSep SAX-2 *nec*

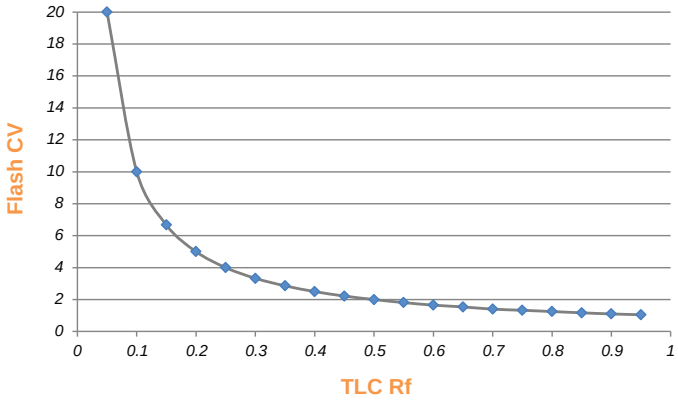
For bigger columns, please consult the Process & Industrial Purification section page 247.

Method Development - Prediction of Column Volumes (*CV*)

TLC data can be used to predict column elution based on the relationship between TLC retention factor (*Rf*) and flash retention time (*measured in column volume, CV*). CV is the number of column volumes required to elute the component from the column, regardless of column dimensions. So the first step to convert a TLC method in flash chromatography is to convert Rf in CV. Rf and CV are inversely proportional:

CV = 1 / Rf

You will find below a graph showing lower Rfs in TLC means greater CVs in flash (*so better analyte retention*). On the right is a chart giving CV values according to typical Rf values.



Rf vs CV

TLC Rf	Flash CV
0.95	1.05
0.90	1.10
0.85	1.17
0.80	1.25
0.75	1.33
0.70	1.40
0.65	1.54
0.60	1.65
0.55	1.81
0.50	2.00
0.45	2.22
0.40	2.50
0.35	2.86
0.30	3.33
0.25	4.00
0.20	5.00
0.15	6.67
0.10	10.00
0.05	20.00

As CV is a measure of analyte retention, then ΔCV is a measure of two analytes separation and resolution:

$$\Delta CV = CV_1 - CV_2 = (1 / Rf_1) - (1 / Rf_2)$$

Here is a chart giving ΔCV values according to Rf_1 and Rf_2 values.

Rf_2 / Rf_1	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95
0.05	0.00																		
0.10	10.00	0.00																	
0.15	13.33	3.33	0.00																
0.20	15.00	5.00	1.67	0.00															
0.25	16.00	6.00	2.67	1.00	0.00														
0.30	16.67	6.67	3.34	1.67	0.67	0.00													
0.35	17.14	7.14	3.81	2.14	1.14	0.47	0.00												
0.40	17.50	7.50	4.17	2.50	1.50	0.83	0.36	0.00											
0.45	17.78	7.78	4.45	2.78	1.78	1.11	0.64	0.28	0.00										
0.50	18.00	8.00	4.67	3.00	2.00	1.33	0.86	0.50	0.22	0.00									
0.55	18.19	8.19	4.86	3.16	2.16	1.52	1.05	0.69	0.41	0.19	0.00								
0.60	18.35	8.35	5.02	3.35	2.35	1.68	1.21	0.85	0.57	0.35	0.16	0.00							
0.65	18.46	8.46	5.13	3.46	2.46	1.79	1.32	0.98	0.68	0.46	0.27	0.11	0.00						
0.70	18.60	8.60	5.27	3.60	2.60	1.93	1.46	1.10	0.82	0.60	0.41	0.25	0.14	0.00					
0.75	18.67	8.67	5.34	3.67	2.67	2.00	1.53	1.17	0.89	0.67	0.48	0.32	0.21	0.07	0.00				
0.80	18.75	8.75	5.42	3.75	2.75	2.08	1.61	1.25	0.97	0.75	0.56	0.40	0.29	0.15	0.08	0.00			
0.85	18.83	8.83	5.50	3.83	2.83	2.16	1.69	1.33	1.05	0.83	0.64	0.48	0.37	0.23	0.16	0.08	0.00		
0.90	18.90	8.90	5.57	3.90	2.90	2.23	1.76	1.40	1.12	0.90	0.71	0.55	0.44	0.30	0.23	0.15	0.07	0.00	
0.95	18.95	8.95	5.62	3.95	2.95	2.28	1.81	1.45	1.17	0.95	0.76	0.60	0.49	0.35	0.28	0.20	0.12	0.05	0.00

Correlation between ΔCV and Rf_1 & Rf_2

Method Development - From TLC to Low Pressure Chromatography

It is now understood that TLC methods should be optimized so that compounds of interest elute with lower Rfs, ideally between 0.1 and 0.4. Adjust the TLC solvent mixture (*solvent polarity and composition of the mixture*) to obtain the preferred Rfs. An optimized TLC method will assure you a better separation and purification of your compounds in low pressure chromatography, with optimal loading capacity (*you will be able to load more on the cartridge if your compounds are well separated*). We recommend using a flash cartridge phase matching the TLC plate, for a more linear and easy method conversion. You should also run your flash chromatography with the same solvent conditions as your TLC method (*in isocratic mode*).

Case Study

We need to separate two analytes, 1 and 2. We will study two different TLC configurations.

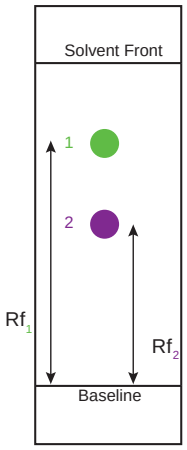


Plate 1

1 and 2 TLC spots are high and well distinct

Converting TLC to Low Pressure Chromatography

	Rf_1	CV_1	Rf_2	CV_2	ΔCV
Plate 1	0.75	1.33	0.5	2	0.67
Plate 2	0.2	5	0.1	10	5

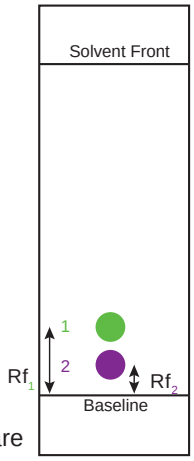
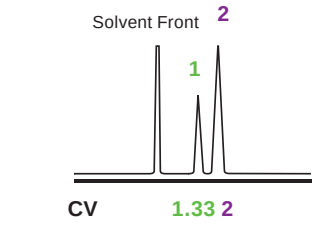
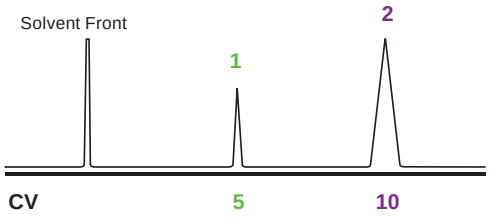


Plate 2

1 and 2 TLC spots are low and quite close



1 and 2 are poorly retained and separated in flash chromatography



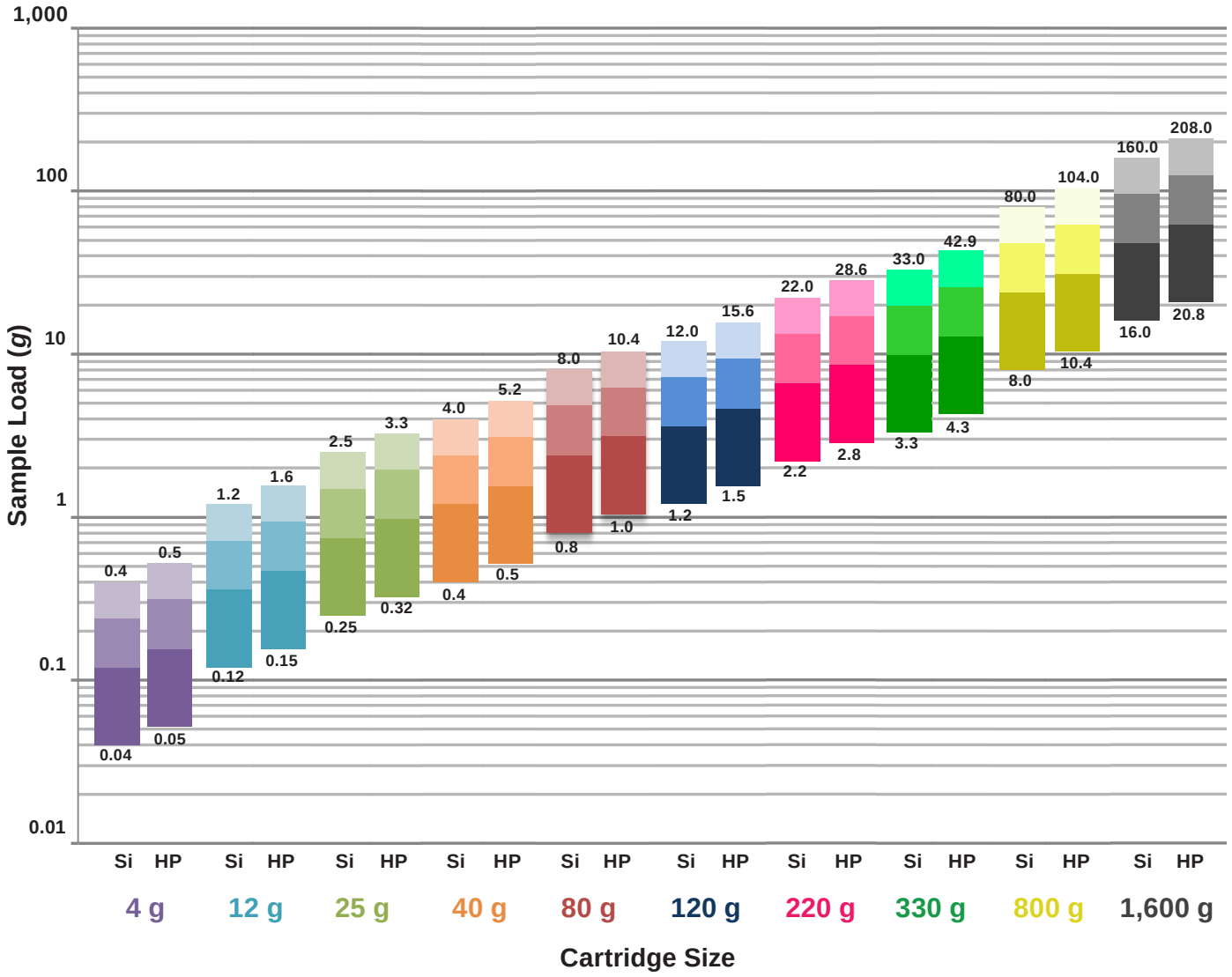
1 and 2 are well retained and separated in flash chromatography

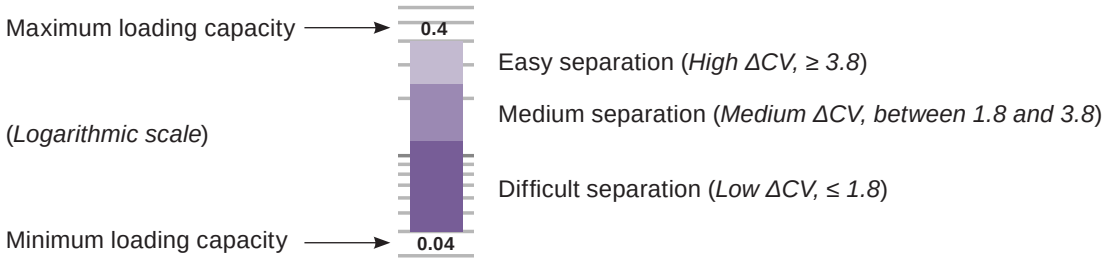
To sum up:

- **The lower the Rfs, the greater ΔCV.**
- **The greater ΔCV, the greater the separation and resolution between the spots (*easier separation*).**
- **The greater ΔCV, the more sample can be loaded onto the column.**

Low Pressure Chromatography Loading Chart

The chart below will help you choose the right cartridge size according to your sample size and your TLC results.





Low Pressure Chromatography Loading Chart

Loading capacity depends on the sample itself, the column dimension and the column chemistry. You will find below the sample loading we recommand with our Silia*Sep* flash cartridges. For easily separated compounds (*ΔCV > 6*) we suggest to load up to 5 % on bonded phases, up to 10 % on bare silica and up to 13 % on bare silica HP.

Low Pressure Chromatography Loading Chart

Dimension ID x Length (*mm x mm*)	Silia*Sep* Format	Silia*Sep* Phase	Load (*g*)									
			ΔCV = 0.1 - 0.6	ΔCV = 0.7 - 1.2	ΔCV = 1.3 - 1.8	ΔCV = 1.9 - 2.4	ΔCV = 2.5 - 3.1	ΔCV = 3.2 - 3.8	ΔCV = 3.9 - 4.5	ΔCV = 4.6 - 5.2	ΔCV = 5.3 - 6.0	ΔCV > 6
12 x 98	4 g	Bare Silica	0.040	0.080	0.120	0.160	0.200	0.240	0.280	0.320	0.360	0.400
		Bare Silica HP	0.052	0.104	0.156	0.208	0.260	0.312	0.364	0.416	0.468	0.520
		Bonded	0.020	0.040	0.060	0.080	0.100	0.120	0.140	0.160	0.180	0.200
21 x 117	12 g	Bare Silica	0.120	0.240	0.360	0.480	0.600	0.720	0.840	0.960	1.080	1.200
		Bare Silica HP	0.156	0.312	0.468	0.624	0.780	0.936	1.092	1.248	1.404	1.560
		Bonded	0.060	0.120	0.180	0.240	0.300	0.360	0.420	0.480	0.540	0.600
21 x 165	25 g	Bare Silica	0.250	0.500	0.750	1.000	1.250	1.500	1.750	2.000	2.250	2.500
		Bare Silica HP	0.325	0.650	0.975	1.300	1.625	1.950	2.275	2.600	2.925	3.250
		Bonded	0.125	0.250	0.375	0.500	0.625	0.750	0.875	1.000	1.125	1.250
27 x 169	40 g	Bare Silica	0.400	0.800	1.200	1.600	2.000	2.400	2.800	3.200	3.600	4.000
		Bare Silica HP	0.520	1.040	1.560	2.080	2.600	3.120	3.640	4.160	4.680	5.200
		Bonded	0.200	0.400	0.600	0.800	1.000	1.200	1.400	1.600	1.800	2.000
31 x 237	80 g	Bare Silica	0.800	1.600	2.400	3.200	4.000	4.800	5.600	6.400	7.200	8.000
		Bare Silica HP	1.040	2.080	3.120	4.160	5.200	6.240	7.280	8.320	9.360	10.400
		Bonded	0.400	0.800	1.200	1.600	2.000	2.400	2.800	3.200	3.600	4.000
36 x 256	120 g	Bare Silica	1.200	2.400	3.600	4.800	6.000	7.200	8.400	9.600	10.800	12.000
		Bare Silica HP	1.560	3.120	4.680	6.240	7.800	9.360	10.920	12.480	14.040	15.600
		Bonded	0.600	1.200	1.800	2.400	3.000	3.600	4.200	4.800	5.400	6.000
60 x 195	220 g	Bare Silica	2.200	4.400	6.600	8.800	11.000	13.200	15.400	17.600	19.800	22.000
		Bare Silica HP	2.860	5.720	8.580	11.440	14.300	17.160	20.020	22.880	25.740	28.600
		Bonded	1.100	2.200	3.300	4.400	5.500	6.600	7.700	8.800	9.900	11.000
60 x 268	330 g	Bare Silica	3.300	6.600	9.900	13.200	16.500	19.800	23.100	26.400	29.700	33.000
		Bare Silica HP	4.290	8.580	12.870	17.160	21.450	25.740	30.030	34.320	38.610	42.900
		Bonded	1.650	3.300	4.950	6.600	8.250	9.900	11.550	13.200	14.850	16.500
78 x 382	800 g	Bare Silica	8.000	16.000	24.000	32.000	40.000	48.000	56.000	64.000	72.000	80.000
		Bare Silica HP	10.400	20.800	31.200	41.600	52.000	62.400	72.800	83.200	93.600	104.000
		Bonded	4.000	8.000	12.000	16.000	20.000	24.000	28.000	32.000	36.000	40.000
104 x 429	1,600 g	Bare Silica	16.000	32.000	48.000	64.000	80.000	96.000	112.000	128.000	144.000	160.000
		Bare Silica HP	20.800	41.600	62.400	83.200	104.000	124.800	145.600	166.400	187.200	208.000
		Bonded	8.000	16.000	24.000	32.000	40.000	48.000	56.000	64.000	72.000	80.000

For alumina sorbent, refer to the bare silica loading capacity.
Note: There is no linearity between TLC and flash for bonded phases (*not the exact same silica*). The loading capacities for bonded phases written above are just informative, they won't necessarily match the ΔCVs measured in TLC.

Silia*Sep* Solid-Load Cartridges

The use of solid-load technique (*also called dry-load*) will improve chromatography resolution, especially for compounds soluble only in strong solvents or in large volumes of solvents. Silia*Sep* Solid-Load luer-lock cartridges are designed to be used with Silia*Sep* flash cartridges for sample loading. To better suit your needs, two formats are available:

- **Silia*Sep* pre-packed solid-load** (*for liquid injection, various choices of media available: silica, amine, diol, cyano and C18*). You should be able to dilute your sample in 1 column volume at the most. If not, choose a bigger pre-packed solid-load cartridge.
- **Silia*Sep* empty solid-load** (*for silica-sample slurry, dry by evaporating the solvent for a more concentrated sample and to eliminate any solvent effect on the purification*). For a dry sample slurry, use a 1:1 ratio (*1 g of silica for 1 g of dry sample*) but for an oily sample prefer a 3:1 ratio (*3 g of silica for 1 g of oily sample*).

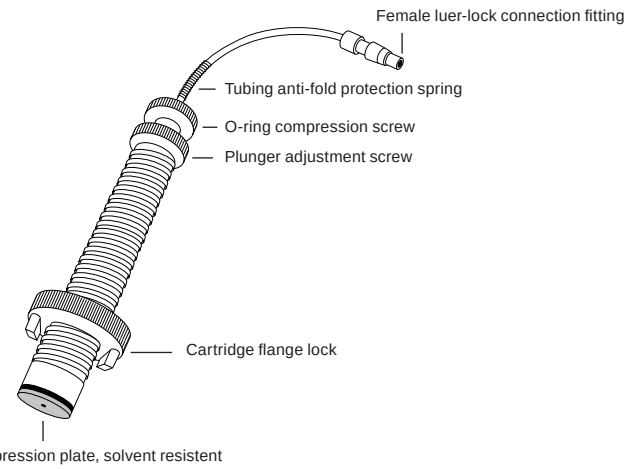
Silia*Sep* Solid-Load Cartridges (*Luer-Lock*)				
Product Number	**Sorbent**	**Weight / Volume**	**Description**	**Qty / Box**
SPL-R10030B-10U	Silica (*40 - 63 µm*)	2 g / 10 mL	Silia*Sep* Silica Pre-packed Solid-Load Cartridge, 2 g, 10 mL	20
SPL-R10030B-10X	Silica (*40 - 63 µm*)	5 g / 10 mL	Silia*Sep* Silica Pre-packed Solid-Load Cartridge, 5 g, 10 mL	20
SPL-R10030B-60Y	Silica (*40 - 63 µm*)	10 g / 60 mL	Silia*Sep* Silica Pre-packed Solid-Load Cartridge, 10 g, 60 mL	16
SPL-R10030B-60K	Silica (*40 - 63 µm*)	25 g / 60 mL	Silia*Sep* Silica Pre-packed Solid-Load Cartridge, 25 g, 60 mL	16
SPL-R10030B-065	Silica (*40 - 63 µm*)	65 g / 150 mL	Silia*Sep* Silica Pre-packed XL Solid-Load Cartridge, 65 g, 150 mL	12
SPL-R10030B-270	Silica (*40 - 63 µm*)	270 g / 700 mL	Silia*Sep* Silica Pre-packed XL Solid-Load Cartridge, 270 g, 700 mL	6
SPL-R52030B-10X	Amine	5 g / 10 mL	Silia*Sep* Amine Pre-packed Solid-Load Cartridge, 5 g, 10 mL	20
SPL-R52030B-60K	Amine	25 g / 60 mL	Silia*Sep* Amine Pre-packed Solid-Load Cartridge, 25 g, 60 mL	16
SPL-R35030B-10X	Diol	5 g / 10 mL	Silia*Sep* Diol Pre-packed Solid-Load Cartridge, 5 g, 10 mL	20
SPL-R35030B-60K	Diol	25 g / 60 mL	Silia*Sep* Diol Pre-packed Solid-Load Cartridge, 25 g, 60 mL	16
SPL-R38030B-10X	Cyano	5 g / 10 mL	Silia*Sep* Cyano Pre-packed Solid-Load Cartridge, 5 g, 10 mL	20
SPL-R38030B-60K	Cyano	25 g / 60 mL	Silia*Sep* Cyano Pre-packed Solid-Load Cartridge, 25 g, 60 mL	16
SPL-R33230B-10X	C18 (*17 %*)	5 g / 10 mL	Silia*Sep* C18 (*17 %*) Pre-packed Solid-Load Cartridge, 5 g, 10 mL	20
SPL-R33230B-60K	C18 (*17 %*)	25 g / 60 mL	Silia*Sep* C18 (*17 %*) Pre-packed Solid-Load Cartridge, 25 g, 60 mL	16
SPL-0009-010	Empty	- / 10 mL	Silia*Sep* Empty Solid-Load Cartridge, 10 mL (*with 200 frits*)	100
AUT-0134	-	-	Frits for Silia*Sep* Empty Solid-Load Cartridge, 10 mL	100
SPL-0012-060	Empty	- / 60 mL	Silia*Sep* Empty Solid-Load Cartridge, 60 mL (*with 200 frits*)	100
AUT-0135	-	-	Frits for Silia*Sep* Empty Solid-Load Cartridge, 60 mL	100
AUT-0090-150	Empty	- / 150 mL	Silia*Sep* Empty Solid-Load Cartridge, 150 mL (*with 24 frits*)	12
AUT-0090-700	Empty	- / 700 mL	Silia*Sep* Empty Solid-Load Cartridge, 700 mL (*with 12 frits*)	6

Other Pre-Packed Solid-Load Cartridges phases can be offered, contact us for more information.
Note: for optimal purification performance, solvent removal under vacuum is highly recommended.

Silia*Sep* Plungers

SiliaSep Plungers*	
Product Number	**Description**
AUT-0060-010	Plunger for 10 mL Solid-Load Cartridge (*16 mm*)
AUT-0060-060	Plunger for 60 mL Solid-Load Cartridge (*27 mm*)

*Ask for Silia*Sep* Plungers Operating Instructions Guide



Silia*Sep* System Compatibility

The table below will help you determine the compatibility of Silia*Sep* cartridges with your system.

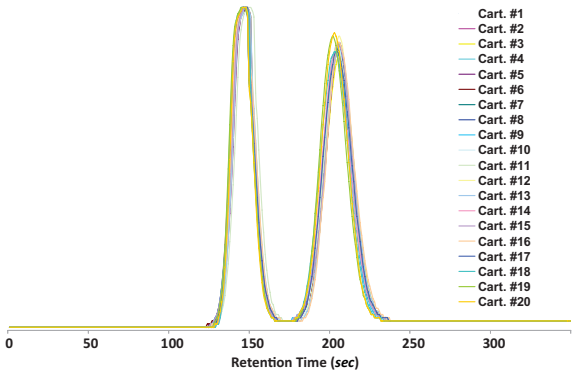
Silia*Sep* System Compatibility		
System	**Silia*Sep* Cartridges**	**Comments**
Teledyne Isco™ CombiFlash®		100 % compatible
Varian® (*Analogix*®) IntelliFlash® & SimpliFlash®		100 % compatible
Interchim PuriFlash™ 430 evo & Spot II (*Armen*®)		100 % compatible
Büchi Sepacore™		100 % compatible
Grace Reveleris™		100 % compatible
Biotage Isolera™		100 % compatible
Biotage Horizon™		Use the Biotage Adapter Kit (*PN: KAD-1006*) or the Solvent Line Replacement (*PN: KAD-1014*)
Biotage SP1 & SP4		Use Support Rings to allow the Silia*Sep* cartridge to sit on the instrument (*Support Ring Kit PN: KAD-1008*)
Biotage FlashMaster™		Use the FlashMaster Adapter Kit (*PN: KAD-1016*) or connect a Silia*Sep* OT cartridge (*see page 246*)

 Direct compatibility

 Compatibility via an adapter

Silia*Sep* Reproducibility

Silia*Sep* and Silia*Sep* HP flash cartridges offer incredible performance over competitive products, due to higher silica gel quality and innovative packing technology. Both cartridge series allow superior results and can be considered the products of choice for all purification needs.



Silia*Sep* 40 g

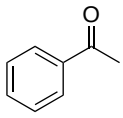
Silia*Sep* Superior Performance

AstraZeneca and Exelixis independently evaluated the performance of Silia*Sep* cartridges against some established players in chromatography and purification*. In this study, cartridge performances were evaluated by the determination of different parameters including selectivity (*α*), plate count (*N*) and resolution factor (*R*). In all cases, Silia*Sep* showed excellent performance over the competition.

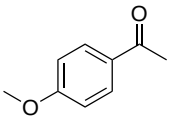
Pre-packed cartridges were chosen with the same apparent irregular silica gel grade: **SiliCycle Silia*Sep*** 40 g, **ISCO Redi*Sep*®** 40 g and **Biotage® SNAP** 40 g. Columns were compared on the same system and with the same conditions. Flow rate was set at 40 mL/min.

*Find the article: *Molecular Diversity*, **2009**, *13*, 247-252

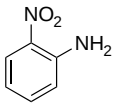
Observed Chromatographic Parameters									
Cartridge	*Acetophenone 4-Methoxyacetophenone 400 mg*			*Acetophenone 4-Methoxyacetophenone 2 g*			*2-Nitroaniline 4-Nitroaniline 2 g*		
	α	N	R	α	N	R	α	N	R
SiliCycle Silia*Sep* 40 g	2.96	153	2.49	0.68	59	1.62	3.29	15.3	1.39
ISCO Redi*Sep*® 40 g	3.00	122	0.29	0.71	43	0.67	3.05	13.7	1.23
Biotage® SNAP 40 g	2.81	54	low	0.591	low	low	3.34	low	low



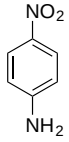
Acetophenone



4-Methoxyacetophenone

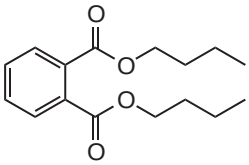


2-Nitroaniline

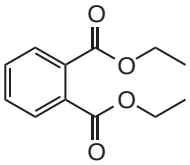


4-Nitroaniline

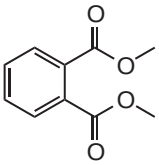
SiliaSep HP - Save Time with Faster Flow Rates



a) Dibutylphthalate



b) Diethylphthalate

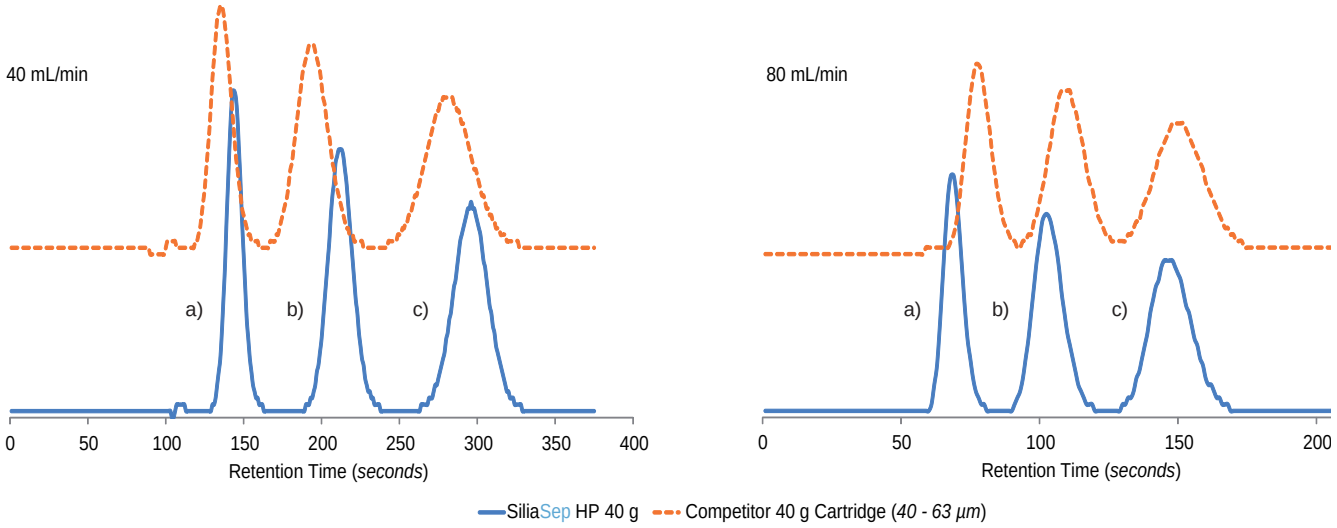


c) Dimethylphthalate

Chromatographic Conditions

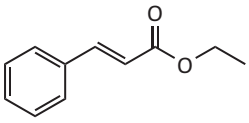
Mobile phase: 20 % EtOAc in Hexane
Injection volume: 5 mL
Wavelength: 254 nm

The greater resolution from SiliaSep HP allows the purification to be run at a higher flow rate with the same efficiency without compromising the quality of the separation.

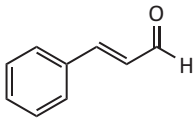


SiliaSep XL - Superior Resolution

SiliCycle evaluated the performance of SiliaSep XL cartridges compared to a well-known brand. For both sizes, 800 g and 1,600 g, SiliaSep XL outperforms the competition.



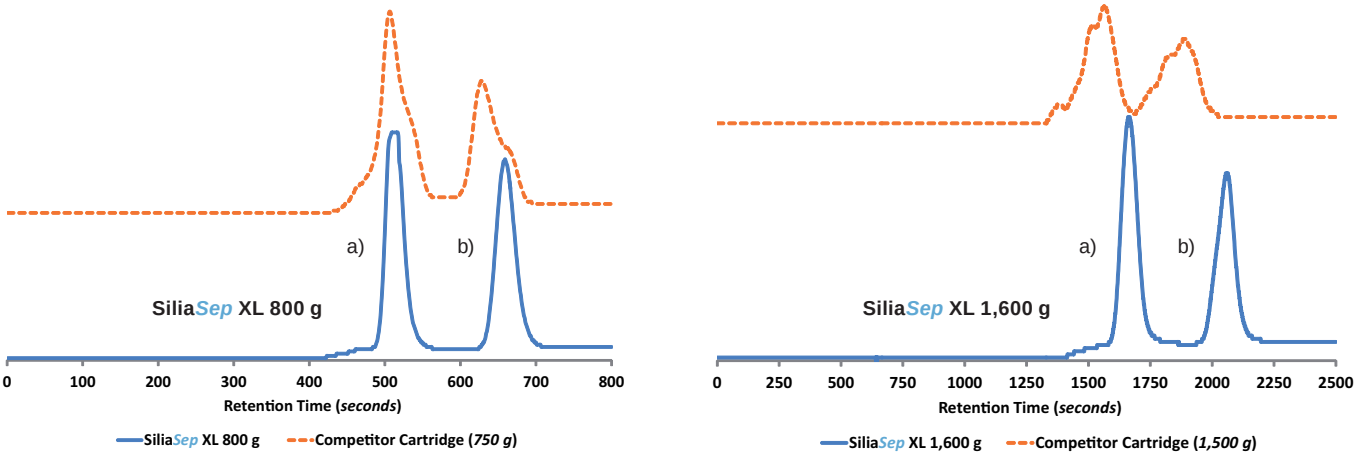
a) t-Ethyl Cinnamate



b) t-Cinnamaldehyde

Chromatographic Conditions

Mobile phase: gradient of EtOAc in Hexane
Injection volume: 5 mL
Wavelength: 254 nm



Other Cartridge Type Available: Silia*Sep* OT (*Open Top Flash Cartridges*)

Silia*Sep* OT cartridges are mainly used with vacuum manifolds and automated SPE equipments. They are also directly compatible with FlashMaster™ systems.

Silia*Sep* OT Cartridges (*rated 60 psi*)			
Silica Weight	2 g	5 g	10 g
Dimension (*ID x Length*)	15.8 x 90 mm	20.5 x 100 mm	26.8 x 154 mm
Volume	12 mL	25 mL	70 mL
Qty / Box	20	20	16
Silia*Sep* OT Phases			
Silia*Sep* OT Silica	FLH-R10030B-15U	FLH-R10030B-25X	FLH-R10030B-70Y
Silia*Sep* OT Amine	SPE-R52030B-12U	SPE-R52030B-20X	FLH-R52030B-70Y
Silia*Sep* OT Diol *nec*	SPE-R35030B-12U	SPE-R35030B-20X	FLH-R35030B-70Y
Silia*Sep* OT Cyano	SPE-R38030B-12U	SPE-R38030B-20X	FLH-R38030B-70Y
Silia*Sep* OT C8	SPE-R30830B-12U	SPE-R30830B-20X	FLH-R30830B-70Y
Silia*Sep* OT Phenyl	SPE-R34030B-12U	SPE-R34030B-20X	FLH-R34030B-70Y
Silia*Sep* OT PFP	SPE-R67530B-12U	SPE-R67530B-20X	FLH-R67530B-70Y
Silia*Sep* OT SCX	SPE-R60530B-12U	SPE-R60530B-20X	FLH-R60530B-70Y
Silia*Sep* OT C18 (*17 %*)	SPE-R33230B-12U	SPE-R33230B-20X	FLH-R33230B-70Y
Silia*Sep* OT SCX-2	SPE-R51230B-12U	SPE-R51230B-20X	FLH-R51230B-70Y
Silia*Sep* OT SAX *nec*	SPE-R66530B-12U	SPE-R66530B-20X	FLH-R66530B-70Y
Silia*Sep* OT SAX-2 *nec*	SPE-R66430B-12U	SPE-R66430B-20X	FLH-R66430B-70Y

Silia*Sep* OT Cartridges (*rated 60 psi*)						
Silica Weight	15 g	20 g	25 g	50 g	70 g	100 g
Dimension (*ID x Length*)	26.8 x 154 mm	26.8 x 154 mm	38.2 x 170 mm	38.2 x 170 mm	38.2 x 170 mm	40.0 x 220 mm
Volume	70 mL	70 mL	150 mL	150 mL	150 mL	276 mL
Qty / Box	16	16	10	10	10	12
Silia*Sep* OT Phases						
Silia*Sep* OT Silica	FLH-R10030B-70i	FLH-R10030B-70Z	FLH-R10030B-95K	FLH-R10030B-95M	FLH-R10030B-95N	FLH-R10030B-276F
Silia*Sep* OT Amine	FLH-R52030B-70i	FLH-R52030B-70Z	FLH-R52030B-95K	FLH-R52030B-95M	FLH-R52030B-95N	FLH-R52030B-276F
Silia*Sep* OT Diol *nec*	FLH-R35030B-70i	FLH-R35030B-70Z	FLH-R35030B-95K	FLH-R35030B-95M	FLH-R35030B-95N	FLH-R35030B-276F
Silia*Sep* OT Cyano	FLH-R38030B-70i	FLH-R38030B-70Z	FLH-R38030B-95K	FLH-R38030B-95M	FLH-R38030B-95N	FLH-R38030B-276F
Silia*Sep* OT C8	FLH-R30830B-70i	FLH-R30830B-70Z	FLH-R30830B-95K	FLH-R30830B-95M	FLH-R30830B-95N	FLH-R30830B-276F
Silia*Sep* OT Phenyl	FLH-R34030B-70i	FLH-R34030B-70Z	FLH-R34030B-95K	FLH-R34030B-95M	FLH-R34030B-95N	FLH-R34030B-276F
Silia*Sep* OT PFP	FLH-R67530B-70i	FLH-R67530B-70Z	FLH-R67530B-95K	FLH-R67530B-95M	FLH-R67530B-95N	FLH-R67530B-276F
Silia*Sep* OT SCX	FLH-R60530B-70i	FLH-R60530B-70Z	FLH-R60530B-95K	FLH-R60530B-95M	FLH-R60530B-95N	FLH-R60530B-276F
Silia*Sep* OT C18 (*17 %*)	FLH-R33230B-70i	FLH-R33230B-70Z	FLH-R33230B-95K	FLH-R33230B-95M	FLH-R33230B-95N	FLH-R33230B-276F
Silia*Sep* OT SCX-2	FLH-R51230B-70i	FLH-R51230B-70Z	FLH-R51230B-95K	FLH-R51230B-95M	FLH-R51230B-95N	FLH-R51230B-276F
Silia*Sep* OT SAX *nec*	FLH-R66530B-70i	FLH-R66530B-70Z	FLH-R66530B-95K	FLH-R66530B-95M	FLH-R66530B-95N	FLH-R66530B-276F
Silia*Sep* OT SAX-2 *nec*	FLH-R66430B-70i	FLH-R66430B-70Z	FLH-R66430B-95K	FLH-R66430B-95M	FLH-R66430B-95N	FLH-R66430B-276F

Other phases can be offered, contact us for details.
For Metal Scavengers Cartridges, see page 208 for more information.
Silia*Sep* OT are also available with bar code for automation purposes.

Silia*Sep* Flash Cartridges for Process & Industrial Purification

SiliCycle designs, develops and manufactures innovative and versatile products for world class pharmaceutical and biotechnology companies with gram to multi-ton production capabilities.

For large scale purifications, our state-of-the-art facility allows us to produce high quality chromatographic phases in large batches to supply the most demanding applications. At SiliCycle, we truly understand the needs and challenges you encounter when trying to satisfy both regulatory requirements and the need for economical validated manufacturing. That's why we guarantee on-time delivery and we offer batch reservations, customized products and phases, adapted batch and packaging sizes and complete documentation for regulatory filings.

Our portfolio of process and industrial purification solutions can support scale-up projects from a few grams to several kilograms, while assuring robust and reliable methods.

Make your own Silia*Sep* Flash Cartridges

You can customize your flash cartridges by choosing silica properties and selectivity.

Most all irregular Silia*Flash* silica gels are available to be packed in flash cartridges. Just refer to pages 223 to select the particle size and pore diameter you need.

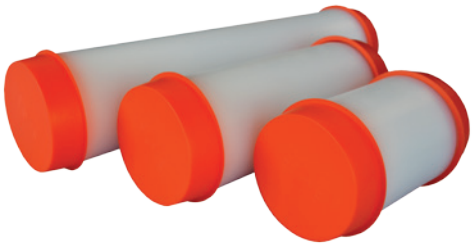
You can also adapt the cartridge's selectivity to your chemistry by choosing any of our metal or organic scavengers as bonded phase. See pages 137 for more information.

Silia*Sep* BT 75 Cartridges

These cartridges are designed to enhance your purifications when using the Biotage™ Flash 75 development-scale purification system. Containing up to 800 g of the highest quality 40 - 63 µm 60 Å silica gel, the Silia*Sep* BT 75 pre-packed cartridges allow purification up to 80 g of sample at maximum 250 mL/min. These cartridges offer a faster and safer solution compared to traditional glass columns.

Specifications & Ordering Information

Silia*Sep* BT 75 Specifications			
Cartridge Type	75S	75M	75L
Cartridge Code	75iS	75iM	75iL
Silica Weight	200 g	400 g	800 g
Qty / Box	Bare: 2* Bonded: 1		
Dimension (*ID x Length*)	75 x 90 mm	75 x 170 mm	75 x 350 mm
Column Volume	300 mL	500 mL	1 L
Recommended Flow Rate	100 - 250 mL/min		
Loading Capacity	0.2 - 20 g	0.4 - 40 g	0.8 - 80 g
Max Operating Pressure	90 psi / 6.5 bar (*inside the compression module*)		



Silia*Sep* BT 75 Ordering Information			
Cartridge Type	75S	75M	75L
Silia*Sep* Bare Phase			
Qty / Box*	2	2	2
Silia*Sep* BT Silica	FLH-R10030B-75iS	FLH-R10030B-75iM	FLH-R10030B-75iL
Silia*Sep* BT Bonded Phases			
Qty / Box	1	1	1
Silia*Sep* BT Amine	FLH-R52030B-75iS	FLH-R52030B-75iM	FLH-R52030B-75iL
Silia*Sep* BT Diol *nec*	FLH-R35030B-75iS	FLH-R35030B-75iM	FLH-R35030B-75iL
Silia*Sep* BT Cyano	FLH-R38030B-75iS	FLH-R38030B-75iM	FLH-R38030B-75iL
Silia*Sep* BT C18 (*17 %*)	FLH-R33230B-75iS	FLH-R33230B-75iM	FLH-R33230B-75iL
Silia*Sep* BT C8	FLH-R30830B-75iS	FLH-R30830B-75iM	FLH-R30830B-75iL
Silia*Sep* BT Phenyl	FLH-R33830B-75iS	FLH-R33830B-75iM	FLH-R33830B-75iL
Silia*Sep* BT PFP	FLH-R67530B-75iS	FLH-R67530B-75iM	FLH-R67530B-75iL
Silia*Sep* BT SCX	FLH-R60530B-75iS	FLH-R60530B-75iM	FLH-R60530B-75iL
Silia*Sep* BT SCX-2	FLH-R51230B-75iS	FLH-R51230B-75iM	FLH-R51230B-75iL
Silia*Sep* BT SAX *nec*	FLH-R66530B-75iS	FLH-R66530B-75iM	FLH-R66530B-75iL
Silia*Sep* BT SAX-2 *nec*	FLH-R66430B-75iS	FLH-R66430B-75iM	FLH-R66430B-75iL

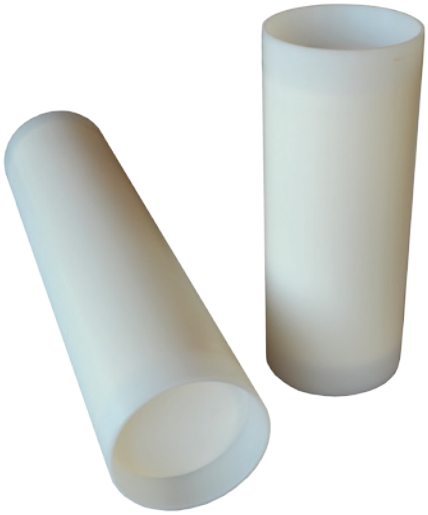
* Box of 10 also available. For part numbers, just add "-10" at the end.
Other phases can be offered, contact us for more information.
For Metal Scavengers Cartridges, please contact us.

Silia*Sep* BT 150 Cartridges

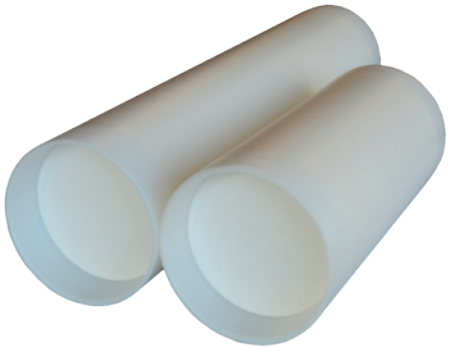
Used on a Biotage™ Flash 150 development-scale purification system, these cartridges allow purification up to 320 g of crude compound at maximum 1 L/min. They are available in two formats: 2.5 kg and 5 kg of high quality 40 - 63 µm 60 Å silica gel. Get higher performances in less time thanks to Silia*Sep* BT 150 cartridges!

Specifications & Ordering Information

Silia*Sep* BT 150 Specifications		
Cartridge Type	150M	150L
Cartridge Code	150iM	150iL
Silica Weight	2.5 kg	5 kg
Qty / Box	Bare: 2* Bonded: 1	
Dimension (*ID x Length*)	150 x 300 mm	150 x 600 mm
Column Volume	4 L	8.5 L
Recommended Flow Rate	0.5 - 1 L/min	
Loading Capacity	3 - 160 g	6 - 320 g
Max Operating Pressure	90 psi / 6.5 bar (*inside the compression module*)	



Silia*Sep* BT 150 Ordering Information		
Cartridge Type	150M	150L
Silia*Sep* Bare Phase		
Qty / Box*	2	2
Silia*Sep* BT Silica	FLH-R10030B-150iM	FLH-R10030B-150iL
Silia*Sep* BT Bonded Phases		
Qty / Box	1	1
Silia*Sep* BT Amine	FLH-R52030B-150iM	FLH-R52030B-150iL
Silia*Sep* BT Diol *nec*	FLH-R35030B-150iM	FLH-R35030B-150iL
Silia*Sep* BT Cyano	FLH-R38030B-150iM	FLH-R38030B-150iL
Silia*Sep* BT C18 (*17 %*)	FLH-R33230B-150iM	FLH-R33230B-150iL
Silia*Sep* BT C8	FLH-R30830B-150iM	FLH-R30830B-150iL
Silia*Sep* BT Phenyl	FLH-R33830B-150iM	FLH-R33830B-150iL
Silia*Sep* BT PFP	FLH-R67530B-150iM	FLH-R67530B-150iL
Silia*Sep* BT SCX	FLH-R60530B-150iM	FLH-R60530B-150iL
Silia*Sep* BT SCX-2	FLH-R51230B-150iM	FLH-R51230B-150iL
Silia*Sep* BT SAX *nec*	FLH-R66530B-150iM	FLH-R66530B-150iL
Silia*Sep* BT SAX-2 *nec*	FLH-R66430B-150iM	FLH-R66430B-150iL

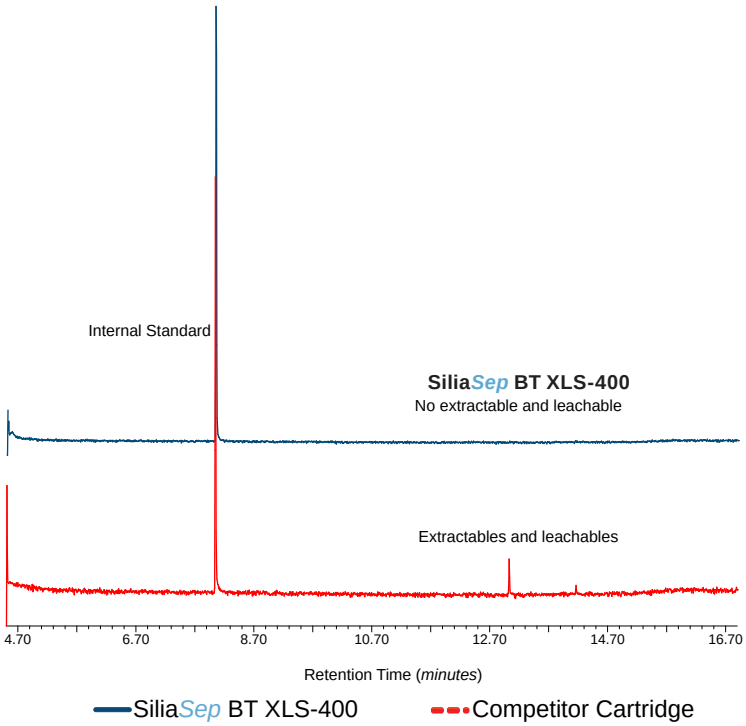


* Box of 10 also available. For part numbers, just add "-10" at the end.
Other phases can be offered, contact us for more information.
For Metal Scavengers Cartridges, please refer to page 208.

Silia*Sep* BT XLS-400 Cartridges

These cartridges are designed to enhance your purifications when using the Biotage™ Flash 400 large-scale purification system. The Silia*Sep* BT XLS-400iM cartridge contains 20 kg of the highest quality 40 - 63 µm 60 Å silica gel while the Silia*Sep* BT XLS-400L cartridge contains 41 kg, allowing purification up to respectively 1.3 kg and 2.7 kg of crude reaction mixture.

A more robust black polyethylene body, which provides a really low level of leachables, was chosen. The chromatograms below demonstrate this low to zero leaching of organics from the black polyethylene cartridge, whereas we do observe extractables from the competitor cartridge. Furthermore, the low swelling of our black polyethylene allows the cartridge to be easily removed from the module after use. Lastly, an ingenious endplate sealing system was designed to prevent any silica or solvent leakage.



Solvents tested:

- **Hexane**
- **Acetone**
- **Ethyl acetate**
- **Dichloromethane**
- **Methyl tert-butyl ether**

Silia*Sep* BT XLS-400 Specifications & Ordering Information

Silia*Sep* BT XLS-400 Specifications		
Cartridge Type	XLS-400M	XLS-400L
Cartridge Code	400iM	400iL
Silica Weight	20 kg	41 kg
Qty / Box	Bare: 2* Bonded: 1	
Dimension (*ID x Length*)	400 x 300 mm	400 x 600 mm
Column Volume	28 L	56 L
Recommended Flow Rate	3 - 6 L/min	
Loading Capacity	24 g - 1.3 kg	50 g - 2.7 kg
Max Operating Pressure	90 psi / 6.5 bar (*inside the compression module*)	

XLS-400L

Silia*Sep* BT XLS-400 Ordering Information		
Cartridge Type	XLS-400M	XLS-400L
Silia*Sep* Bare Phase		
Qty / Box*	2	2
Silia*Sep* BT Silica	FLH-R10030B-400iM	FLH-R10030B-400iL
Silia*Sep* BT Bonded Phases		
Qty / Box	1	1
Silia*Sep* BT Amine	FLH-R52030B-400iM	FLH-R52030B-400iL
Silia*Sep* BT Diol *nec*	FLH-R35030B-400iM	FLH-R35030B-400iL
Silia*Sep* BT Cyano	FLH-R38030B-400iM	FLH-R38030B-400iL
Silia*Sep* BT C18 (*17 %*)	FLH-R33230B-400iM	FLH-R33230B-400iL
Silia*Sep* BT C8	FLH-R30830B-400iM	FLH-R30830B-400iL
Silia*Sep* BT Phenyl	FLH-R33830B-400iM	FLH-R33830B-400iL
Silia*Sep* BT PFP	FLH-R67530B-400iM	FLH-R67530B-400iL
Silia*Sep* BT SCX	FLH-R60530B-400iM	FLH-R60530B-400iL
Silia*Sep* BT SCX-2	FLH-R51230B-400iM	FLH-R51230B-400iL
Silia*Sep* BT SAX *nec*	FLH-R66530B-400iM	FLH-R66530B-400iL
Silia*Sep* BT SAX-2 *nec*	FLH-R66430B-400iM	FLH-R66430B-400iL

* Box of 1 also available. For part numbers, just add "-1" at the end.
Other phases can be offered, contact us for more information.
For Metal Scavengers Cartridges, please refer to page 208.

XLS-400M

Silia*Sep* Flash Cartridges - The Whole Picture

Silia*Sep* Flash Cartridges Whole Picture							
Cartridge Format	Scale		Silica Weight	Dimension (*ID x Length*)	Column Volume	Recommended Flow Rate	Loading Capacity
ISO04 to IS330	**Discovery & R&D**		4 g to 330 g	12 x 98 mm to 60 x 268 mm	4.9 mL to 441 mL	15 - 25 mL/min to 80 - 180 mL/min	40 - 400 mg to 3.3 - 33 g
75iS	**Development & Process**		200 g	75 x 90 mm	300 mL	100 - 250 mL/min	0.2 - 20 g
75iM			400 g	75 x 170 mm	500 mL		0.4 - 40 g
75iL			800 g	75 x 350 mm	1 L		0.8 - 80 g
XL 800	**Development & Process**		800 g	78 x 382 mm	1.5 L	200 - 300 mL/min	8 - 80 g
XL 1,600			1.6 kg	104 x 429 mm	2.9 L	300 - 450 mL/min	16 - 160 g
150iM	**Industrial**		2.5 kg	150 x 300 mm	4 L	0.5 - 1 L/min	3 - 160 g
150iL			5 kg	150 x 600 mm	8.5 L		6 - 320 g
400iM	**Industrial**		20 kg	400 x 300 mm	28 L	3 - 6 L/min	24 g - 1.3 kg
400iL			41 kg	400 x 600 mm	56 L		50 g - 2.7 kg

Process Scale-Up Purification Services

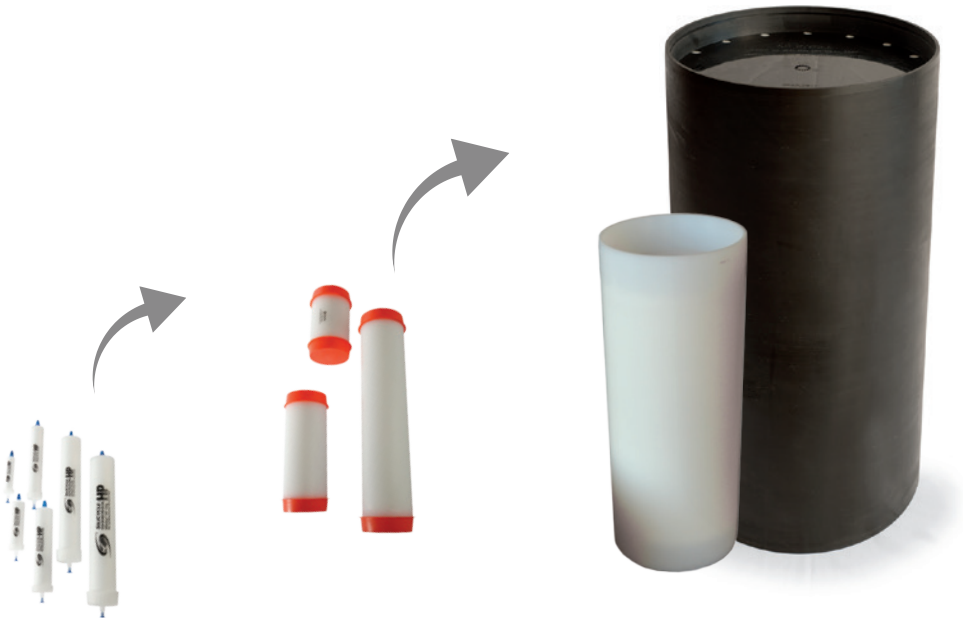
SiliCycle is well equipped to promptly assist you develop a lab-scale method and scaling-up to kilo-scale production efficiently. Our scale-up strategies are based on using the same packing material, which is one of the most important aspects of scalability, allowing constant performance and optimal results throughout your purification process.

SiliCycle can provide turnkey solutions to your purification problems by performing your scale-up process separation with our expert staff in our laboratories. Our broad variety of instrumentations allows us to purify and detect a wide range of molecules.

As a chromatographic medias manufacturer, we have a large inventory of phases readily available which helps reduce lead time and cost for your projects. If your separation requires that we develop a special phase, our production team works hand-in-hand with our R&D to support you. Our process scale-up purification service is flexible to ensure that it will fit your needs.

For example, we can develop a low pressure chromatographic extraction on a 25 g flash cartridge, scale it up to a 5 kg or even a 41 kg cartridge and then provide all needed products for the pilot, scale-up work and commercial production.

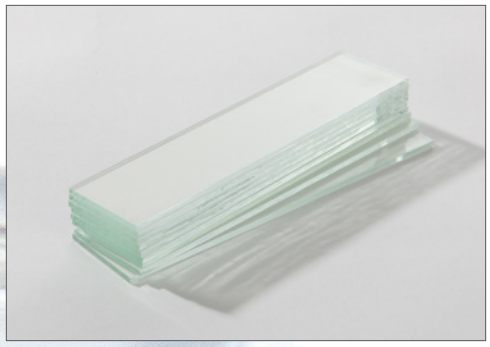
No other manufacturer of chromatography products offers this.

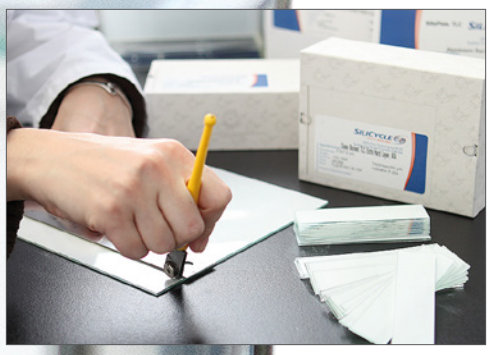


4 g - 330 g cartridges	200 g - 1.6 kg cartridges	2.5 kg - 41 kg cartridges
Discovery & R&D	**Development & Process**	**Industrial**

All cartridges can be packed with the same lot for extreme reproducibility throughout your scale-up.

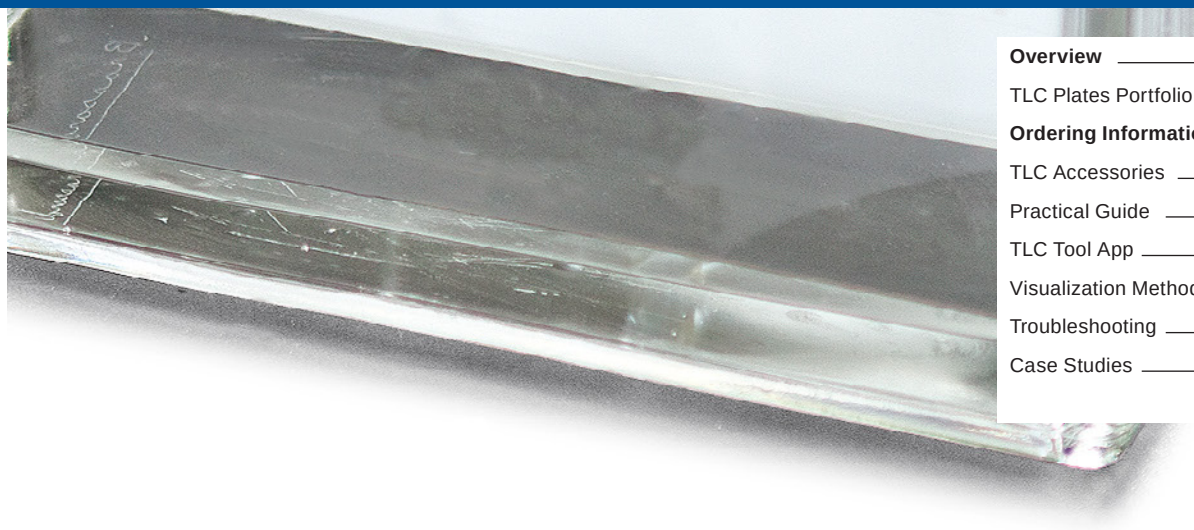
Please discover our full range of R&D Services page 287.





Thin Layer Chromatography

SiliaPlate™ TLC Plates



Thin Layer Chromatography (*TLC*)

SiliCycle is your partner of choice for your purification and chromatography needs

- Optimize your separation conditions by using the same quality silica gel as in your flash columns and cartridges.
- Made with an extra hard layer that ensures the plates don't lose silica upon rubbing and heating.
- The consistent thickness of our Silia*Plate* ensures lot-to-lot reproducibility.

Introduction to Thin Layer Chromatography (TLC)

Thin-layer chromatography (*TLC*) is a quick, simple and inexpensive analytical technique frequently used in various laboratories as it is one of the most verstatile. It is used for:

- Reaction Monitoring
- Screening
- Compound Purity Evaluation

Rapid and cost-efficient selection and optimization of chromatographic conditions prior to flash chromatography purification or HPLC analysis.

Besides speed and low cost, TLC analysis presents other non-negligible advantages like the small quantity of compound required and high sample throughput capability (*up to 20 samples simultaneously*).

Like column chromatography, TLC is a solid-liquid partitioning technique, in which the sample is applied to the plate as a small spot near the base of the plate. The moving liquid phase is then allowed to ascend the plate, causing the sample to partition between moving and stationary phase.

Silia*Plate* Features and Benefits

For more than 20 years, SiliCycle has been offering a wide selection of TLC plates in various sizes (*plate size, thickness, backing*) and chemistries (*10 % Silver Nitrate, CN, C18, NH_2*). Silia*Plate* represents an efficient and economical alternative to other TLC plate manufacturers while demonstrating high separation power, which is due to our narrow particle size distribution silica gel.

The extraordinary silica layer hardness combined to a homogeneous coating and layer thickness allows excellent separation. Each TLC batch is chemically and physically controlled by our Quality Control department to ensure lot-to-lot and layer-to-layer reproducibility.

Types of Plates Available (*TLC / HPTLC / Preparative TLC*)

SiliCycle offers different types of plates for thin-layer chromatography applications: classical TLC, high performance TLC (*also called HPTLC*) and preparative TLC (*PLC*). The plate types are selected based on the type of analysis required and the available budget.

Differences Between Classical TLC, HPTLC and PLC

Properties	Classical TLC	HPTLC	Preparative PLC
Applications	Quick, inexpensive, flexible and classical separations	Highly sophisticated separation, complex samples	Purification on a TLC plate
Analysis	Qualitative	Qualitative & Quantitative	Quantitative
Detection	UV - Stains	Instrumented analysis (*use of scanners for detection*)	UV
Price	Lower prices than HPTLC	Higher prices than TLC	-
Distribution [*Mean Particle Size*]	5 - 20 µm [*10 - 14 µm*]	4 - 8 µm [*5 - 6 µm*]	5 - 40 µm [*22 - 25 µm*]
Layer Thickness	200 - 250 µm	150 - 200 µm	500 - 2,000 µm
Typical Sample Volume	1 - 5 µL	0.1 - 0.5 µL	5 - 20 µL

TLC Backings

TLC plates are available with different backings (*also called supports*): rigid (*glass-backed*) or flexible sheets (*aluminum & plastic-backed*). Glass-backed plates are the most frequently used due to the ease of handling, transparency (*spot can be seen on both sides*) as well as the chemical resistance and inertness of the support. However, glass plates also present certain disadvantages like fragility and higher weight over flexible backings. On the other hand, aluminum and plastic backings also offer both pros and cons as presented in the table below.

TLC Backings Comparison

Properties	Glass	Aluminum	Plastic
Advantages	- Rigid - High chemical resistance - High heating stability and charring resistance - Transparent	- Thin - Low weight and consequent shipping costs - High seating stability - Low fragility - Possible to cut with scissors - Can be stored in notebook	- Thin - Low fragility - Possible to cut with scissors - High chemical resistance - Can be stored in notebook
Disadvantages	- Thick - High fragility - Impossible to cut with scissors - Cannot be stored in lab notebook - High weight and consequent shipping costs - Large shelf space	- Low chemical resistance - Opaque	- Medium weight - Opaque - Heating stability up tp 175°C - Possible cracking of matrix due to high flexibility
Approximate Thickness	2.0 - 2.5 mm	1.5 - 2.0 mm	1.5 - 2.0 mm
Total Weight	High	Low	Medium
Heating Stability	High	High	Below 175°C
Fragility	High	Low	Low
Cutting with Scissors	Impossible	Easily	Possible
Chemical Resistance Against			
Mineral Acids	High	Low	High
Bases (*ammoniac*)	High	Low	High

Available Matrices (*or Adsorbents*)

Various adsorbents can be used for TLC coating; silica, aluminum oxide, florisil, etc. However, silica gel is probably the most versatile since it covers almost all types of separation (*if the right solvent system is selected*). More than 80 % of all purifications are performed using silica gel as the adsorbent.

Silica gel

Can be unmodified or functionalized. It is suitable for a very vast array of molecules with various functionalities or polarity, such as aflatoxins, alkaloids, anabolic compounds, barbiturates, carbohydrates, ethers, esters, fatty acids, flavonoids, glycosides, lipids, nucleosides, peptides and proteins, pesticides, sweeteners, vitamins and so on.

Aluminum oxide (*commonly called Alumina*)

Aluminum oxide is the second most commonly used matrix, and it shows similar selectivity to that of silica. Popular applications include the separation for alkaloids, aliphatic compounds, aromatics, steroids, etc. It is manufactured with three different pH ranges: basic, acidic and neutral.

Before use, the plates need to be activated by heating between 90° and 120°C for 10 minutes (*since water molecules are easily adsorbed and can greatly influence separation*).

Cellulose

Cellulose can be unmodified or positively charged at acidic and neutral pH. This adsorbent is hence frequently used for the partition of hydrophilic molecules and is also useful for challenging separations of sensitive biomolecules or molecules carrying ion exchange groups. The ratio of charged cellulose / unmodified cellulose can be varied, in order to provide more or less retention of negatively charged molecules.

Available Sorbents

Classical Silica Gel: for daily, fast, reliable analysis of the largest spectra of molecules

The particle size distribution used for the silica is related to the nature of the plate. For standard TLC, silica gel with a mean particle size of 10 - 14 µm is used compared to HPTLC where a smaller particle size is required. In both cases, pore diameter is always 60 Å.

Reversed & Special Phases

The two most popular modes of separation employed in TLC are normal and reversed phases. In normal phase separation, the mobile phase is less polar than the stationary phase. Inversely, in reversed mode, the mobile phase (*usually a mixture of water and organic solvent*) is more polar than the stationary phase (*C18*).

Functionalized silica gels can also be used as TLC adsorbents for particular needs when satisfactory separations cannot be achieved by unmodified silica. They are mostly used as pilot methods for ulterior HPLC analysis. Here are some typical issues that can affect separation and can be solved using functionalized phases:

- Aqueous solvent systems
- Ambient humidity
- Direct HPLC correlation
- Degradation of sensitive molecules (*oxidation, hydrolysis, etc.*)

Reversed-phases TLC plates include C2, C8 and C18 phases where functionalization of silica is performed using organosilanes of various chain lengths. Retention of molecules and the ability to tolerate water in the moving phase are directly dependent on the chain length: the shorter the chain, the more water tolerant it is and hence the shorter the migration time will be.

Special phases such as Diol and Nitrile (*CN*) are moderately polar. They can thus be suitable for both normal and reversed phase chromatography, depending on your application. Amino phases (NH_2) have specifically been designed for charged compounds, as they show weak anion exchange characteristics.

Layer Thicknesses

The layer thickness is related to the nature of the analysis (*analytical or preparative*) as well as the performance of the plate (*TLC or HPLTC*). The most common layer thicknesses are:

- 150 - 200 µm (*HPTLC plates*)
- 200 - 250 µm (*analytical TLC plates*)
- 500 - 2,000 µm (*preparative TLC plates*)

Binder & UV Indicator

All standard Silia*Plate* products are made with a Gypsum binder and have an UV indicator (*F254*). Contact us for custom products.

Plate Sizes

Silia*Plate* TLC plates are available in the following standard sizes depending on the coating used:

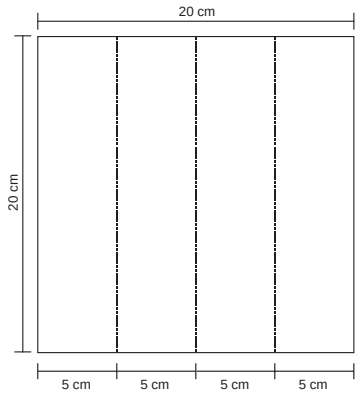
- 20 x 20 cm
- 10 x 20 cm
- 5 x 20 cm
- 5 x 10 cm
- 10 x 10 cm

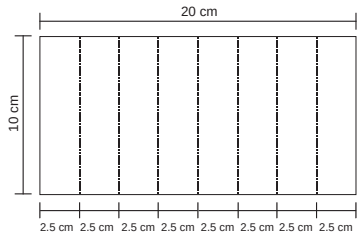
Also for your convenience, SiliCycle provides ready to use micro TLC plates in the following formats:

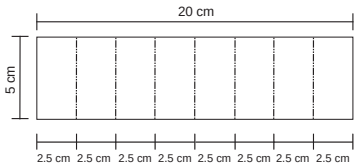
- 2.5 x 10 cm
- 2.5 x 7.5 cm
- 2.5 x 5 cm

An interesting compromise between standard and micro plate sizes is our Scored Silia*Plate* (*glass backing*). Three different formats are available and possible cut combinations are shown in the image below.

- 20 x 20 cm plates scored to four 5 x 20 cm plates (*or multiple of 5 cm width*)
- 10 x 20 cm plates scored to eight 2.5 x 10 cm plates (*or multiple of 2.5 cm width*)
- 5 x 20 cm plates scored to eight 2.5 x 5 cm plates *(or multiple of 2.5 cm width)*







« Many products have been successfully purified with the silica gel. We have had problems with other companies' TLC plates not running the same as their silica gel, but everything was fixed when we switched over to all SiliCycle products. »

William Nguyen from Stanford University, Stanford, CA, USA

Silia*Plate* TLC Plates Portfolio

SiliCycle offers the possibility to analyze reactions on thin layer chromatography support and rapidly develop optimized purification conditions for efficient transfer to flash columns. Maximize the benefits by using our *UltraPure* Silia*Plate* TLC plates with an extra hard layer of silica. For your convenience, SiliCycle offers different sizes, choice of backings, reversed-phase & specialty plates. Contact us for more information.

Various combinations are possible with Silia*Plate* TLC plates and are summarized in the table below.

Silia*Plate* TLC Plates Portfolio			
Properties	**Analytical**	**HPTLC**	**Preparative**
Available Backings			
Glass	Yes	Yes	Yes
Aluminum	Yes	No	No
Plastic	Yes	No	No
Available Adsorbents			
Bare silica	Yes	Yes	Yes
Functionalized Silica	No	Yes	Yes
Silica Specifications			
Mean Particle Size	10 - 14 µm	5 - 6 µm	22 - 25 µm
Mean Pore Diameter	60 Å	60 Å	60 Å
Type of Plate Available			
Scored Plate	Yes	No	Yes
Channeled Plate	Yes	No	No
Layer Thickness	Glass: 250 µm Flexible: 200 µm	Glass: 150 - 200 µm	Glass: 500 µm & 1,000 µm Flexible: 1,500 µm & 2,000 µm
Plate Size*	2.5 x 5 cm; 2.5 x 7.5 cm; 2.5 x 10 cm; 5 x 10 cm; 5 x 20 cm; 10 x 20; 20 x 20 cm	2.5 x 5 cm; 2.5 x 7.5 cm; 2.5 x 10 cm; 5 x 10 cm; 5 x 20 cm; 10 x 20; 20 x 20 cm	20 x 20 cm

*For the glass-backed TLC plates.

Two Types of Glass-Backed, 20 x 20 cm, TLC Plates

SiliCycle offers two types of Silia*Plate* glass-backed 20 x 20 cm TLC Plates, with different sensitivities and areas of applications.

The difference between the two plates is in the binder chemistry:

- **TLG-R10014B-323** 's layer is polymeric: it has been added a small percentage of inorganic, hardening agent for a uniform and hard surface, smooth and dense, that will not crack, blister nor swell up. They were designed for maximum robustness of the binder: they are very easy to handle and to write on, as well as completely wettable.
  They are compatible with all solvents, yet, they might oxidize a bit faster when dipped into $KMnO_4$ (*fading in a few minutes from flashy purple to yellow ocher*). Also, spots are a bit less definite when using CAM as a revelatory.
  Such binder also contains a higher percentage of fluorescent indicator for greater brilliance of spots and less background noise from the silica layer.
- **TLG-R10014BK-323** 's layer is gypsum (*calcium sulfate*), and do not contain the polymeric additive that provides the former plates a harder surface and ruggedness. This means that the layer is softer, so spots can be easily scrapped off from the glass support, and are particularly recommended for aggressive visualization methods (*strong charring, CAM staining solution*) or, if dipped into $KMnO_4$, ought to remain bright-purple a longer period of time.

Here is a chart which can hopefully help you quiclky choose the right plate for your specific application.

General View of Specificities & Characteristics to be Considered		
TLC Plate PN	**TLG-R10014B-323**	**TLG-R10014BK-323**
UV Fluorescence (F_{254})	• Higher brightness • Less background noise from layer	• Yes
Binder Sensitivity	Stable in almost all organic solvents	
	• Increased separation efficiency	• Resistant to aggressive visualization methods
Surface Layer	• Robust and rugged	• Easily scratched off
Water Tolerance	• Up to 80 %	• Up to 40 %
Specific Surface (*BET*)	≈ 500 m^2/g	
Mean Pore Size	60 Å	
Mean Pore Volume	0.75 mL/g	
Distribution (*Mean Particle Size*)	5 - 20 µm [10 - 14 µm]	
Layer Thickness	≈ 250 µm	
Stain Compatibility		
$KMnO_4$	Compatible	**Highly compatible**
CAM	Compatible	
p-Anisaldehyde	Compatible	**Highly compatible**
Ninhydrin	**Highly compatible**	
Vanilin	**Highly compatible**	

Silia*Plate* Ordering Information

All our plates bear an F_{254} UV indicator for direct visualization of results or derivatization, but all can be available with no UV indicator. A long-wavelength (F_{366}) UV indicator is also available upon request.

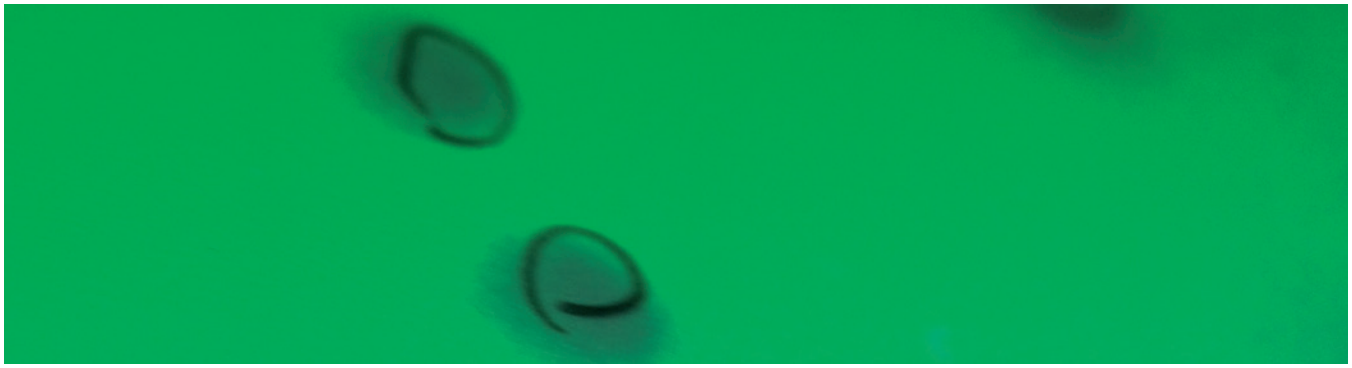
Please note that this is an overview of plates that SiliCycle offers. Different sizes are available, as well as more exotic layers for special separations (chiral layers, layers for surfactant separations, for PAH analysis, layers for basic or acidic ion exchange, cellulose layers, etc.). Contact us.

CLASSICAL TLC Plates Portfolio

GLASS Silia*Plate* TLC				
SiliCycle PN	**Product Name**	**Plate Size (*cm*)**	**Thickness (*µm*)**	**Qty / Box**
Analytical Silia*Plate* Glass				
TLG-R10014B-417	Micro Silia*Plate* Glass	2.5 x 5	250	200
TLG-R10014B-124	Micro Silia*Plate* Glass	2.5 x 7.5	250	100
TLG-R10011B-624	Micro Silia*Plate* Glass	2.5 x 10	250	100
TLG-R10011B-527	Silia*Plate* Glass	5 x 10	250	200
TLG-R10011B-424	Silia*Plate* Glass	5 x 20	250	100
TLG-R10011B-723	Silia*Plate* Glass	10 x 20	250	25
TLG-R10014B-323	Silia*Plate* Glass, Extra Hard Layer, Increased UV Content	20 x 20	250	25
TLG-R00014BK-323	Silia*Plate* Glass, Optimized Layer for $KMnO_4$ Revelation	20 x 20	250	25
Scored Analytical Silia*Plate* Glass				
TLGSR10011B-723	Silia*Plate* Glass (*scored to 2.5 x 10*)	10 x 20	250	25
TLGSR10011B-423	Silia*Plate* Glass (*scored to 2.5 x 5*)	5 x 20	250	25
TLGSR10011B-424	Silia*Plate* Glass (*scored to 2.5 x 5*)	5 x 20	250	100
TLGSR10011B-323	Silia*Plate* Glass (*scored to 5 x 20*)	20 x 20	250	25
Channeled Analytical Silia*Plate* Glass *(with Preadsorbent Zone)*				
TLGCZ-R10011B-323	Channeled Silia*Plate* Glass (*w/ PreAd.*)	20 x 20	250	25
TLGCZ-R10011B-723	Channeled Silia*Plate* Glass (*w/ PreAd.*)	10 x 20	250	25
TLGCZ-R10011B-423	Channeled Silia*Plate* Glass (*w/ PreAd.*)	5 x 20	250	25

ALUMINUM Silia*Plate* TLC Plates				
SiliCycle PN	**Product Name**	**Plate Size (*cm*)**	**Thickness (*µm*)**	**Qty / Box**
Silia*Plate* Al *(Aluminum)*				
TLA-R10011B-124	Micro Silia*Plate* Aluminum	2.5 x 7.5	200	200
TLA-R10011B-515	Silia*Plate* Aluminum	5 x 10	200	50
TLA-R10011B-415	Silia*Plate* Aluminum	5 x 20	200	50
TLA-R10011B-712	Silia*Plate* Aluminum	10 x 20	200	20
TLA-R10011B-323	Silia*Plate* Aluminum	20 x 20	200	25
TLA-R10011B-323N	Silia*Plate* Aluminum (*no UV*)	20 x 20	200	25
Silia*Plate* Al C18 *(Aluminum)*				
TLA-R30411B-303	Silia*Plate* Aluminum C18	20 x 20	150	25

PLASTIC Silia*Plate* TLC Plates				
SiliCycle PN	**Product Name**	**Plate Size (*cm*)**	**Thickness (*µm*)**	**Qty / Box**
Silia*Plate* Pl (*Plastic*)				
TLP-R10011B-2575	Micro Silia*Plate* Plastic	2.5 x 7.5	200	200
TLP-R10011B-323	Silia*Plate* Plastic	20 x 20	200	25



HPTLC TLC Plates Portfolio

BARE Silia*Plate* HPTLC Plates with Glass Backing (*Thickness: 150 microns, 25 plates / Box*)			
SiliCycle PN	**Plate Size (*cm*)**	**SiliCycle PN**	**Plate Size (*cm*)**
Silia*Plate* Silica HPTLC			
HPTLG-R10011B-1010	10 x 10	HPTLG-R10011B-2020	20 x 20
HPTLGSR10011B-1010	10 x 10 (*scored to 5 x 5 cm*)	HPTLGSR10011B-1020	10 x 20 (*scored to 2.5 x 10 cm*)

FUNCTIONALIZED Silia*Plate* HPTLC with Glass Backing (*25 plates / Box*)				
SiliCycle PN	**Plate Size (*cm*)**	**SiliCycle PN**	**Plate Size (*cm*)**	**Thickness (*µm*)**
Silia*Plate* REVERSED-PHASE MODIFIED HPTLC				
Silia*Plate* C18 HPTLC				
TLG-R30414BK-213	10 x 10	TLG-R30414BK-313	20 x 20	200
Silia*Plate* C8 HPTLC				
TLG-R31014BK-203	10 x 10	TLG-R31014BK-303	20 x 20	200
Silia*Plate* C2 HPTLC				
TLG-R32614BK-713	10 x 20	TLG-R32614BK-313	20 x 20	200
Silia*Plate* NORMAL-PHASE MODIFIED HPTLC				
Silia*Plate* NH_2 *(Amine)* HPTLC				
TLG-R52014BK-213	10 x 20	TLG-R52014BK-313	20 x 20	200
Silia*Plate* CN *(Cyano)* HPTLC				
TLG-R38014BK-213	10 x 10	TLG-R38014B-313	20 x 20	200
Silia*Plate* Diol HPTLC				
TLG-R35014BK-213	10 x 10	TLG-R35014BK-313	20 x 20	200

SPECIALITY SORBENTS SiliaPlate TLC Plates with Glass Backing (25 plates / Box) *				
SiliCycle PN	Plate Size (cm)	SiliCycle PN	Plate Size (cm)	Thickness (µm)
SiliaPlate Ag (*Silver Nitrate 10 % impregnated*) TLC				
TLG-R23511B-423	5 x 20	TLG-R23511B-303	20 x 20	250
TLG-R23511B-433	5 x 20	TLG-R23511B-333	20 x 20	500
SiliaPlate Ag (*Silver Nitrate 15 % impregnated*) TLC				
TLG-R23611B-423	5 x 20	TLG-R23611B-323	20 x 20	250
TLG-R23611B-433	5 x 20	TLG-R23611B-333	20 x 20	500
SiliaPlate Ag (*Silver Nitrate 20 % impregnated*) TLC				
TLG-R23711B-423	5 x 20	TLG-R23711B-323	20 x 20	250
TLG-R23711B-433	5 x 20	TLG-R23711B-333	20 x 20	500
SiliaPlate Aluminum Oxide (*Neutral*) TLC				
TLG-AUT0337-423N	5 x 20	TLG-AUT0337-323N	20 x 20	250
TLG-AUT0337-433N	10 x 20	TLG-AUT0337-333N	20 x 20	500
SiliaPlate Cellulose TLC (*Contact us for a specific ratio of charged cellulose / unmodified cellulose to suit your application*)				
TLG- AUT0307-423	5 x 20	TLG- AUT0307-323	20 x 20	250

* Scored plates are also available, please contact us for dimension inquiry.

PREPARATIVE TLC Plates Portfolio

PREPARATIVE TLC Plates Portfolio			
SiliCycle PN	Plate Size (cm)	Thickness (µm)	Qty / Box
Preparative SiliaPlate Prep (*Glass Preparative*)			
TLG-R10011B-333	20 x 20	500	25
TLG-R10011B-341	20 x 20	1,000	25
TLG-R10011B-363	20 x 20	1,500	25
TLG-R10011B-353	20 x 20	2,000	25
Scored SiliaPlate Prep (*Glass Preparative*)			
TLGSR10011B-333	20 x 20 (*scored to four 5 x 20*)	500	25
TLGSR10011B-341	20 x 20 (*scored to four 5 x 20*)	1,000	25
TLGSR10011B-363	20 x 20 (*scored to four 5 x 20*)	1,500	25
TLGSR10011B-353	20 x 20 (*scored to four 5 x 20*)	2,000	25
SiliaPlate Prep C18 (*Glass Preparative*)			
TLG-R30411B-341	20 x 20	1,000	25

TRIAL PACKAGES

Trial Package of Functionalized SiliaPlate TLC Plates with Glass Backing (5 plates of each / Box) *			
SiliCycle PN	Plate Size (cm)	Composition	Thickness (µm)
TLGSR1234511B-723	10 x 20 (*scored to 2.5 x 10 cm*)	C18, C8, C2, NH_2 & CN	250

* Other scored plates are also available, please contact us for dimension inquirie.

Silia*Plate* TLC Accessories

Silia*Plate* TLC Developing Chamber

The most commonly used accessory to develop a TLC plate.

AUT-0161	Silia*Plate* Rectangular TLC Developing Chamber

Other Silia*Plate* TLC Accessories

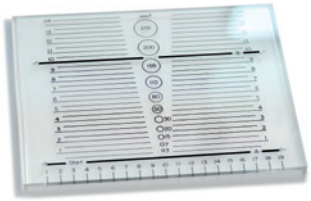
AUT-0162	Silia*Plate* TLC Scraper
AUT-0163	Silia*Plate* TLC Spotting Capillary Tubes
AUT-0164	Silia*Plate* TLC Spotting Guide
AUT-0182	TLC Cutter for Silia*Plate* (*up to 20 x 20 cm*)
AUT-1182	Pencil Glass Cutter for Silia*Plate*
AUT-0183	Replacement Scriber for Silia*Plate* TLC Cutter

PN: AUT-1182

PN: AUT-0162

PN: AUT-0161

PN: AUT-0182



PN: AUT-0164

An Ideal Partnership Between SiliCycle and AR2i

SiliCycle has entered into an exclusive strategic specialty worldwide distribution partnership with the company AR2i specialized in the conception and the manufacturing of innovative devices in the field of Thin-Layer Chromatography.

Chromimage® Documentation

- Perform qualitative analysis on TLC plates in a few minutes.
- Detect and numerize your TLC plates under UV254 nm and visible mode.
- Classify and archive your TLC analyses under several storage formats (*jpg, eps, pdf, etc.*).
- Suitable for reading 10 x 10 cm, 10 x 20 cm and 20 x 20 cm plates.

Derivapress® System

It's as simple as opening and closing a book: the Derivapress immersion derivatization system provides a cost-effective, efficient and safe alternative to perfect this essential stage of TLC and to move towards densitometric measurements like quantitative and semi-quantitative TLC.

Furthermore Derivapress complies with the GLP requirements and can be used in 21 CFR Part 11 work environments.

PN: AUT-0165

PN: AUT-0166

Thin Layer Chromatography Practical Guide

Select a Stationary Phase

As almost 80 % of all separations can be performed using **silica gel plates**, it is suggested to try using this coating first. However, for acid sensitive compounds, alumina is probably a better choice (*useful for amine purification*). If you are working with highly polar compounds, reversed-phase mode is more suitable.

Select a Mobile Phase (*Solvent Systems*)

The selection of the mobile phase (*also called solvent system or eluent*) is perhaps the most important parameter to achieve efficient thin-layer chromatography separation. It is based on the compound's solubility with the solvent and the difference in the affinity for the mobile phase versus the stationary adsorbent (*silica, alumina or cellulose*).

In normal phase chromatography, where non-polar solvents such as hexane or pentane are used, non-polar compounds will move up the plate while most polar compounds will stay on the baseline. Inversely, polar solvents will allow polar compounds to move off the origin. The most suitable solvent system is the one that moves all components off the baseline with Rf values between 0.15 and 0.85 (*ideally, close to 0.2 - 0.4*).

For most applications, a common solvent system to start with is **EtOAc / Hexane (*1:1*)**. Varying the ratio can have a pronounced effect on the Rf. If it is not working, then try: MeOH / DCM (*2:8 - 10:90*); or toluene with acetone, EtOAc, or DCM.

Remember: in normal phases, to increase the compound's Rf, increase the polarity of the mobile phase; increase the ratio of the polar solvent or choose another solvent. Inversely, to decrease Rf, decrease the polarity of the eluent.

Rules of Thumb

- Standard compounds (*most popular solvent system*): 10 - 50 % EtOAc / Hexane
- Polar compounds: 100 % EtOAc or 5 - 10 % MeOH / DCM
- Non-polar compounds: 5 % EtOAc (*or ether*) / Hexane or 100 % Hexane
- For basic compounds: (*amine or nitrogen containing*), it could be useful or required to add a small quantity of triethylamine (Et_3N) to the solvent mixture (*0.1 - 2.0 % but typical quantity is 0.1 %*) or 1 - 10 % ammonia (NH_3) in MeOH / DCM.
- For acidic compounds: it could be useful to add acetic (*AcOH*) or formic acid (*FA*) to the solvent mixture (*0.1 - 2.0 %*).

Reversed-phase mode

In reversed-phase chromatography, the typical solvent systems are:

- Mixtures of water or aqueous buffers and water miscible organic solvents such as acetonitrile (*ACN*), methanol and tetrahydrofuran (*THF*). Other solvents can be used such as ethanol (*EtOH*) & isopropanol (*IPA*).
- MeOH, to improve peak shape in flash chromatography, 0.1 % of acetic, formic or trifluoroacetic acid (*TFA*) can be added to the solvent system.

« Have given your products to other folks within organisation and used it myself with great success (both the Prep SPE, HPLC columns, TLC plates and silica gel). »

Kerry M. Keertikar, Merck Research Labs, Kenilworth, NJ, USA

TLC Plate Preparation

Using a pencil, lightly draw a straight-line parallel to the width of the plate at about 1 cm from the base end of the plate. Sample application will be done on this line called baseline or origin.

Note: never use a pen because ink can move with some solvents used as eluent.

Sample preparation

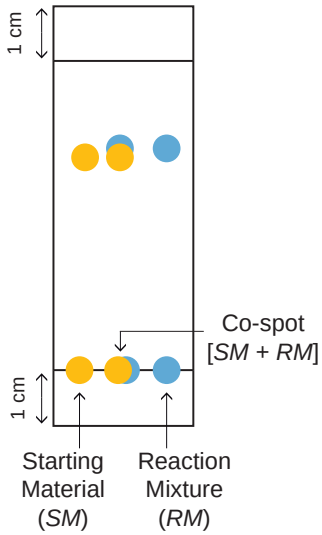
Thorough sample preparation is a prerequisite for an optimal and efficient TLC separation. Typical sample preparation processes could consist in a sample crushing, filtration, extraction or concentration of the product of interest.

Sample Application

Sample preparation will differ depending on the nature of the plate (*analytical or preparative*). For analytical plates, because thin layer chromatography is extremely sensitive, it is really important to apply a small quantity using a glass capillary (*or a micro pipette*) to get optimal resolution. For preparative plates, apply a series of small adjacent spots to form a band or a streak using a glass capillary (*or a microliter syringe*). In both cases, a spotting guide can be used to facilitate sample application.

Co-spotting

For analytical chromatography, co-spotting is frequently used for similar polarity products. This consists to apply on the same spot, the starting material and reaction mixture as shown by the image below.



TLC Plate Development

The most commonly used method to perform thin layer chromatography separation is to place vertically the TLC plate inside a sealed developing chamber to ensure solvent saturation. Place approximately 0.5 cm of the suitable solvent system inside the chamber. Slowly place the TLC inside the chamber and allow the eluent to travel up the plate until it gets to 1 cm from the top of the plate. Immediately remove the plate and draw a line along the solvent front.

***Note**: for optimal solvent saturation, a filter paper can be added inside the TLC chamber. This also prevents eluent evaporation. The solvent level needs to be below the baseline; otherwise the spots will be dissolved.*

TLC Plate Visualization

If components of the reaction are colored, no visualization method is required (*spots can be seen directly on the silica layer*). However, most of the time it is not the case, therefore one of the methods described below should be used to reveal the spots.

Non-destructive methods

As a general visualization procedure, before treating the TLC plate with any destructive methods, UV-active compounds can be viewed under an ultraviolet lamp (*usually for polyconjugated compounds like benzophenones and anthracenes*). Furthermore, an iodine chamber can be useful for thiols, phosphines and alkenes but it works in about 50% of cases for alkanes. It is recommended to circle the spots with a pencil on the TLC plate prior to visualization by destructive methods.

Destructive methods

For compounds that are not UV-active, there are several varieties of stains that can be used depending on the nature of the compound of interest. To use a stain, simply dip the TLC plate into the staining solution as quickly as possible, and then immediately absorb the excess stain with paper and heat carefully with a heat gun or on a hot plate at 110°C until spots are revealed. See next pages.

Chromatogram Interpretation

Retention factor (*Rf*) definition

Retention factor analysis is used to evaluate if the solvent system is adequate. Rf is defined as the distance traveled by the compound divided by the distance traveled by the solvent front. This means: the larger the Rf value of a compound, the larger is the distance traveled by the compound. In other words, when comparing Rf values of various compounds under identical chromatography conditions, the compound with the larger Rf is less polar because it interacts less strongly with the polar adsorbent on the plate.

Remember, a good solvent system is one that moves all components off the baseline with Rf values between 0.15 and 0.85 (*ideal Rf is 0.2 - 0.4*). Otherwise, when possible, it is preferable to chose another solvent system.

$$\text{Retention factor } (Rf) = \frac{\text{distance traveled by the compound}}{\text{distance traveled by the solvent front}}$$

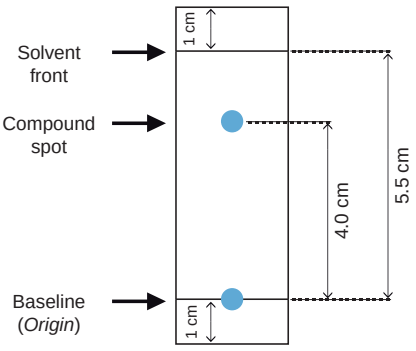
Rf calculation based on the example shown here:
Rf = 4.0 cm / 5.5 cm = 0.73

Prediction of Column Volumes (*CV*)

TLC data can be used to predict column elution based on the relationship between the retention factor and the column volume. CV is the number of column volumes required to elute the component from the column regardless of column dimensions [*(bed volume) - (volume of packing)*].

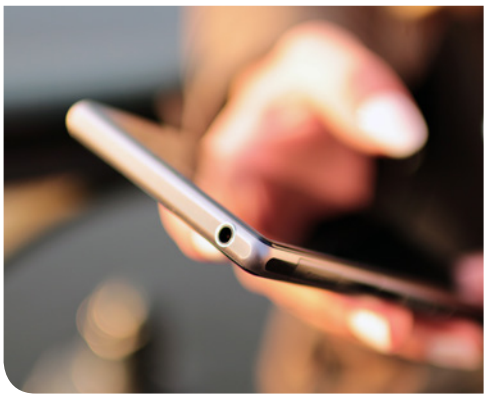
$CV = 1 / Rf$ & $\Delta CV = 1 / Rf_1 - 1 / Rf_2$

The greater the ΔCV, the greater will be the separation and resolution between the spots (easier separation).
A bigger ΔCV will therefore allow more sample to be loaded onto the column.



TLC Tool App

NEW

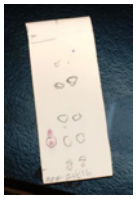


TLC has become as easy as taking a picture!

This mobile application is the perfect tool to help you save time for real chemistry issues: it will automatically calculate Rfs, store the TLC picture in your phone before the spots fade away (*so you can eventually print it or share it with other lab members*), it can even notify you if the mobile phase travels up to far and reaches the top of the plate !

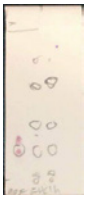
Please find more information visiting us at:
http://www.silicycle.com/tlcapp

Features



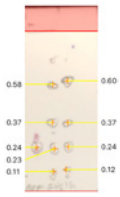
AUTO CROP

- Crops TLC from photo automatically
- Removes things you don't need



AUTO DETECTION
AUTO CALCULATE RF

- Detects spots automatically
- Calculates Rf without need for ruler nor calculator



SMART STORAGE

- TLC is hard to store or to find when needed
- Plus, spots eventually fade away or the layer oxidizes, making pencil marks hard to detect
- Your TLC plates are now just a click away in your phone!

SMART TIMER

- Automatically detects if colors in the specific area change over time

Plus, you can have access to all SiliCycle's offering of TLC Plates, from the most standard ones to most exotic layers.

Proudly developed by PoChu Hsu© 2015 PoChu Hsu http://tlc.ai-help-hi.com/

Described below are the most frequently used TLC visualization methods (*also called stains*) in alphabetical order.

Stains for Thin Layer Chromatography

Name	Visualization of...	Stain Recipe	Comments
p-Anisaldehyde #1	**Universal stain** *Good for nucleophiles and oxygenated compounds*	**Prepare stain as follows** • 2 mL of glacial acetic acid • 5 mL of p-anisaldehyde • 7 mL of conc. sulfuric acid • 185 mL of 95 % ethanol ***Tip*: *Add dropwise the acid at the end and stir vigorously.***	**Visualization Colors** • Spots: Various colors • BG: Orange to pink **Appropriate Storage** • Aluminum wrapped at 0°C
Note: Tends to be insensitive to alkenes, alkynes and aromatic compounds unless other functional groups are present.			
p-Anisaldehyde #2	*Acronycine* *Cineoles* *Terpenes*	**Prepare stain as follows [*1:10:20:80*]** • p-anisaldehyde • perchloric acid • acetone • water	**Visualization Colors** • Spots: Various colors • BG: Orange to pink **Appropriate Storage** • Aluminum wrapped at 0°C
Bromocresol Green	*Acidic groups (pK_a < 5)* *Carboxylic acids*	**Prepare stain as follows** • 0.04 g of bromocresol green • 100 mL of 95 % ethanol • 0.1 M solution of sodium hydroxide ***Tip*: *Add the base slowly at the end until the solution turns pale blue.***	**Visualization Colors** • Spots: Yellow to green • BG: Blue **Appropriate Storage** • Aluminum wrapped at 0°C ***Heating NOT required***
Cerium Molybdate (*CAM or Hanessian's Stain*)	**Universal stain** *Good for peptides*	**Prepare stain as follows** • 12 g of ammonium molybdate • 0.5 g of ceric ammonium molybdate • 15 mL of conc. sulfuric acid • 235 mL of water	**Visualization Colors** • Spots: Blue • BG: White **Appropriate Storage** • Aluminum wrapped
Note: Highly sensitive stain; very low concentration of product may appear as a significant impurity.			
Cerium Sulfate ($Ce(SO_4)_2$)	**Difficultly stainable compounds**	**Prepare stain as follows** • 15 % aqueous sulfuric acid saturated with ceric sulfate	**Visualization Colors** • Spots: Black • BG: Yellow to white
Chromic Acid	**Difficultly stainable compounds**	**Prepare stain as follows** • 2.5 g of potassium chromate • 100 mL of 20 % sulfuric acid in water	
Cobalt Chloride ($CoCl_2$)	**Universal stain** *Used in conjunction with PMA when this one is not effective enough*	**Prepare stain as follows** • 2 g of cobalt chloride • 100 mL of water • 10 mL of conc. sulfuric acid ***Tip*: *Simply dip PMA treated plate in $CoCl_2$ solution.***	**Visualization Colors** • Spots: Various colors • BG: Pink ***Heating NOT required***
p-Dimethylamino-benzaldehyde (*PDAB or Ehrlich's Reagent*)	*Amines* *Indoles*	**Prepare stain as follows** • 0.5 g of p-dimethylamino-benzaldehyde • 10 mL of conc. hydrochloric acid • 40 mL of acetone *(or 95 % ethanol)*	**Visualization Colors** • Spots: Blue • BG: White

N.B. Shaded lines refer to "Universal stains"

Stains for Thin Layer Chromatography (*Con't*)

Name	Visualization of...	Stain Recipe	Comments
2,4-Dinitrophenyl-hydrazine (*DNP*)	*Aldehydes* *Ketones*	**Prepare stain as follows** • 12 g of 2,4-dinitrophenylhydrazine • 60 mL of conc. sulfuric acid • 80 mL of water • 200 mL of 95 % ethanol	**Visualization Colors** • Spots: Yellow to red • BG: Light orange ***DO NOT HEAT dipped plate***
Dragendorff Reagent	**Nitrogenous Compounds** *Alkaloids, amines, organics bases, etc.* **Phenols**	**Prepare stain as follows** **Solution A** • 1.7 g of bismuth nitrate • 80 mL of water • 20 mL of acetic acid **Solution B** • 40 g of potassium iodide • 100 mL of water ***Tip:*** *mix 5 mL of each solution A and B to a solution of 20 mL of acetic acid in 70 mL of water.*	**Visualization Colors** • Spots: Orange to red • BG: Yellow **Appropriate Storage** • Aluminum wrapped **Stain Shelf-Life** • One or two weeks • Solutions A and B are long term storable ***DO NOT HEAT dipped plate***
Ferric Chloride ($FeCl_3$)	*Phenols*	**Prepare stain as follows** • 2 g of ferric chloride • 102 mL of 0.5 N hydrochloric acid	**Visualization Colors** • Spots: Red • BG: Yellow
Iodine	*Unsaturated & Aromatic compounds*	**Prepare stain as follows** • Iodine crystals in an amber bottle	**Visualization Colors** • Spots: Dark brown • BG: Light brown
Note: iodine stain can be removed by heating.			
Morin Hydrate (*Hydroxy Flavone*)	**Universal stain** *Fluorescently active*	**Prepare stain as follows** • 0.1 % of morin hydrate in methanol	**Visualization Colors** • Spots: Various colors • BG: White
Ninhydrin (*Indanetrione Hydrate*)	*Amino acids* *Amino sugars* *Amines*	**Prepare stain as follows** • 1.5 g of ninhydrin • 3 mL acetic acid • 100 mL of n-butanol	**Visualization Colors** • Spots: Various colors • BG: White
Phosphomolybdic Acid (*PMA*)	**Universal stain** *Very effective against diluted sample*	**Prepare stain as follows** • 10 % of PMA solution in ethanol • or 10 g of PMA in 100 mL of ethanol	**Visualization Colors** • Spots: Dark green to black • BG: Light green
Potassium Permanganate ($KMnO_4$)	*Olefins* *Readily oxidized groups* *Alcohols, aldehydes, alkenes, alkynes, etc.*	**Prepare stain as follows** • 1.5 g of potassium permanganate • 10 g of potassium carbonate • 1.25 mL of 10 % sodium hydroxide • 200 mL of water	**Visualization Colors** • Spots: Yellow to light brown • BG: Purple to pink **Stain Shelf-Life** • Three months
Note: Can be used for detection of alcohols, amines, sulfides and mercaptans groups when gently heated.			
Vanillin	**Universal stain** *Very effective for same polarity products (Rf)*	**Prepare stain as follows** • 15 g of vanillin • 250 mL of 95 % ethanol • 2.5 mL of conc. sulfuric acid	**Visualization Colors** • Spots: Various colors • BG: Light tan

Note: Occasionally, spots can be seen more clearly from glass side with glass backed TLC plate. Otherwise mentioned, stains are long-term stable when stored in a tightly-closed container to prevent solvent evaporation.
"BG" stands for "background".
N.B. Shaded lines refer to "Universal stains"

SiliaPlate TLC Troubleshooting

Problem: Streaking or elongated spot rather than a defined spot?

Possible Solutions:

- Sample was overloaded: run the TLC again using a more diluted solution of your sample.
- In presence of a base sensitive compound: try to add acetic or formic acid to the eluent (*0.1 - 2.0 %*).
- In presence of an acid sensitive compound: try to add triethylamine to the eluent (*0.1 - 2.0 %*) or 1 - 10 % ammonia in MeOH / DCM. If it is not working use Alumina as TLC coating.
- In presence of too highly polar compounds: try using a specialized silica TLC plate like reversed-phase (*C18 for example*).

Problem: Unable to see any spots on the TLC?

Possible Solutions:

- If you have not been able to visualize any spots on your TLC using UV light, try another method; maybe your compound is not UV-active.
- Maybe your sample is too diluted. Try to apply several times your sample on the same spot (*do not forget to dry solvent between each application for optimal results*) or to concentrate your solution.
- Make sure the solvent level inside the tank is lower than the spotting line to avoid sample dissolution by the eluent.

Problem: How to monitor a reaction in presence of similar Rfs for both starting materials and product of interest?

Possible Solutions:

- Try the co-spotting method (*see page 272*).
- Try to visualize the plate using anisaldehyde or molybdene. Spot color or brightness differ for two compounds when using these stains.
- If none of the two previous solutions work, change solvent systems (*use another class of solvent*).

Tips: in chromatography, there are three classes of solvent systems providing significantly different results:

1: Mixture of polar / hydrocarbon solvents (*i.e.: EtOAc / Hexane; Ether / Petroleum ether*).

2: Mixture of polar / dichloromethane solvents (*examples of polar solvent: Ether, EtOAc, MeOH*).

3: Mixture of polar / benzene (*or toluene*) solvents (*examples of polar solvent: Ether, EtOAc, MeOH*).

Problem: Compounds stay too close to the baseline or solvent front.

Possible Solutions:

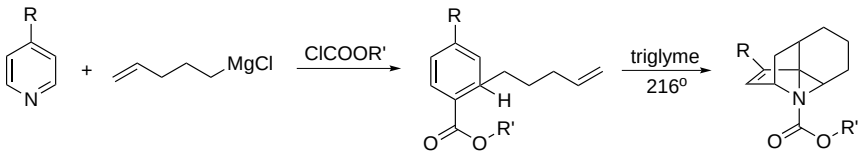
- Too close to the baseline: your eluent is not polar enough; increase the proportion of polar solvent in the same solvent system or chose a more polar solvent.
- Too close to the solvent front: inversely, your eluent is too polar; decrease the proportion of polar solvent in the same solvent system or chose a less polar solvent.

Silia*Plate* TLC Case Studies

Diels-Alder Cyclization of a Dihydropyridine

Structural studies of the *N*-(2,4-dinitrophenyl) derivative of a Diels-Alder-cyclized 1,2-dihydropyridine both unequivocally established the polycyclic framework and revealed interesting distortions of aromatic structure and unique dimeric clustering of the aromatic entities in the solid state.

SiliCycle Silia*Plate* TLC were used to monitor the conversion of a 1,2-dihydropyridine to the intramolecular Diels-Alder corresponding adduct, that was shown to be almost quantitative.



9a	^{t}Bu	Et
9b	Me	Me
9c	^{t}Bu	^{t}Bu

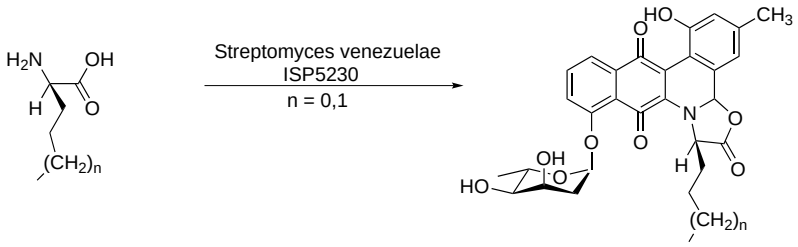
10a	^{t}Bu	Et
10b	Me	Me

Related Publication:
Helvetica Chimia Acta, **2014**, *97*, 1365-1382

Jadomycins Derived from the Assimilation and Incorporation of Norvaline and Norleucine

Streptomyces venezuelae ISP5230 is recognized for the production of chloramphenicol and the jadomycin family of natural products. The jadomycins are angucycline natural products containing a unique oxazolone ring incorporating an amino acid present in the minimal culture media. Substitution of different amino acids results in products of varying biological activity. Analysis of cultures of S. venezuelae ISP5230 incubated with L and D-norvaline and L and D-norleucine indicated that only the D-configured amino acids were incorporated into the natural products. Subsequently, jadomycin DNV and jadomycin DNL were isolated and characterized (*titers 4 and 9 mg L-1, respectively*). The compounds were evaluated in the National Cancer Institute cell line cancer growth inhibition and cytotoxicity screens, for antimicrobial activity against selected Gram-positive and Gram-negative bacteria, and as DNA-cleavage agents in vitro.

Glass-backed preparative TLC Silia*Plate* (*extra hard layer, 60 Å, 1,000 µm, UV indicator F_{254}*, PN: ***TLG-R10011B-341***) were used throughout the study for reactions monitoring.



Related Publication:
J. Nat. Prod., **2011**, *74*, 2420-2424

« We had tried working with TLC plates of another brand and realized that the SiliCycle brand was the most durable and long-lasting as well as clear when visualizing with UV light so we switched back. »

Jessica Kisunzu from UC Berkeley, Berkeley, CA, USA

Enantioselective Synthesis of an Ophiobolin Sesterterpene

Terpenes are a large and highly diverse class of natural products, produced by plants and mostly conifers.

They derive biosynthetically from isoprene, which cannot undergo by itself linking in a head-to-tail fashion, followed by a rearrangement to form rings. Cyclase enzyzmes are often used in the synthetic pathway, but are difficult to emulate under abiotic conditions.

Maimone et al. report in Science a impressive strategy to complex terpenes whereby simple prenyl-derived chains are cyclized using radical, rather than cationic, reaction pathways. This approche lead to the synthesis of 5-8-5 fused ring systems found in numerous complex natural product classes and also enabled a nine-step total synthesis of (–)-6-epi-ophiobolin N.

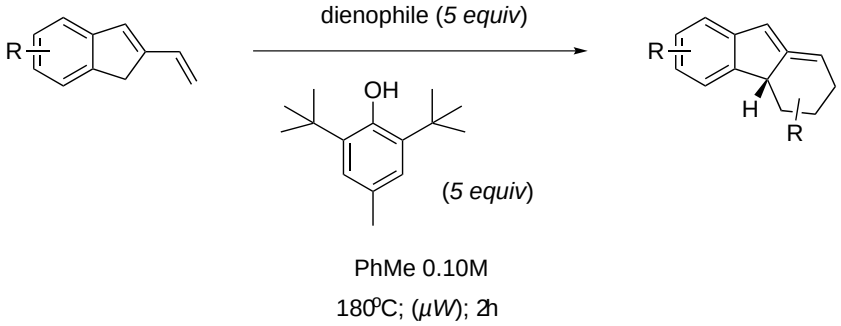
Reactions were followed via *Glass-Backed* TLC Silia*Plate* (*Special Layer for KMnO4, 250 µm, 20x20 cm UV indicator* F_{254}, PN: ***TLG-R10014BK-323***)

Related Publication:
Science, **2016**, 352, 1072-1082

Diels-Alder Reactivity of 2-vinylindenes in the Synthesis of Functionalized Tetrahydrofluorenes

Functionalized terahydrofluorenes are well-known starting block in the synthesis of various natural products, including kinamycins, taiwaniaquinoids, pharmaceutical compounds (for instance a selective estrogen receptor β-antagonist.

Sarpong et al. studied the synthesis of functionalized tetrahydrofluorenes using a normal electron-demand Diels-Alder cycloaddition reaction between 2-vinylindenes and various dienophiles. Electron rich 2-vinylindenes bearing methoxy groups at the 4- and 7- positions were accessed through their corresponding 2-indenylpivalates obtained using a Pt-catalyzed cycloisomerization reaction.



All reactions were assessed using Glass-backed TLC Silia*Plate* (*Glass-Backed, Hard Layer, 250 µm, 20x20 cm, UV indicator* F_{254}, PN: ***TLG-R10014B-323***).

Related Publication:
Tetrahedron, **2016**, *72*, 3635-3640

One-Step Synthesis of Methanesulfonyloxymethyl Ketones via Gold-Catalyzed Oxidation of Terminal Alkenes: A Combination of Ligand and Counter-Anion Enables High Efficiency and a One-Pot Synthesis of 2,4-Disubstituted Thiazoles

By using Mor-DalPhos as the P,N-bidentate ligand and mesylate as the counter-ion, the resulting gold(I) complex catalyzes efficient oxidative transformations of various terminal alkynes into synthetically versatile methanesulfonyloxymethyl ketones. The mild reaction conditions and high efficiency permit the one-pot synthesis of a range of valuable 2,4-disubstituted thiazoles by subjecting the resulting reaction mixture to a further condensation with thioamides under mild conditions.

All reactions were monitored by thin layer chromatography using SiliCycle analytical Silia*Plate*.

Related Publication:
Adv. Synth. Catal., **2014**, *356*, 1229-1234

Utilizing Mor-DalPhos/Palladium-Catalyzed Monoarylation in the Multicomponent One-Pot Synthesis of Indoles

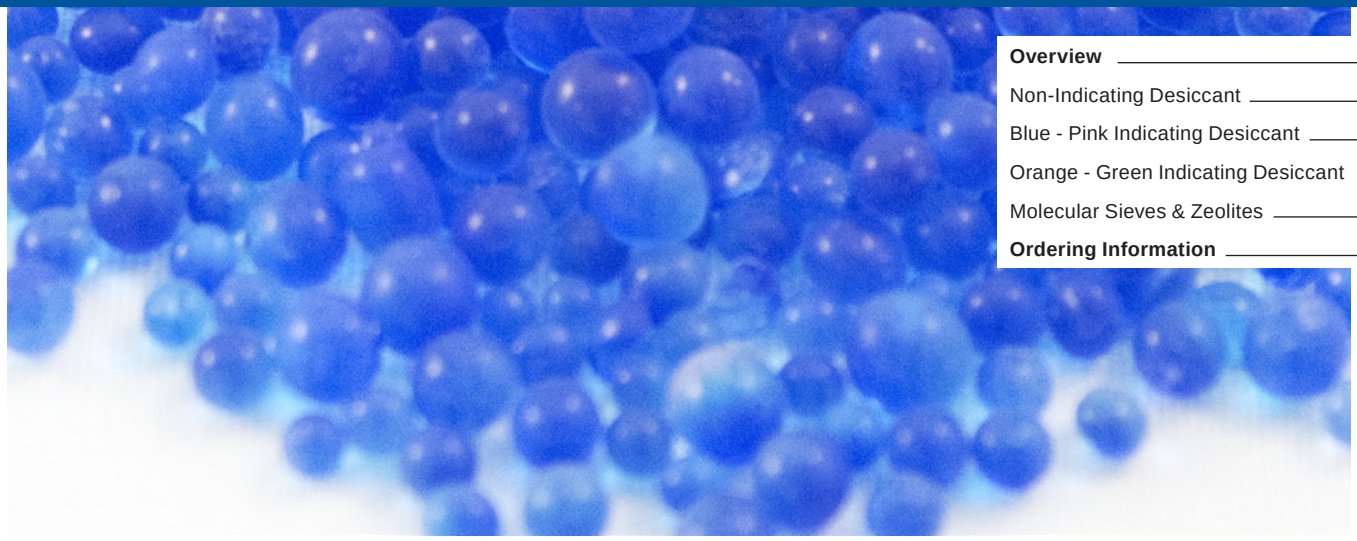
The application of a Mor-DalPhos/palladium catalyst system in the one-pot, multicomponent assembly of substituted indoles from ortho-chlorohaloarenes, alkyl ketones (*including acetone*) and primary amines is reported. The described protocols offer improved substrate scope in all three reaction components, under more mild conditions and without the need for an additional drying agent. Also reported are the first examples of such multicomponent reactions where all reactants are combined at the start of the reaction, without the need for inert atmosphere reaction conditions.

Preparatory thin layer chromatography to monitor monoarylations was carried out using SiliCycle glass-backed TLC Silia*Plate* (*extra hard layer, 60 Å, 1,000 µm, UV indicator F_{254}, PN:* ***TLG-R10011B-341***).

Related Publication:
Adv. Synth. Catal., **2015**, *357*, 100-106

Desiccants

SiliaDry™



SiliaDry Desiccants Against Moisture

SiliaDry desiccants keep your goods safe from ambient moisture

- Safe and eco-friendly material
- Wide range of pore and particle sizes
- Excellent adsorption capacitt
- Different moisture indicator to signal when saturation is reached
- Inexpensive solution to protect your goods

SiliaDry Silica Desiccants

Desiccants draw in moisture but do not physically become wet. This is the reason they can quickly dehumidify environments, preserve metals and other stored goods.

Many believe heating your material will remove the threat of humidity, but this is more likely to yield an opposite effect: warmer air can hold more moisture and is therefore likely to release a greater deal of moisture.

Keep Your Goods Safe from Ambient Moisture

Desiccants are a powerful moisture-prevention tool of high safety used in various fields of our daily life as a strong adsorbent. It has an excellent adsorption capacity at low relative humidity for keeping materials dry and preventing rust.

Usual applications include but are not limited to:

Various uses for desiccants

Research & Laboratories	Industrial Equipment & Gases		Electronics	Coating, Sealants & Adhesives	... And so much more	
Laboratories desiccators	Hydrocarbon streams decontamination	Ethanol dehydration	Photographic equipment	Pigments	Cosmetics	Drying flowers
Bulk & packaged medical gases	High purity industrial gases (O_2, N_2, H_2, CO)	Air dryers	Optical equipment	Caulks	Shipping containers	Transformer tank breathers
Pharmaceutical stoppers	Craked gases & olefin streams dehydration	Conditioning systems	Telecommunication equipment	Paper manufacturing	Clothing & leather goods	Foods (*dried seaweeds, salted meats)*
Humidity-sensible reagents	Natural Gas Processing	-	Decontamination of hydrocarbon streams in rafinery applications	-	Insulated windows	-

Great and Effective Adsorption

Desiccants adsorb moisture from surrounding environments by capillarity. This method prevents the desiccant from physically changing during usage, allowing peak efficiency to be maintained for quite a while. This great effectiveness and adsorption quality makes this material useful for a very vast array of conditions and media.

Silica gel is an amorphous form of silicon dioxide, which is synthetically produced in the form of hard irregular granules that have the appearance of crystals or hard irregular beads. A microporous structure of interlocking cavities gives a very high surface area. It is this structure that makes silica gel a high capacity desiccant. Water molecules adhere to the gel surface because it exhibits a lower vapour pressure than the surrounding air.

When an equilibrium of equal pressure is reached, no more adsorption occurs. Thus the higher the humidity of the surrounding air, the greater the amount of water that is adsorbed before equilibrium is reached. It is in these higher humidity conditions (*above 50 % relative humidity*) that stored or in-transit items are susceptible to damage.

Approximately 40 g of desiccant will adsorb the moisture from three cubic feet of air.

Wide Choice of Packagings

Silia*Dry* desiccants come in either bulk (*industrial, commercial and lab applications*) or specialized bags and canisters that will not moisten nor break as the desiccant adsorbs moisture. Desiccant packs are made of Tyvek® (*FDA approved*) and laminated film to last for a lengthy period of time. Thus, you will never have to face bags bursting or spilling, which can happen with poor-quality or cheap containers.

Recycling of Desiccant

Heating drives off the adsorbed moisture of silica gel, and as it does so, the indicating desiccant will switch back to its original color. When drying objects, it is important to keep the container size small in relation to the object being dried. This helps ensure more rapid and thorough drying.

Typical regeneration procedure involves two hours of heating at 150°C (*300°F*) in an oven. Various conditions can be tested ranging from 150 to 200°C (*300 to 400°F*), for one to five hours, with or without rest.

Advantages of Silica Gel as a Desiccant

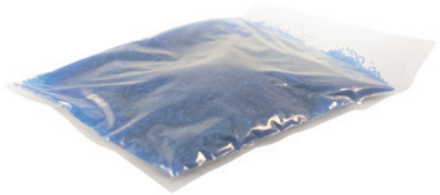
Silica gel has many other properties that make it a material of choice as a desiccant. It will adsorb up to one third of its own weight in water vapour. This adsorption efficiency is approximately 35 % greater that typical desiccant clays, making silica gel the preferred choice where weight or efficiency are important factors.

It has an almost indefinite shelf-life if stored in airtight conditions.

It can be regenerated and reused if required. Gently heating silica gel will drive off the adsorbed moisture and leave it ready for reuse.

It is a very inert material, it will not normally attack or corrode other materials and with the exception of strong alkalis and hydrofluoric acid is itself resistant to attack. It is non-toxic and non-flammable.

It is most frequently and conveniently used packed in a breathable sachet or bag. These are available in a wide range of sizes suitable for use with a wide range of applications.



SiliaDry Features and Technical Specifications

Non-Indicating Desiccant

White, non-indicating desiccant is one of the oldest and most popular desiccant and adsorbent used for a countless number of industrial and consumer applications.

Non-indicating silica gel will adsorb moisture in the exact same way as indicating silica, except it will not change color upon saturation.

Technical Parameters		
Properties		**Specifications**
Shape		Spherical beads
Assay (*as SiO_2*)		97 %
Bulk Density		0.50 - 0.60 g/mL
Appearance		White
Friability		99.5 %
Adsorption Capacity	RH 50 % RH 100 %	> 20 > 35 - 40
Loss at Heating		< 6.0 %
Chloride (*as NaCl*)		< 0.05 %
Cobalt (*as CoCl*)		NIL
Sulfates (*as Na_2SO_4*)		< 0.5 %
Binder (*as $CaSO_4$*)		NIL

Blue - Pink Indicating Desiccant

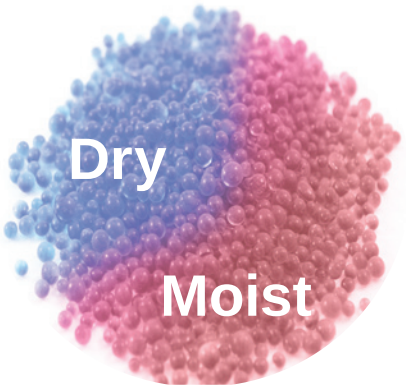
When the desiccant is completely dry, its color is deep blue.

As it picks up the surrounding moisture, the color indicator shifts from blue to pink. Desiccants may be re-dried by heating for two hours at 150°C (*300°F*).

It uses an organic substance as indicating agent that changes color from blue to pink on saturation. It is environmentally safe, free from foreign impurities such as chlorides, sulphates and other organic matters and has high adsorption efficiency.

It is 100 % free of cobalt (*widely present in most desiccants*), a human carcinogen and toxic agent to aquatic organisms, as well as being innocuous and non polluting.

Technical Parameters		
Properties		**Specifications**
Shape		Spherical beads
Appearance		Blue
Adsorption Capacity	RH 50 % RH 100 %	> 20 > 30
Loss at Heating		< 4.0 %
Adsorption Color Change	RH 50 % > RH 80 % >	Purplish red Pinky red
Bead Size up to Grade		> 90 %



Orange - Green Indicating Desiccant

When the desiccant is completely dry, its color is bright orange.

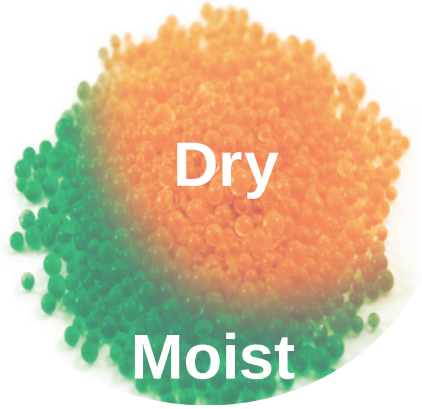
This type of indicating desiccant, also known as **Enviro Gel**, uses an organic substance as indicating agent that changes color from orange to green on saturation. It is an environmently safe product.

Our gel is free from foreign impurities such as chlorides, sulphates and other organic matter and has high adsorption efficiency.

It is also 100 % free of cobalt (*widely present in most desiccants*), a human carcinogen and toxic agent to aquatic organisms. It is therefore innocuous and non-polluting. Desiccant may be re-dried by heating for two hours at 150°C (*300°F*).

Technical Parameters

Properties		Specifications
Shape		Spherical beads
Appearance		Orange
Adsorption Capacity	RH 50 % RH 100 %	> 20 > 30
Loss at Heating		< 4.0 %
Adsorption Capacity	RH 50 % > RH 80 % >	Light orange - light green Dark green
Bead Size up to Grade		> 90 %

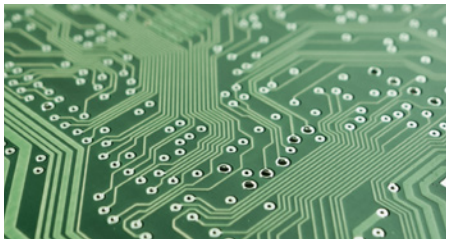


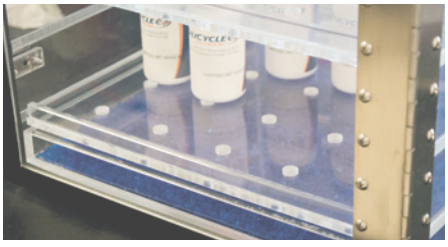
Typical Uses

Typical uses include - *but are not limited to*:

Various Uses for Color Indicating Desiccants

Research & Laboratories	Industrial Equipment	Electronics	Shipping
• Laboratories desiccators • Drying and cleaning of air • Diagnostic and medical equipment • Transformers breathers • Drying of analytical samples, solvents or synthesis products • Sample preparation for Karl-Fischer titrations	• Engines and generators	• Protection of moisture damage to electronic and communication goods • Electronic circuits and semiconductors • Optical instruments and devices	• Protection of Export Consignments from moisture in salty and / or humide atmosphere • Drying and storage of flowers and seeds • Clothing, leather goods and food conservation





Molecular Sieves & Zeolites

Molecular Sieves

A molecular sieve is a material containing tiny pores of a precise and uniform size that is used as an adsorbent for gases and liquids.

Molecules small enough to pass through are adsorbed, while larger molecules are not. It is different from a common filter in that it operates on a molecular level. Molecular sieves are mostly used in the petroleum industry, for the purification of gas streams.

Molecular sieves come in many different forms: as microporous, mesoporous or macroporous cavities.

Zeolites

Zeolites are a microporous form of molecular sieves, with aluminosilicates as a skeletal composition and pore diameters less than 2 nm (*or 20 Å*).

They are capable of adsorbing nearly 22 % of their weight in water and are largely used for gas drying applications.

When developing applications for Zeolites, one must keep in mind that there are nearly 40 different types of Zeolites with different physical specifications, chemical properties and composition.

Particle density, molecular pore size, crystal structures are only few differences that can discriminate one type of Zeolite from another.

It is imperative to specifically know what type of Zeolite is needed for one's application.

Typical uses include - but are not limited to:

Most Popular Applications of Zeolites	
Pore Diameter	**Most Popular Applications**
Type 3 Å	
Nominal Pore Diameter: 3 Å **Molecules Excluded:** > 3 Å effective diameter (*e.g.: C_2H_6*) **Base:** Alumina - Silicate **Cation:** Potassium (K^+)	• Type 3 Å will adsorb molecules having a critical pore diameter of less than 3 Å. e.g.: Helium (*He*), Hydrogen (*H*) and Carbon Monoxide (*CO*). • Preferred adsorbent for the commercial dehydration of unsaturated hydrocarbon streams such as cracked gas, propylene, butadiene and acetylene. • Essential for storing Electron Microscopy specimen stubs (*SEM, TEM, REM, STEM*). • Recommended for drying unsaturated hydrocarbons and highly polar compounds such as methanol and ethanol. • Particularly effective in dehydrating the inner space of insulating glass windows as well as refrigerant gases. • Potassium form of Zeolite.
Type 4 Å	
Nominal Pore Diameter: 4 Å **Molecules Excluded:** > 4 Å effective diameter (*e.g.: C_3H_8*) **Base:** Alumina - Silicate **Cation:** Sodium (Na^+)	• Preferred adsorbent for static dehydration in a closed gas or liquid system. Will adsorb molecules having a critical pore diameter of less than 4 Å. (*e.g.: Methanol, Ethane and Propane*). • Typically used in regenerable drying systems to remove water vapor or contaminants that have a smaller critical diameter than 4 Å. • Used as a static desiccant in household refrigerating systems, packaging of drugs, electronic components, perishable chemicals and as a water scavenger in paint and plastic systems. • Also used commercially in drying saturated hydrocarbon streams (*Ethane, Butane*). • Sodium form of Zeolite.
Type 5 Å	
Nominal Pore Diameter: 5 Å **Molecules Excluded:** > 5 Å effective diameter **Base:** Alumina - Silicate **Cation:** Calcium (Ca^+)	• Typically used to separate isomeric alkanes (*less than 5 carbons*) from branched-chain and cyclic hydrocarbons through a selective adsorption process. • Will adsorb those molecules having a critical pore diameter of less than 5 Å (*e.g.: Methanol, Ethane and Propane*). • Calcium form of Zeolite.
Type 10 Å & 13 X	
Nominal Pore Diameter: 10 - 13 Å **Molecules Excluded:** > 10 - 13 Å effective diameter **Base:** Alumina - Silicate **Cation:** Sodium (Na^+)	• Preferred molecular sieve adsorbent for dynamic dehydration in a closed gas or liquid system. • Used commercially for general gas drying, air plan feed purification (*simultaneous removal of H_2O and CO_2*) and liquid hydrocarbon (C_{5+}) and natural gas sweetening (*H_2S and mercaptan removal*). • Ensure dryness of medical and air compressor systems. • All molecules which can be adsorbed on Molecular Sieves 3 Å, 4 Å and 5 Å can be adsorbed on type 13 X. In addition, 13 X can adsorb molecules of larger critical diameters, such as aromatics and branched-chain hydrocarbons. • A modified sodium form of Zeolite.

SiliaDry Ordering Information

SiliaDry Desiccant, non-indicating, Bulk

Non-Indicating Desiccant, Bulk			
Product Number	Particle Size		Packaging
	mm	mesh	
DES-5-15W	5.0 - 15	1 - 3	25 kg Drum
DES-4-5W	4.0 - 5.0	3 - 4	
DES-2-5W	2.0 - 5.0	3 - 8	
DES-2-3W	2.0 - 3.0	5 - 8	
DES-1-1-5W	1.0 - 1.5	9 - 16	1,000 kg Bag
DES-0-5-1W	0.5 - 1.0	16 - 30	1,000 kg Bag
DES-0-15-0-5-W	0.15 - 0.5	30 - 100	1,000 kg Bag

SiliaDry Desiccant, Blue - Pink Indicating, Bulk

Blue - Pink Desiccant, Bulk			
Product Number	Particle Size		Packaging
	mm	mesh	
DES-1-3BR	1.0 - 3.5	6 - 18	25 kg Drum
DES-1-3BR-50KG			2 x 25 kg Drum
DES-2-4BR	2.0 - 4.0	5 - 10	25 kg Drum
DES-2-4BR-50KG			2 x 25 kg Drum
DES-2-5BR	2 .0 - 5.0	4 - 10	25 kg Drum
DES-2-5BR-50KG			2 x 25 kg Drum
DES-3-5BR	3.0 - 5.0	4 - 6	25 kg Drum
DES-3-5BR-50KG			2 x 25 kg Drum

SiliaDry Desiccant, Orange - Green Indicating, Bulk

Orange - Green Desiccant, Bulk			
Product Number	Particle Size		Packaging
	mm	mesh	
DES-2-5MOV	2.0 - 5.0	4 - 10	25 kg Drum
DES-3-5MOV	3.0 - 5.0	4 - 6	25 kg Drum

SiliaDry Ordering Information

SiliaDry Desiccant, Blue - Pink Indicating, Pillow-Packed

Blue - Pink Desiccant, in Pillow-Packs				
Product Number	Particle Size		Packet Size	Packaging
	mm	mesh		
DES-2-5BRP-5	2.0 - 5.0	4 - 10	5 g	20 kg (*5 g Packets*) (*50 x 20 kg min*)
DES-2-5BRP-10			10 g	25 kg (*10 g Packets*) (*40 x 25 kg min*)
DES-2-5BRP-50			50 g	25 kg (*50 g Packets*) (*40 x 25 kg min*)
DES-2-5BRP-100			100 g	25 kg (*100 g Packets*) (*40 x 25 kg min*)
DES-2-5BRP-1,000			1 kg	25 kg (*1 kg Packets*) (*40 x 25 kg min*)
DES-3-5BRP-5	3.0 - 5.0	4 - 6	5 g	20 kg (*5 g Packets*) (*50 x 20 kg min*)
DES-3-5BRP-10			10 g	25 kg (*10 g Packets*) (*40 x 25 kg min*)
DES-3-5BRP-50			50 g	25 kg (*50 g Packets*) (*40 x 25 kg min*)
DES-3-5BRP-100			100 g	25 kg (*100 g Packets*) (*40 x 25 kg min*)
DES-3-5BRP-1,000			1 kg	25 kg (*1 kg Packets*) (*40 x 25 kg min*)

SiliaDry Desiccant, Molecular Sieves, Bulk

Molecular Sieves Desiccant, Bulk				
Product Number	Particle Size		Pore Diameter	Packaging
	mm	mesh		
MS3-2-5-50KG	2.0 - 5.0	4 - 10	3 Å	2 x 25 kg Drum
MS3-3-5-50KG	3.0 - 5.0	4 - 6		
MS4-2-5-50KG	2.0 - 5.0	4 - 10	4 Å	
MS4-3-5-50KG	3.0 - 5.0	4 - 6		
MS5-2-5-50KG	2.0 - 5.0	4 - 10	5 Å	
MS5-3-5-50KG	3.0 - 5.0	4 - 6		
MS10-2-5-50KG	2.0 - 5.0	4 - 10	10 Å	
MS10-3-5-50KG	3.0 - 5.0	4 - 6		
MS13-2-5-50KG	2.0 - 5.0	4 - 10	13 Å	
MS13-3-5-50KG	3.0 - 5.0	4 - 6		

R&D Services

Reinvesting our experts' talent in your project

R&D Services

We thrive on making your projects come to life

- We listen. We understand. We work with you.
- We are flexible, commited, reliable, innovative, fast & affordable.
- Our objective: reinvesting our experts' talent in your very own expertise.
- Assistance to start-ups & young tech companies.
- Wide range of services offered.

At a Glance

One Partner: SiliCycle

SiliCycle is devoted to serving the global chemical & pharmaceutical industry and constantly focuses on quality.

SiliCycle is a leading service provider, offering turnkey solutions based on its long expertise in organic chemistry, catalysis, material science and analytical chemistry. We are recognized worldwide for the development, the manufacturing and the commercialization of high value silica-based and specialty products for chromatography, analytical and organic chemistry.

Overview of Our Services

We offer high-throughput R&D services to pharmaceutical, medicinal & combinatorial industries, to drug discovery, development & manufacturing markets, to analytical, clinical & QC labs, official organizations as well as academic & government institutions.

Our R&D Services are categorized into 7 streams:

Metal & Organic Scavenging Screenings

- Best Screening Conditions Evaluation
- Process Scaling-Up & Transfer to Production
- Metal Recovery

Synthetic Chemistry Services

- Custom Chemical Synthesis
- Catalysis Services
- Process Services

You can learn more about these various branches throughout the next pages.

Separation Center

- Compound Extraction & Sample Preparation
- Method Development, Optimization & Transfer
- Impurity Isolation & Structure Elucidation

Custom Column Packing

- Exotic Phases & Column Dimensions Available
- Packing of Custom-Made Phases
- Batch Reservation

Material Science

- Grafting & Encapsulation
- Optimization of Grafted Catalysts
- Customized Particle Size Distribution

Analytical Laboratory & Quality Control

- Cost-Effective Quality Control Support
- SOPs, Site Master Files Redaction
- Regulatory Compliance Assistance

Microbiology

- Food, Diesel, Soil Microbiological Testing
- Commercial Sterility
- Bug Monitoring

The Customer: Always at the Center of Our Focus

Our services were created in response to the growing gap between the urge for rapid innovation while remaining profitable.

More and more, there is pressure bulding-up on the industry to meet new challenges: become greener, increase competitiveness and leverage the opportunities of global markets.

SiliCycle's main priority is to ensure you real innovation, tangible ROI, quality assurance and intellectual property within your tight timeframes. Our programs focus on issues of strategic importance for your venture: a unique value proposition to deliver results of high impacts.

Our flexible approach for each project brings added value to our services to match each client's requirements. Whatever stage you are at in the product development process, it is never too early or too late to benefit from our input to ensure that things are on track. **Our business models:**

- Full Time Equivalent (*FTE*)
- Fee for Service (*FFS*)
- Milestone Based

Fuelling R&D & leading to firsts in the marketplace is what drives us and motivates us

Facility & Lab Infrastructure

SiliCycle Headquarters

Built in 2009 and located in Quebec City (*Canada*), the SiliCycle Headquarters is a new cutting-edge plant with a multi-ton scale manufacturing capability. Since its construction, SiliCycle has been successfully audited several times (> *100 audits*).

In 2012, it was also the first site to pass an audit by AstraZeneca with a perfect score of 100 %.

As a certified ISO 9001-2008 company, we have rigourous quality system in place: all procedures and employees are in line to assure you ultimate quality and an unbeatable customer service. With state-of-the-art instrumentation park in the areas of chromatography, spectroscopy and manufacturing combined to an application support laboratory, we are devoted to extend your R&D and make your project a success.

Photo: Stéphane Groleau

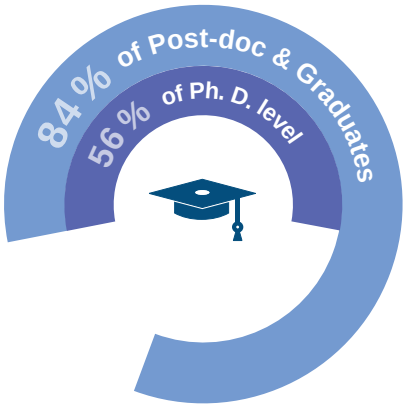
Our Scientific Team Expertise & Talents

Scientific Team & Know-How

SiliCycle's mandate is to offer on-time tailored package of work with communication report format, cost and timeframe in lined with your projects.

Our domain of expertise lies in our experts' vast knowledge and skills in a variety of core competencies in various domains.

They all are passion-driven scientists with University levels and very own individual expertise.



A Brief Overview of Our Scientist' Competencies

- **Analytical Chemistry**
  - Analytical method development and optimization (*UPLC, HPLC, GC, etc.*)
  - Extraction of natural compounds
  - Sample preparation using various techniques (*SPE, QuEChERS, etc.*)
  - Method validation under Good Laboratories Practices norms
- **Medicinal & Organic Chemistry**
  - Total synthesis of natural products, active ingredients and small molecules
  - Synthesis of very elaborated heterocycles, building block and complex intermediates
  - Enantioselective total synthesis and asymmetric catalytic synthesis of various compounds
  - Boronic acids, fluorine and peroxide-based chemistries
  - Green chemistry and organic chemistry in water
- **Biology, Biochemistry**
  - Interactions of biomolecules and biochemical signaling
  - Genetics, metabolism and PCR
  - Molecular-scale biological chemistry
- **Catalysis & Organometallic Chemistry**
  - Homogeneous and heterogeneous catalysis (*coupling, hydrogenation, oxidation, etc.*)
  - Development of solid-supported catalysts
  - Synthesis of chiral ligands
- **Chemical Engineering, Mesostructured Material, Physical & Petrochemistry**
  - Encapsulation of active ingredients in many matrices
  - Materials characterization using various techniques
  - Surface modifications and functionalization of materials
  - Synthesis of organosilanes, organosilicon compounds and mesoporous molecular sieves

We aim at establishing long-term partnership with our customers by offering an all-inclusive service. That is, over 75 % of our services are repeat business, an evidence of our engagement and commitment to meet and exceed expectations.

Metal & Organic Scavenging Screenings

CONFIDENTIALITY GUARANTEED

This service is specially designed for scientists that are either faced with a residual impurity that needs to be removed, or that concentration needs to be reduced.

With increasing regulatory requirements (*FDA, ICH*) for residual levels of metal catalysts or organic potentially genotoxic impurities (*PGI compounds*), the removal of post-reaction metal residues has become a major issue in the industry. Not only SiliCycle offers an unparalleled range of metal and organic scavengers, which significantly reduce the levels of these impurities, but we also offer screening services.

Our scavenging screening services are innovative as they provide a solution to quickly develop the most efficient scavenging process providing both time and cost savings. Confidentiality is assured, as in most cases the solution involves working with API and other patented materials, and easy technology transfers are guaranteed.

Over the years, SiliCycle has developed a number of screening services to assist customers in their projects and help identify solutions for purification challenges, at all stages & scales, from R&D to production.

➔ Main objective is to **accelerate research, optimize production costs**, while remaining fully in compliance with **new regulations & environmental challenges**

➔ Scavenging strategies imply **lower volumes of solvent, less person-days and higher yields** by minimizing loss of product via classical purification processes

Take the step many major pharmaceutical companies have taken, and contact us to discuss how we can help you reach your purity goals.

Such analysis has become routine for us, so you can be assured of the best quality services. What we are able to offer is a unique, confidential, full screening program on a particular metal residue or organic impurity.

This is a comprehensive service focussing on a removal or recovery challenge using a broad range of functionalities and conditions to identify the optimal experimental procedure for your needs and requirements.

Depending on your project needs, various parameters can be evaluated such as:

- Screening condition: scavengers type, solvent, amount of scavenger, reaction time and temperature
- Optimization and scale-up
- Recovery and purity evaluation

Full Process Scale

We can also offer an exclusive partnership program designed to run scavenging on Full Process Scale. We will be working closely with you to identify your needs and requirements. This optimisation of your R&D project can either take place as a slurry, in your reactor (*bulk mode*), or through a cartridge in a flow mode.

➔ ***Need help? We can also provide an expedited service, offering an initial look at an impurity removal issue.***

Process Outline

All our scavenging screening services are carried out in our laboratories at our Headquarters in Quebec City by our experienced team.

From the beginning through the end of the project, our team works closely with you to report progress on the screening. A complete report is sent and we work with you to ensure a successful, easy technology transfer.

If needed, our experts can do on-site visits to help during the process transfer.

Many screening services are available and can be adapted to your needs & budgets.

1. NDA signed for confidentiality purpose
2. Scavenging questionnaire completed by customer and revised by our experts
3. Communications to determine the objectives of the service
4. Customer's sample sent to SiliCycle
5. Initial lab-scale screening to select the most efficient scavengers and generate data
6. Optimization of the conditions
7. Scale-up trials and purity evaluation
8. Preparation of the report and wrap up meeting to present results to customer
9. Detailed experimental procedure for easy technology transfer & plant trials

Chemistry Services

SiliCycle is one of the world's leading manufacturers of specialty supported products and can help you with more than your separation challenges. Our team of synthetic chemists have been successful in numerous industries from pharma to material sciences. Our highly skilled scientists are ready to develop for you cost-effective synthetic processes using either solution or solid-phase chemistry from milligram to kilogram scale at competitive prices.

Here is a brief overview of available services.

Custom Chemical Synthesis

SiliCycle has a wide experience in the design and synthesis of new organic molecules and the development of novel methodology for their preparation. In especially challenging synthetic pathways, we can help you out with your most difficult synthetic reactions, using cutting-edge technology to develop cost-effective solutions.

Available Technologies

- Flow chemistry
- High-pressure chemistry
- Solid-supported chemistry
- Microwave-assisted reaction
- Parallel synthesis and purification
- Targeted library synthesis

➔ We **accelerate drug development** by setting up & optimizing crutial steps using an **innovative silica-based technology** in a matter of weeks

➔ Proper optimization = lower catalyst / reagents cost & **simpler downstream processing**

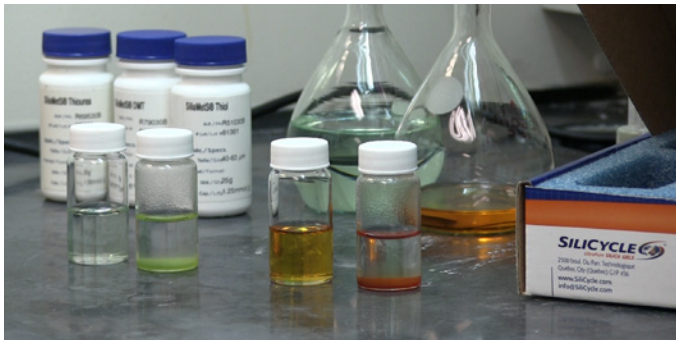
➔ We develop safer & cleaner processes leading to **atom economy** and **further cost reduction**

Molecules We Have Expertise With

- Small molecules and API
- Peptides
- Very elaborate heterocycles
- Building blocks and complex intermediates
- Complex monomers
- Innovative routes and compounds
- Reference compounds (*standards*)

Most Popular Custom Chemical Services

- Project evaluation and literature searches
- Synthesis of active compounds, building blocks and intermediates from mg to kg scale
- Synthetic route design, realization & optimization
- Synthesis of targeted library
- Scale-up of existing or new reactions
- Transfer of heterogeneous batch process to flow
- Transfer of homogeneous process to heterogeneous
- Scavenging of residual metal catalyst



Catalysis Services

Our main objective is to extend your R&D or production and help you bring your product to market more quickly.

Our approach combines a broad scope of expertise which can accelerate your catalyst's screening, optimize an existing catalytic process, test the feasibility of a new one or understand metal-catalyzed reaction.

As a catalyst manufacturer with multiple patents, our skilled and competent catalysis group can investigate any reaction parameter (*catalyst loading, solvent, ligand, base / additive nature, concentration, temperature, time, etc.*) to maximize yields and purity as well as to reduce wastes and costs.

Most Popular Catalysis Services

- Catalysts screening and evaluation
- Catalytic process optimization
- Tailor-made catalyst development to fit your requirements
- Scale-up of catalytic reactions: up to kg & process transfer to pilot scale (*1 - 5 kg*)

Process Services

SiliCycle understands the importance of having a robust and cost-effective synthesis when it comes to process development and manufacturing. We offer flexible process services based on a structured approach to increase yields and purities at reduced costs. Being 100 % committed, our process experts can help you make your project a success story and work with you on process enhancements.

Most Popular Process Services

- Identification of safety issues and synthetic opportunities
- Route scouting & feasibility
- Yield and purity optimization
- Resolution of challenging bottleneck steps
- Process scale-up from laboratory to kilo-lab synthesis
- Manufacturing support & process engineering
- Scavenging of residual metal catalyst

Typical Process Enhancement Parameters

For each process service, these parameters can be further refined upon request:

- Safety
- Reproducibility
- Cost optimization
- Yield & purity improvement
- Time constraints (*productivity*)
- Solvent substitution (*greener, safer or cheaper*)
- Volume constraints
- Robustness

Partial instrumentation list:

- Centrifuges, Evaporators, Ovens & Pumps
- Fully Functional Chemistry Fume Hoods
- High Shear Mixers & Sonicators
- Microwave Synthesizer & Flow System

Separation Center Services

For decades, SiliCycle has been dedicated to silica gel manufacturing and has built a strong skilled team in this field. You can now benefit from years of experience in chromatography, purification and method development.
Our expertise covers a wide spectrum of applications on various purification scales.

We offer

- ➡ Compound Extraction & Sample Preparation
- ➡ Purity Determination
- ➡ Method Scale-up or Preparative Chromatography
- ➡ Preparative Liquid Chromatography (*low / medium / high pressure*)
- ➡ Milligram to Large-Scale Separations
- ➡ Analytical Method Development, Optimization & Transfer
- ➡ Impurity Isolation & Structure Elucidation

Compound Extraction & Sample Preparation

Looking to extract a specific product from a complex matrix? Let our experts develop a process for you. We can screen various methods and determine the most efficient ones to extract any value-added product from biomass or solution. Some typical molecules we have worked with include polyphenols and phytonutrients, omega-3 & omega-6, fatty acids, pesticides, vitamins, dioxins, pollutants, conjugate polymers.

Furthermore, we can optimize your sample preparation processes using SPE cartridges, well plates, QuEChERS, liquid-liquid extraction to maximize recovery and reduce interferences.

Our generic approach for method extraction will decrease development time and costs.

➔ We enable scientists to quickly separate mixtures, isolate molecules or elucidate structures for **rapid commercialization onto global markets**

➔ We help ensure that compounds fall into FDA's and Pharmacopeia's **stringent regulations**

➔ We ensure quick, reliable, efficient **transfer of complex chemistry to timely scale-up** for early stage clinical API

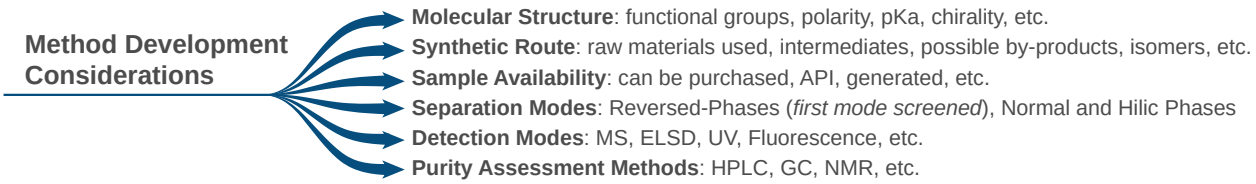
Partial instrumentation list:

- Grinder, Atomizer Air Classifying Mill
- Centrifuge
- Molecular Distillation System
- Shaker & Vacuum Manifold
- Automated SPE and Liquid Handling System

Analytical Method Development, Optimization & Transfer

Our experts in method development, optimization and transfer can help you with your projects. You will benefit from our highly experienced team dedicated to develop or optimize methods in different matrices (*biological, food, beverages, water, etc.*) and for a wide range of molecules (*small to large*).

Our approach is flexible and can be customized to support your product development timeline. We work with you to establish the scope of the project and determine the most suitable factors to consider for the method development.



With the availability of different HPLC column formats (*ID from 2.1 to 100 mm*) combined to various particle sizes (*2.5, 3, 5 and 10 µm*) and phases (*RP, NP, Hilic and specialized phases*), we can achieve selective and reproducible chromatographic separations for your analysis. All experiments are performed in-house with our analytical instrumentation and based on your requirements, various parameters can be investigated such as:

Analytical Method Development Optimization & Transfer	
Parameter	**Definition**
Accuracy	Is the agreement between measured value and real (*or reference*) value.
Detection and quantification limits (*LOD and LOQ*)	Are respectively the lowest concentration which may be detected and the lowest and highest concentrations that can be quantitatively determined.
Linearity & range	Is the ability to obtain values that are directly proportional to the concentration of the analyte within a determined range.
Precision	Is the variability in the result from replicate determinations of the same homogeneous sample.
Repeatability and reproducibility	Is the precision under the same operating conditions over a short interval of time and between laboratories.
Robustness	Is the capacity to remain unaffected by small but deliberate changes in test conditions.
Specificity and selectivity	Is the ability to obtain unequivocally the target analyte in the presence of impurities, degradants, or other components which may be expected to be present.

At the end of the project, we deliver a comprehensive report including the method development for an efficient and easy method transfer.

Partial instrumentation list:

- High Pressure Liquid Chromatography (*HPLC*) Systems with Evaporative Light Scattering (*LC-ELSD*), Photo Diode Array (*LC-PDA*), Mass Spectroscopy (*LC-MS/MS*) & Ultraviolet (*LC-UV*) Detectors
- Gas Chromatography (*GC*) Systems with Flame Ionization (*GC-FID*) & Mass Spectroscopy (*GC-MS*) Detectors

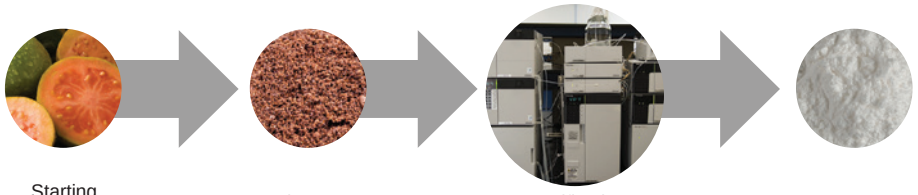
Process Scale-Up Purification

SiliCycle is well equipped to promptly assist you develop an analytical method on lab-scale and scaling-up to kilo-scale production efficiently. Our scale-up strategies are based on using the same packing material, which is one of the most important aspects of scalability. This allows easy scale-up with constant performance, which guarantees optimal results throughout your purification process.

SiliCycle can provide turnkey solutions to your purification problems by performing your scale-up process separation with our expert staff in our laboratories. Our broad variety of instrumentations allows us to purify and detect a wide range of molecules even the ones with lower stability (*heat sensitive compounds for example*).

As a chromatographic medias manufacturer, we have a large inventory of phases readily available which helps reduce lead time and cost for your projects. If your separation requires that we develop a special phase, our production team works hand-in-hand with our R&D to support you.

Our process scale-up purification service is flexible to ensure that it will fit your needs.
Here is a brief overview of the service workflow.



From small to large scale purification

Partial instrumentation list:

- Load and Lock Column (*Dynamic Axial Compression* [*DAC*]) & Packing Station
- Preparative HPLC Systems Coupled with Mass Spectroscopy (*LC-MS Prep*), Evaporative Light Scattering (*LC-ELSD*) & Ultraviolet (*LC-UV Prep*) Detectors
- Flash-Preparative HPLC Systems Coupled with Diode Array Detector
- High Capacity Evaporators
- Lyophilizers

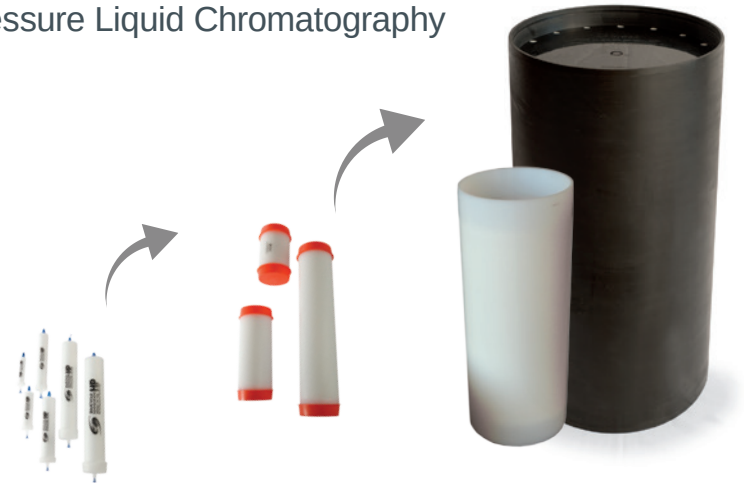
Process Scaling-Up in Low / Medium Pressure Liquid Chromatography

Need to run low pressure chromatography?
For example, we can develop a low pressure chromatographic extraction on a 25 g flash cartridge and scale it up to a 5 kg or even a 41 kg cartridge, further develop the HPLC method for analysis and then provide all needed products for the pilot, scale-up work and commercial production.

No other manufacturer of chromatography products offers this.

Partial instrumentation list:

- SPOT PREP Preparative Chromatography
- HPLC Systems with Mass Spectroscopy Detector (*LC-MS/MS*)
- Flash-Preparative HPLC Systems Coupled with Diode Array Detector



4 g - 330 g cartridges | 200 g - 1.6 kg cartridges | 2.5 kg - 41 kg cartridges

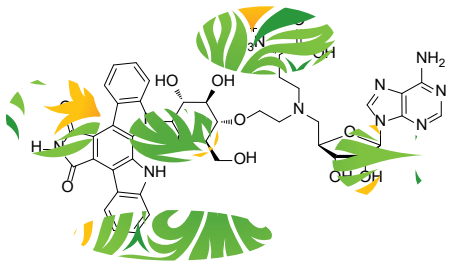
Discovery & R&D | **Development & Process** | **Industrial**

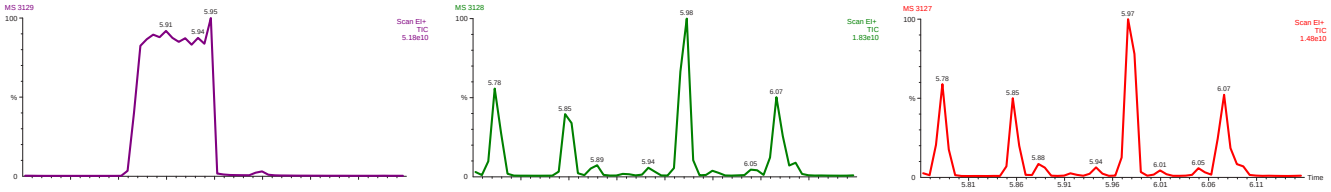
All cartridges can be packed with the same lot for extreme reproducibility throughout your scale-up.

Impurity Isolation & Structure Elucidation

We can help you identify, isolate and characterize impurities present in the final product or potential contamination source from a specific synthesis pathway. Our unique approach using state-of-the-art techniques and strategies allows the detection of a wide range of products even at low concentration. Based on your project requirements, many type of services are available:

- Structure elucidation of unknown degradation or by-products
- Preparative isolation of contaminants from the final product
- Targeted synthesis of the impurity, followed by its analytical qualification (*reference standard*) for higher concentration compared to the specified accepted limit value
- Detection in trace range (*ppb*) of genotoxic impurities
- Stability studies of final product





Partial instrumentation list:

- Elemental Analysis (*CNS*)
- Fourier Transform Infrared Spectroscopy (*FTIR*)
- HPLC Systems with Mass Spectroscopy Detector (*LC-MS/MS*)
- Nuclear Magnetic Resonance (*NMR*)

Purity Determination

SiliCycle can also perform analyses for the determination of the purity percentage of various compounds (*chemicals, API, peptides, etc.*) and optimize chemical processes by monitoring trace impurities and side-products. We are equipped to work with sensitive products and can deliver products with extremely high purity.

Partial instrumentation list:

- Karl-Fisher Coulometric / Volumetric Titrators
- Gas Chromatography (*GC*) Systems with Flame Ionization (*GC-FID*) & Mass Spectroscopy (*GC-MS*) Detectors
- HPLC Systems with Evaporative Light Scattering (*LC-ELSD*) or Mass Spectroscopy (*LC-MS/MS*) Detectors
- Nuclear Magnetic Resonance (*NMR*)

Custom Column Packing Services

Your Need, Our Production, Your Satisfaction

SiliCycle has been refining its expertise in Column Manufacturing and is always committed to offer superior product quality. As we strive for continuous growth and bring on board rare expertise, the acquisition in 2012 of “Chromatography Sciences Company Inc.” (*CSC*), a Canadian pioneer in the manufacturing of HPLC columns, has strengthened our position in the analytical field.

A dedicated crew of scientists with over thirty years of column packing experience is ready to meet head-to-head with your most difficult challenges in terms of phase, particle size and column dimensions.

➔ Quickest and most efficient proceeding for **your own optimized & personalized HPLC purification**

➔ Significantly **less expensive than screenings** through multiple phases conditions

➔ Extreme and hardly achievable reproducibility throughout each and every of your columns, by way of our **batch reservation services**

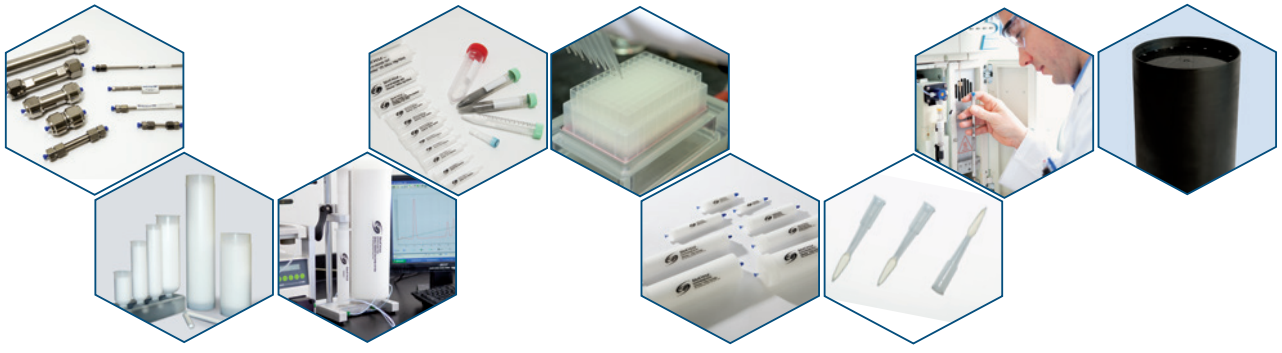
Performance & Reproducibility

An extensive range of different formats, sizes, phases, particle and pore sizes are readily available. Should you be looking for a custom column whether it is a unique phase, particular bonding, unusual column dimension, particle size or pore size, please contact us and we will confidentially address your demand and study its feasibility.

Upon request, SiliCycle may also pack columns with custom-made stationary phases supplied by the customer.

Custom Column Packing Services	
Formats Available	**Medias Availble**
• HPLC columns (*analytical, semi-preparative & preparative*) • Luer-lock type Flash cartridges (*from 4 g to 1.6 kg*) • Compatible flash 150 and 400 cartridges (*2.5 kg, 5 kg, 20 kg and 41 kg*) • Solid-phase extraction cartridges (*from 1 mL to 276 mL*) • Well plates (*24, 48,96 & 384 well plates*)	• Silica or polymer-based phases • Functionalized chromatographic & ion exchange phases • Silica-based scavengers (*metal, organic & genotoxic impurities*) • Other supports available (*alumina, florisil, activated carbon, etc.*)

If the off-the-shelf product is not working for your application and you know exactly what you are looking for, we offer packing solutions for the widest range of formats and phases available on the market.



Batch Reservation Service

SiliCycle is well aware of the importance of column-to-column reproducibility and always makes this a priority and a factor of absolute importance. Yet, very demanding separations call for extremely hard standards to reach. In order to meet these very rigorous needs, SiliCycle now offers a ***batch reservation service*** especially designed for very tight separations requiring maximal resolutions between analytes of interest.

Material Science Services

We have over two decades of experience with silica, microporous and mesoporous materials.

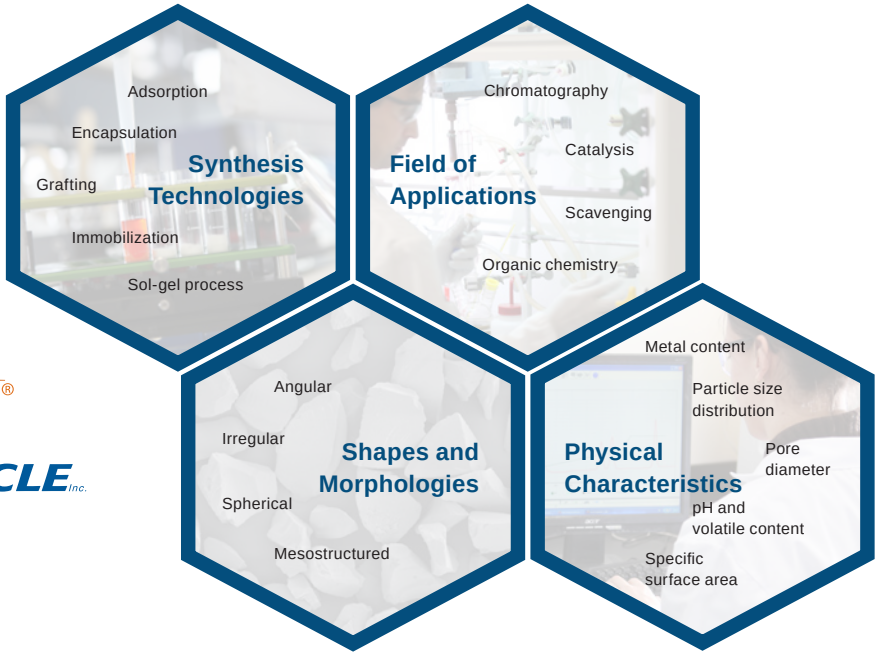
We can work closely with you to design and manufacture customized products that will meet your requirements.
Our experienced chemists can graft demanding organic or inorganic molecule on many matrices to meet your needs.

➔ We develop tailor-made sorbents to **adapt to the customer's process** *- not the other way around -* optimizing flow rate, back pressure & any other relevant parameter

➔ We unlock the door to **unique sorbents & catalysts** giving our customers a competitive edge by synthesizing **advanced materials with specific properties**

Most Popular Material Science Services

- Custom material synthesis based on your requirements
- Immobilisation, grafting, encapsulation or adsorption of organic & inorganic molecules on silica or other materials
- Customized particle size distribution, water content, etc.
- Catalyst support, mixed-oxides or organic moieties synthesis
- Improvements of your own catalysts to enhance activity, selectivity, etc.



SILICYCLE Inc.

Partial instrumentation list:

- Elemental Analysis (*CNS*)
- Thermographic Analyzer coupled to Mass Spectrometer
- Neutron Activation Reactor
- Karl-Fisher Titrator
- Tap Density Tester
- pH meter

Analytical Laboratory & Quality Control Services

SiliCycle's analytical testing laboratory operates under stringent ISO 9001-2008 procedures and therefore always focus on quality and customer satisfaction. All procedures and employees are in line to assure you ultimate quality work at extremely competitive pricing.

SiliCycle has earned its international reputation through our commitment to high quality standards. Now everyone can take benefit of our state-of-the-art instrumentation park and expertise in analytical chemistry to guarantee the quality of your products.

Please see p. 301 for a quick overview of the analytical lab services that we provide on a very regular basis.

➔ We provide a strong assistance in **defining a QA / QC program** that meets the full scope of all regulatory requirements

➔ **Ideal for companies** that need cost-effective support for SOPs

➔ We handle **any combination of development, validation and QC release testing** for individual methods or complete release packages

Available Instrumentation

SiliCycle also possesses several synthesis and chromatography equipments to help you achieve your project goals. Please see below for a quick overview of our instrumentation park.

Available Instrumentation		
	Analysis & Apparatus	**Typical Applications**
Chromatography	**Dynamic Axial Compression (*DAC*) Technology** Agilent, Load and Lock Column (*DAC*) 500 mm x 25 mm Agilent, Load and Lock Column (*DAC*) 500 mm x 50 mm Agilent, Load and Lock Hydrolic Packing Station	Packing system for process preparative LC. Packing capacities for applications ranging from development (*multigrams*) to production (*multi-kilo*) of pharmaceutical compounds, peptides and natural products with unique fluid / sample distribution system to maximize productivity.
	Flash Chromatography Gilson®, Flash Chromatography System, Spot Prep II Büchi®, Flash Chromatography system, Sepacore	Integrated purification system with gradient solvent delivery, sample detection and fraction collection UV-directed. Designed for easy and straigtforward flash purification.
	High Performance Liquid Chromatography Applied Biosystems / MDS Sciex®, LC/MS/MS, API 3000 Gilson®, Preparative LC-MS systems , Flexar SQ 300MS Shimadzu®, Prominence®, Preparative Liquid Chromatograph Thermo, HPLC with Photodiode Array Detector, Surveyor Plus® Thermo Finnigan®, HPLC, Surveyor®	Analytical tools for method development. Reaction mixtures and purified products analysis. Structural information based on the MS/MS fragmentation and liquid chromatographic separation. Optical purity determination (*diastereomeric & enantiomeric excess*). Stereoisomers separation & isolation.
Synthesis	**Parallel Evaporation** Büchi®, Syncore® Polyvap	Parallel evaporation of multiple samples for increased productivity in parallel and multistage synthesis.
	Microwave Synthesis CEM®, Discover®, Microwave Synthesizer	Energy transfer from electric field to molecules through dipole rotation and ionic conduction.
	Flow Chemistry Syrris Asia®, 220 Flow Chemistry	Great variety of chemical reactions, with wide ranges of temperatures, pressures and reaction times on scales from mg to kg.
	Parallel Synthesis SiliCycle MiniBlock® and MiniBlock XT®	Specially designed for carrying multiple reactions simultaneously, with refluxing and inerting capabilities. Compatible with solution & solid-phase synthesis.
	Automated Sample Preparation Gilson®, Solid Phase Extraction, GX-274 ASPEC	Automated sample preparation system for sample prep and run: positive pressure extractions and filtrations. SPE process performed in either batch or sequential mode.
	Freeze Drying Labconco, Lyophilizer, FreeZone™ Bulk Tray Dryers	Product drying following HPLC purification.

Analytical Lab Services

	Analysis & Apparatus	Resolution & Detection Specifications	Typical Applications
Analysis Technologies	**Elemental Analysis** PerkinElmer®, 2400 Series II CHNS/O Analyzer	3 modes: CHN, CHNS and Oxygen **Temperature range**: 100 - 1,000°C	Rapid determination of carbon, hydrogen, nitrogen, sulfur and oxygen content in organic and other types of materials.
	Tap Density Electrolab, Tap Density Tester, ETD-1020	Two-stations tester USP I, USP II, ASTM test methods **Minimal sample required**: 25 g	Tapped density measurements of powders, granules, pellets, flakes and other bulk substances.
	Sieve Shaking Gilson®, Tapping Sieve Shakers, SS-8R	**Particle range**: 20 - 4,000 µm **Agitation mode**: tapping **Minimal sample required**: 10 g	Consistent & repeatable particle size testing over a broad range of irregular particle sizes and material types.
	Particle Size Analysis by Laser Diffraction Malvern Instruments™, Mastersizer 2000™, Hydro 2000S	**Particle range**: 0.01 - 3,000 µm **Minimal sample required**: 0.5 - 1 g	Metal powder particle size distribution measurement. Optical diffusion of laser light on particle in suspension.
	pH Measurement VWR®, pH meter, SympHony SB70P®	**Minimal sample required**: 5 mL (*liquids*) or 5 g (*solids*)	Acidity or alkalinity measurement.
	Water Content Determination Mettler Toledo®, Karl Fischer, Coulometric KF Titrator C20 Mettler Toledo®, Karl Fischer, Volumetric KF Titrator V20 Sartorius®, Moisture Balance, MA30	**Minimal sample required**: 10 mg 200 mg	Simple, secure water determination by electrolysis or chemical titration.
	Surface Area & Porosity Analysis Micromeritics®, BET, TriStar Micromeritics®, BET, TriStar II	**Range**: From 20 to 250 Å Hg porosimetry available for sizes above 250 Å **Minimal sample required**: 1 g	Surface area and porosity analysis, determined by physical adsorption of a gas (N_2) on surface of the solid (*amount of adsorbate gas vs monomolecular layer on surface*). Amount of gas adsorbed can be measured by volumetric or continuous flow procedure.
	Neutron Activation Analysis (*NAA*) SLOWPOKE Reactor coupled to 4 gamma-rays spectrometers, each incorporated with germanium detectors (*HPGe*)	5 kg of uranium enriched to 20 % U-235. At full power (*20 kW*), neutron flux in the five irradiation sites reaches 10^{12}/cm^2/s.	Nuclear process for determination of elements concentrations in a vast array of materials. NAA allows discrete sampling of elements and disregards the chemical form of a sample (*nucleus focus*).
	Inductively Coupled Plasma (*ICP*) Analysis PerkinElmer®, Optima™ 2100 DV ICP-OES Thermo Scientific, XSERIES 2 ICP-MS	Specifications of analysis, detections limits largely dependent on subtrate, element, interferences, initial concentration, dilution solvent etc.	Identification and concentration measurement of up to 70 elements simultaneously (*mostly metals*). Solid samples must be digested prior to analysis.
GC	**Gas Chromatography (*GC*)** PerkinElmer®, GC/FID, GC, Clarus 400® PerkinElmer®, GC/MS, GC, Clarus 600®, MS, Clarus 600C	**Min. sample required**: 1,000 µL Molecular ions up to m/z 500	Separation & analysis of compounds that can be vaporized without decomposition, for purity testing, components separation and relative amounts.
Spectroscopy	**Spectrophotometry** Agilent, Spectrophotometer, Cary 60	**λ range**: 190 - 1,100 nm	Transmission and reflection (*diffuse and specular*) color, concentration (*solution*).
	Infrared Spectroscopy PerkinElmer®, FT-IR Spectrometer, Spectrum 100®	**Minimal sample required**: 1 mL (*liquids*) or 1 g (*solids*)	High spectral resolution data collection over a wide spectral range, for structural analysis or non-destructive measurement applications.
Nuclear Magnetic Resonance	**Liquid Nuclear Magnetic Resonance (*NMR*)** Agilent, Inova 400 MHz	Dual channels, PFG 5 mm probe direct detection of multinuclei **Frequency range**: ^{15}N, ^{31}P, ^{1}H, ^{19}F **Temperature range**: -80 to 120°C	Characterization of structured organic and inorganic compounds, allowing detection and characterization of smaller amounts of material and more complex molecules. Besides the hydrogen atom, many other nuclei such as carbon and nitrogen are well suited to study by NMR.
	Solid Nuclear Magnetic Resonance (*NMR*) Bruker, Biospin Avance 300 MHz	Dual channels MAS 7 mm (*probe*) triple ^{15}N, ^{13}C, ^{1}H MAS 4 mm (*probe*) triple ^{15}N, ^{31}P, ^{1}H **Dual static probe**: ^{15}N, ^{31}P, ^{1}H **Temperature range**: -20 to 100°C	In media with no or little mobility (*e.g.: crystals, powders, large membrane vesicles, molecular aggregates*), anisotropic interactions have a substantial influence on the behavior of a system of nuclear spins.
Microscopy	**Scanning Electron Microscopy (*FIB/SEM*)** FEI™, Quanta™ 3D FEG	**Electron gun**: 200 V - 30 kV, 0 - 200 nA Resolution: 1.2 nm **Ga ion source**: 2 - 30 kV, 1 pA - 65 nA Resolution: 7 nm	Sample observation at the nanoscale (*SEM*), elemental analysis by X-ray (*SEM*), etching nanoscale (*FIB*), analysis of cross-sections of multilayer deposition (*FIB-SEM*).
	Transmission Electron Microscopy (*TEM*) JEOL, JEM-1230	Bright field and dark field imaging Electronic diffraction information	High resolution imaging of atomic structures (*carbon nanotubes, nanoparticles, nanoclays, etc.*). Spatial distribution of nanoprecipitates in steels. Crystalline structure identification using SAED.
Thermal Analysis	**Thermogravimetric Analysis (*TGA & TGA-MS*)** TA Instruments®, TGA 2950 TA Instruments®, TGA Q500 Pfeiffer Vacuum, ThermoStar™ GSD 301 T	**Mass**: 0.1 mg **Temperature**: ~0.1°C **MS**: 0 - 300 amu	Mass change vs time and temperature, identification of volatile degradation components.
Food Safety	**Food Testing** Determination of Ash, Dietary Fibers, Vitamins, Fat, Proteins; Salts, Cholesterol and Metallic Content; Carbohydrate Counting & Caloric Value	**Methods**: AOAC 945.30; 925.11; 935.42; AOAC 985.29; AOAC 18th 2001.13; 992.04; AOAC 967.27; 985.33; AOAC 991.36, AOAC 911.06; 933.05; 925.32; 948.15; 950.54; AOAC 996.06; AOAC 963.15; AOAC 2001.11; 955.04; 950.36;991.20;970.22; 992.23; AOAC 9373.09; 935.47; 935.43; AOAC 976.26; AOAC 985-01 Atwater Method (*G.E.P.A 2003*)	
	Drinking Water Quality Turbidity Determination of Metals and Salts Content	**Methods**: MA. 103 - Tur 1.0; MA.200 Hg 1.0 and EPA 245.5 or MA.203 - Hg; MA.200 - Met 1.2; MA.300-CN 1.2; MA.303 - Anion 1.1; MA.303 - Nutrients	

Microbiology Testing Services

In collaboration with Microbios Analytique, a company specialized in microbiology in which SiliCycle is a shareholder, we can provide a complete array of services from assessment to confirmation of microbial activity / contamination.

All tests are conducted under the strict quality control guidelines specified by ISO/IEC 17025, ANSI, SCC, NELAP and other international and national standards.

Microbiology testing for bacteria and fungi is available for food and food ingredients, agricultural products, cosmetics, water, fuels, pharmaceuticals, other products and materials.

Fast turnaround and data tracking provide results quickly and efficiently, and your results are sent within a short timeframe. In case of problematic results, we are available to discuss and advise new avenues of investigation.

MICROBIOS ANALYTIQUE

www.microbiosanalytique.com

Most Popular Microbiology Testing Services

- Food microbiological testing services
- Commercial sterility
- Environmental microbiology testing
- Product microbial sanitation claims testing
- Microbiological testing for cosmetics and personal care products
- Bug monitoring
- Microbial corrosion testing
- Bacteria contamination of diesel fuel or in the oil & gas industry

Case Studies

Custom Phase Synthesis & Method Development for Small Oncology Start-Up

This company synthesizes imaging agents that are very difficult to purify and they needed to step-up their production for trials.

Problem: Molecule was highly polar and not very soluble. Standard C18 columns gave inadequate recovery and purity.

Proposal: Screen different phases and optimize the separation for larger scale.

Solution: Developed a custom Si-PFP phase that gave purities higher than 99.4 % with very good recoveries.

Results: The PFP phase was adapted and packed into a 5 kg cartridge and the customer was able to purify the desired amount. At this time, these analytical columns are used for method validation.

> – SiliCycle was able to manufacture and deliver a 5 kg PFP cartridge for use in our preparative separation in less than three weeks. This was key to our purification of our API. The results were excellent.

Impurity Determination for a Generic Drug Manufacturer

This company produces a ready-to-inject generic drug. The non-generic version is a powder that is solubilized just before injection.

Problem: There was an impurity that is generated in this generic version that was absent in the non-generic one. Rapid identification and quantification of this impurity was mandatory. This contract had been given to at least one other lab without success.

Proposal: Isolate the impurity to determine its nature and then produce enough of it to product standards for quantification.

Solution: We were able to isolate the compound even though it was unstable at room temperature and the desired amount was produced.

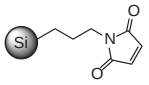
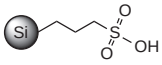
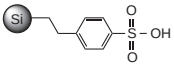
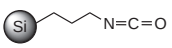
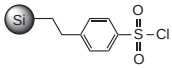
Results: We were able to find a way to purify the compound at low temperature by chromatography and then use lyophilisation to remove the solvent without the compound deteriorating. The method developed is robust and was validated in-house.

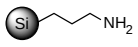
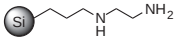
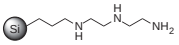
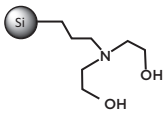
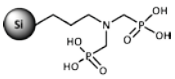
> – Thank you very much to everyone at SiliCycle! We really appreciate the quality of your work and we will need your expertise for another project.

Functionalized Silicas Portfolio

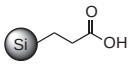
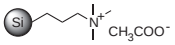
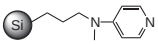
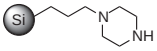
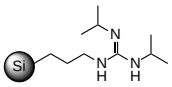
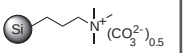
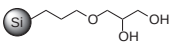
SiliaBond®, SiliaCat® & SiliaMetS®

METAL AND ORGANIC SCAVENGERS

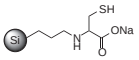
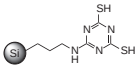
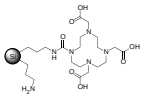
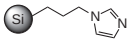
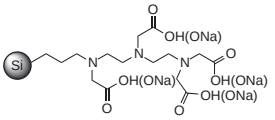
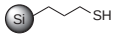
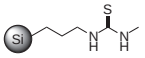
	ORGANIC SCAVENGERS				
Functionnal Group	**Maleimide**	**Propylsulfonic Acid (*Si-SCX-2*)**	**Tosic Acid* (*Si-SCX*)**	**Isocyanate**	**Tosyl Chloride**
Product Number	R71030B ◊◊◊	R51230B ◊◊◊	R60530B ◊◊◊	R50030B ◊◊◊	R44030B ◊◊◊
Structure					
Minimal Loading	0.64 mmol/g	0.63 mmol/g	0.54 meq/g	1.16 mmol/g	0.63 mmol/g
Approx. Density (*g/mL*)	0.644	0.728	0.698	0.741	0.761
Acyl Chlorides & Sulfonyl Chlorides					
Acids & Acidic Phenols					
Alcohols & Alkoxides					
Aldehydes, Anhydrides, Chloroformate, Isocyanate, Ketones					
Amines & Anilines					
Boronic Acids					
Hydrazines					
Thiol / thiolates & Organometallics					

Functionnal Group	**Amine**	**Diamine**	**Triamine**	**DEAM**	**AMPA**
Product Number	R52030B ◊◊◊	R49030B ◊◊◊	R48030B ◊◊◊	R54430B ◊◊◊	R85130B ◊◊◊
Structure					
Minimal Loading	1.20 mmol/g	1.28 mmol/g	1.11 mmol/g	0.85 mmol/g	0.80 mmol/g
Approx. Density (*g/mL*)	0.700	0.728	0.736	0.691	0.707
Typical Metals Scavenged	**Cd, Cr, Pt, Rh & Ru** Co, Cu, Fe, Hg, Pb, W & Zn	**Cr, Pd, Pt, W & Zn** Cd, Co, Cu, Fe, Hg, Ni, Pb, Ru & Sc	**Cr, Pd, Pt, W & Zn** Ag, Cd, Co, Cu, Fe, Hg, Ni, Os, Pb, Rh, Ru & Sc	**Ag, Fe, Sn, Ti & Zn**	**Al, Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Mn, Nd, Ni, Pm, Pr, Sb, Sm, Tb, Tm, V & Yb** Co, Cu, Fe, Mg & Zn
Acyl Chlorides & Sulfonyl Chlorides					
Acids & Acidic Phenols					
Alcohols & Alkoxides					
Aldehydes, Anhydrides, Chloroformates, Isocyanates, Ketones					
Amines & Anilines					
Boronic Acids					

ORGANIC SCAVENGERS

Carboxylic Acid (*Si-WCX*)	TMA Acetate (*Si-SAX-2*)	DMAP	Piperazine*	Guanidine*	Carbonate*	Diol
R70030B ◊◊◊	R66430B ◊◊◊	R75630B ◊◊◊	R60030B ◊◊◊	R68230B ◊◊◊	R66030B ◊◊◊	R35030B ◊◊◊
						
0.92 mmol/g	0.71 mmol/g	0.53 mmol/g	0.83 mmol/g	0.80 mmol/g	0.46 mmol/g	0.97 mmol/g
0.687	0.665	0.674	0.671	0.732	0.608	0.687

METAL SCAVENGERS

Cysteine	DMT	DOTA	Imidazole	TAAcOH	TAAcONa	Thiol	Thiourea
R80530B ◊◊◊	R79030B ◊◊◊	R91030B ◊◊◊	R79230B ◊◊◊	R69030B ◊◊◊	R69230B ◊◊◊	R51030B ◊◊◊	R69530B ◊◊◊
							
0.30 mmol/g	0.50 mmol/g	0.38 mmol/g	0.96 mmol/g	0.41 mmol/g	0.41 mmol/g	1.20 mmol/g	1.07 mmol/g
0.665	0.732	0.681	0.681	0.635	0.712	0.682	0.767
Cd, Fe, Ir, Os, Ru, Sc & Sn Ca, Cr, Cs, Cu, La, Mg, Pd, Pt, Rh & Zn	**Ir, Ni, Os, Pd, Pt, Rh & Ru** Cd, Co, Cu, Fe, Sc & Zn	**Ca, Cu, Gd, La, Ni & Zn** Co, Fe, Mg, Pd, Pt & Rh	**Cd, Co, Cu, Fe, Ir, Li, Mg, Ni, Os, W & Zn** Cr, Pd & Rh	**Ca, Co, Ir, Li, Mg, Ni, Os, Ru & Sc** Cr, Cs, Fe, Pd, Rh & Sn	**Ca, Cd, Cs, Cu, Fe, Ir, La, Li, Mg, Ni, Os, Rh, Sc & Sn** Cr, Pd, Ru & Zn	**Ag, Hg, Os, Pd & Ru** Cu, Ir, Pb, Rh & Sn	**Pd & Ru** Ag, Cu, Fe, Os, Rh, Sc & Sn

LEGEND

RXXX30B: Endcapped
RXXX30B: NON-Endcapped

◊ MONOfunctionalized
◊◊◊ TRIfunctionalized

Metal: Best Scavenged Metals
Metal: Scavenged Metals

Organic molecule:
- Best Scavenged Electrophiles
- Best Scavenged Nucleophiles
- Ionic Scavenging

- BASE
- ACID

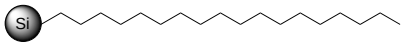
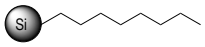
All functionnalized gels should be kept dry
Keep cool (≤ 8°C) when marked with
Keep under Argon when marked with

All functionalized gels are typically made on standard Silia*Flash* silica gel R10030B, with 40 - 63 µm, 60 Å. But all functionalities are available on both Spherical or Irregular silica particles, as well as on any particle or pore size you may desire, for both spherical or irregular particles. Contact us for more details.

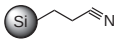
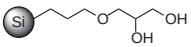
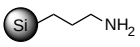
* Also a reagent, please see p. 310-311

CHROMATOGRAPHIC PHASES

REVERSED-PHASES

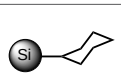
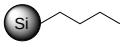
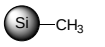
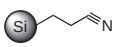
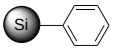
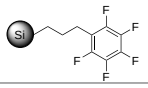
Functionnal Group	Octadecyl (*Si-C18*)						Octyl (*Si-C8*)		
Product Number	R33230B ◊	R33330B ◊	R33530B ◊	R30030B ◊◊◊ R30130B ◊◊◊	R02130B ◊◊◊	R00430B ◊◊◊	R30830B ◊	R31030B ◊◊◊	R31130B ◊◊◊
Structure									
Typical Carbon Load (% *C*)	16	15.5	11	23	17	11	11	11	11.6
Approx. Density (*g/mL*)	0.639	0.640	0.619	0.864	0.735	0.705	0.586	0.708	0.759
Typical Applications	**Indicated for LOW to HIGH polarity compounds, provides reproducible purification without complexity & cost of preparative HPLC** Peptides, pesticides, PCBs, PAHs, toxins, drugs & metabolites in pysiological fluids						**Less retention compared to C18** Highly hydrophobic pesticides, peptides, heavy drugs & metabolites in physiological fluids		

NORMAL PHASES

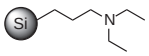
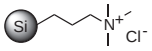
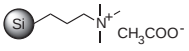
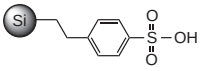
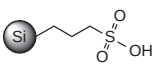
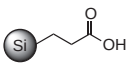
Functionnal Group	Bare Silica (SiO_2)	Cyano (*Si-CN*)	Diol (*Si-Diol*)	Silver Nitrate ($AgNO_3$)	Amine (*Si-WAX*)
Product Number	R10030B	R38030B ◊◊◊ R38130B ◊◊◊	R35030B ◊◊◊	R23530B	R52030B ◊◊◊ R52130B ◊◊◊
Structure					
Minimal Loading	N/A	1.38 mmol/g	0.97 mmol/g	10 % w/w	1.20 mmol/g
Approx. Density (*g/mL*)	0.550	0.703	0.687	0.604	0.700
Typical Applications	Polar phase	Polar, organic compounds (*basic drugs, Π electrons-systems*)	Peptides, proteins, malto-oligo-saccharides	*Cis / trans* isomers of unsaturated compounds such as alkenes, lipids, steroids, terpenes	Week anion exchanger (pK_a = *9.8*), for analysis of sugars, nucleotides, water-soluble

HYDROPHOBICITY –

REVERSED-PHASES

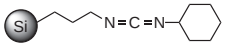
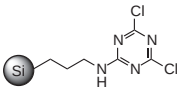
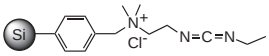
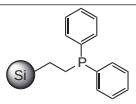
Cyclohexyl (*Si-C6*)	Butyl (*Si-C4*)			Si-C1	Cyano (*Si-CN*)	Phenyl (*Si-PHE*)			Si-PFP
R61530B ◊◊◊	R32730B ◊	R32030B ◊◊◊	R32130B ◊◊◊	R33030B ◊◊◊	R38030B ◊◊◊ R38130B ◊◊◊	R33830B ◊	R34030B ◊◊◊	R34130B ◊◊◊	R67530B ◊◊◊
									
9.5	7	6.67	6.67	5	7	8	8	8	9
0.662	0.700	0.656	0.692	0.559	0.703	0.550	0.637	0.607	0.761
Phenols, chloroanilines & anthelmintics from tissues & water	**Molecules with large hydrophobic regions** Peptides, proteins and zwitterions (*300 Å*)			**Highly hydrophobic molecules and biomolecules** Polar and non-polar pharmaceuticals, natural products	**Intermediate to extreme polarity** Cyclosporine & carbohydrates	**Moderately non-polar sorbent for aromatic compounds** Aflatoxines, caffeine, phenols from water			**Alternate selectivity** Conjugated compounds, or for a new selectivity approach

ION EXCHANGE PHASES

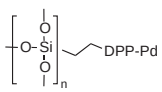
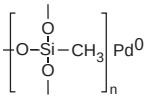
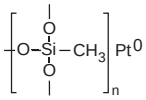
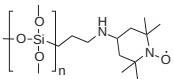
Diethylamine (*Si-WAX-2*)	TMA Chloride (*Si-SAX*)	TMA Acetate (*Si-SAX-2*)	Tosic Acid (*Si-SCX*)	Propylsulfonic Acid (*Si-SCX-2*)	Carboxylic Acid (*Si-WCX*)
R76530B ◊◊◊ R76630B ◊◊◊	R66530B ◊◊◊	R66430B ◊◊◊	R60530B ◊◊◊ R60430B ◊◊◊	R51230B ◊◊◊ R51430B ◊◊◊	R70030B ◊◊◊ R70130B ◊◊◊
					
1.04 mmol/g	0.90 meq/g	0.71 mmol/g	0.54 meq/g	0.63 mmol/g	0.92 mmol/g
0.761	0.700	0.665	0.698	0.728	0.687
Catch & release of compounds bearing a permanent negative charge (pK_a = *10.5*)	Permanently positively charged silica. Used for the extraction of weak anions	Selectively purifies acidic compounds, with readily exchangeable OAc counter-ion	Permanently negatively charged silicas (pK_a < *1*). Strong cation exchangers.		Week cation exchanger at pH ≥ 6.8. Cations can be eluted at pH ≤ 2.8

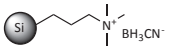
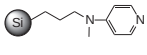
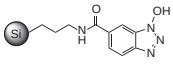
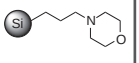
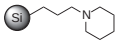
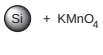
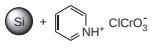
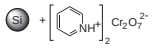
Functionalized Silicas Portfolio

REAGENTS & OXIDANTS

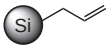
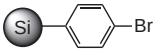
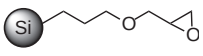
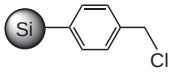
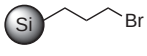
	REAGENTS				
Functionnal Group	**Aluminum Chloride (*Si-AlCl$_3$*)**	**Carbodiimide (*Si-DCC*)**	**Dichlorotriazine (*Si-DCT*)**	**EDC (*Si-EDC*)**	**Diphenylphosphine (*Si-DPP*)**
Product Number	R74530B ◊◊◊	R70530B ◊◊◊	R52230B ◊◊◊	R70630B ◊◊◊	R39030B ◊◊◊
Structure					
Minimal Loading	1.60 mmol/g	0.91 mmol/g	0.60 mmol/g	0.32 mmol/g	0.75 mmol/g
Approx. Density (*g/mL*)	0.781	0.751	0.781	0.770	0.761
Typical Applications	Ether formation, Friedel-Crafts alkylation, acylation	Amide coupling with acids, acyl chlorides and amines			Source of phosphorus-centered radicals
		-	Sulfonamide synthesis		

CATALYSTS

	SILIACAT HETEROGENEOUS CATALYSTS			
Functionnal Group	**DPP-Pd**	**Pd^0**	**Pt^0**	**TEMPO**
Product Number	R390-100	R815-100	R820-100	R723-100
Structure				
Minimal Loading	0.20 - 0.30 mmol/g	0.20 - 0.30 mmol/g	0.15 - 0.25 mmol/g	0.70 mmol/g
Approx. Density (*g/mL*)	0.300 - 0.400	0.300 - 0.400	0.300 - 0.400	0.550 - 0.650
Typical Applications	Borylation, Suzuki, Heck, Negishi, Sonogashira, Kumada, Stille	Debenzylation, hydrogenation, Suzuki, Heck, Sonogashira, Kumada, Stille	Debenzylation, hydrogenation, hydrosilylation	Oxidation of alcohols or aldehydes

	REAGENTS				OXIDANTS		
Cyanoborohydride	DMAP (*Si-DMAP*)	HOBt (*Si-HOBt*)	Morpholine (*Si-MOR*)	Piperidine (*Si-PIP*)	Potassium Permanganate (*Si-$KMnO_4$*)	Pyridinium Chlorochromate (*Si-PCC*)	Pyridinium Dichromate (*Si-PDC*)
R66730B ◊◊◊	R75630B ◊◊◊	R70730B ◊◊◊	R68030B ◊◊◊	R71530B ◊◊◊	R23030B	R24030B	R24530B
							
0.87 mmol/g	0.53 mmol/g	0.56 mmol/g	0.99 mmol/g	1.03 mmol/g	10 % w/w	20 % w/w	20 % w/w
0.705	0.674	0.766	0.666	0.660	0.593	0.693	0.651
Reductive amination	Acylation & esterification	Suppression of the racemization of single-enantiomer chiral molecules, peptide synthesis	Generation of enamines	Knoevenagel condensation	Oxidation of alcohols to acids	Oxidation of alcohols to ketones / aldehydes	

LINKERS

	LINKERS				
Functionnal Group	Allyl (*Si-Allyl*)	Bromophenyl (*Si-BRP*)	Glycidoxy (*Si-GLY*)	Phenylmethylchloride (*Si-PhMeCl*)	Propyl Bromide (*Si-PBR*)
Product Number	R53530B	R55030B	R36030B ◊◊◊	R56530B	R55530B
Structure					
Minimal Loading	1.08 mmol/g	0.99 mmol/g	0.82 mmol/g	1.14 mmol/g	1.39 mmol/g
Approx. Density (*g/mL*)	0.613	0.742	0.662	0.637	0.748
Typical Applications	Can be used to create homemade functionalized silicas according to your very own application				

Analytical Catalog

Take a Look at our Catalog for Analytical Chemistry to See our Other Offerings

SPE Solutions (*Silica-Based SiliaPrep™ & Polymeric SiliaPrepX™*)

- SPE Cartridges (*1 mL / 30 mg to 25 mL / 5 g*)
- Mini-SPE Cartridges – used with a syringe (*300 mg to 1 g*)
- 96-Well Plates (*2 mL / 10 mg to 2 mL / 100 mg*)
- Micro-SPE Tips (*10 µL / 30 µg to 200 µL / 400 µg*)

SiliaPrep (*silica-based*) & SiliaPrepX (*polymeric*) products are made using a state of the art technology, providing the highest quality media and lot-to-lot reproducibility. In addition, strict quality controls and analysis are conducted during the manufacturing process to remove any impurity or defect that could influence your results.

Available SPE Sorbents

Reversed-Phases	Normal Phases	Ion Exchange Phases	Specialty Phases
DVB, HLB	Bare Silica, Bare Silica Widepore	Polymeric SAX, WAX, SCX & WCX	CleanDRUG, CleanENVI
C18, C18 Widepore	Diol, Cyano	TMA Chloride (*SAX*), TMA Acetate (*SAX-2*)	PCB
C8	Florisil and Florisil PR	Amine (*WAX*), Carboxylic Acid (*WCX*)	Mixed-Modes (*C8/SAX-2, SCX-2/SAX*)
PFP	Alumina (*Acidic, Neutral and Basic*)	Tosic Acid (*SCX*), Propylsulfonic Acid (*SCX-2*)	Metal Scavengers (*Thiol, Cysteine, DMT, TAAcOH, TAAcONa, Thiourea, Triamine, Imidazole*)
Phenyl		Carbonate	

QuEChERS (*SiliaQuick™*)

Using SiliaQuick QuEChERS ensures the following benefits:

- Clean extracts from pure products
- High recovery and lot-to-lot reproducibility
- Great variety of QuEChERS to cover the full spectrum of food, beverage and biological fluids applications
- Reduction of analysis cost

The QuEChERS technique can be summarized as a three-step methodology, starting with a **liquid extraction**, followed by a **dispersive solid-phase extraction** clean-up and completed by a **LC or GC analysis**.

Step 1: Extraction of compounds of interest from food, beverage or biological matrices through a solvent (*mainly acetonitrile*).

Step 2: Removal of specific undesired compounds (*sugars, lipids, organic acids, proteins, pigments*) and excess water.

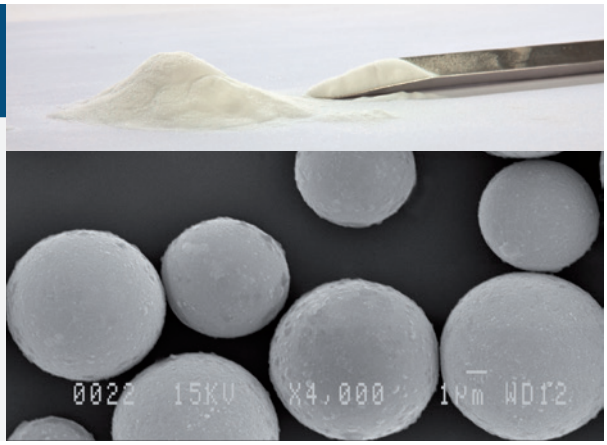
Step 3: Injection into a LC or GC instrument coupled with MS or MS/MS to quantify the analyte concentration.

Some available Bulk QuEChERS Sorbents

Sorbent	C18	$MgSO_4$	PSA (*Diamine*)	Amine	GCB (*Graphitized Carbon Black*)
Product Number	AUT-1313	AUT-0310	AUT-0312	AUT-0412	AUT-0311

Take a Look at our Catalog for Analytical Chemistry to See our Other Offerings

Monodispersed Spherical Silica Gels for HPLC and SFC (*SiliaSphere*™)



Recognized for the outstanding quality of our silica gels, we offer one of the largest selection of silicas for HPLC and SFC:

- Particle sizes: 1.8 µm, 2.2 µm, 3 µm, 5 µm, 7 µm & 10 µm
- Pore diameters: 60 Å, 80 Å, 100 Å, 120 Å, 300 Å & 1,000 Å
- Available phases: bare silica, C18, C8, C4, C1, Cyano, Phenyl, PFP, Amine, Diol, SCX (*Tosic Acid*), SAX (*TMA Chloride*), SAX-2 (*TMA Acetate*) and more

Silia*Sphere* Monodispersed Spherical Silica Gels are manufactured under highly controlled processes to ensure constant reproducibility and easy scale-up. We guarantee the chromatographic performance, loading capacity and chemical & physical stability of our silicas to meet all your separation requirements.

The excellent properties of Silia*Sphere* silica gels make them the packing of choice for high performance liquid chromatography (*HPLC*) and Supercritical Fluid Chromatography (*SFC*).

Consumables

- Syringe Filters, Sterile or Non-Sterile
- Membrane Filters
- Vials & Caps

Syringe filters provide optimal filtration to help you get particulate-free samples prior to injection. They are available with a polypropylene housing, in a wide variety of membranes (*Nylon, PTFE, PVDF, PES, RC and CA*), pore sizes (*0.45 µm and 0.2 µm*) and diameters (*4 mm, 13 mm, 25 mm and 33 mm*). We also offer sterile syringe filters.

You will also find a broad portfolio of **membrane filters** to cover all filtration needs: 25 mm, 47 mm and 142 mm diameters available in 0.2 µm to 5.0 µm pore sizes, with a great choice of membranes (*Nylon, PTFE, PVDF, PES, RC and CA*).

Vials & caps portfolio offers products that are adapted to all types of samples and specific storage conditions. They are compatible with most autosampler systems. To fit your needs, you will be able to select the type of glass (*clear or amber*), the type of closure (*snap, crimp or screw-top vial*), the type of septum (*PTFE / silicone, PTFE / silicone / PTFE or FEP / silicone*) and the vial volume (*from 0.7 mL to 40 mL*).

TEL.: 1 418 874.0054 FAX: 1 418 874.0355 TOLL-FREE: 1 877.SILICYCLE (*NORTH AMERICA ONLY*) WWW.SILICYCLE.COM INFO@SILICYCLE.COM

Take a Look at our Catalog for Analytical Chemistry to see our Other Offerings

HPLC Columns (*SiliaChrom*®)

SiliaChrom columns are made from extremely pure silicas and are well known for their high efficiency and resolution capacity. Based on spherical, totally porous silica, SiliaChrom columns provide enhanced chemical and mechanical stability as well as very high loading capacity. All SiliaChrom columns are packed using our proprietary slurry packing process, to achieve a uniform column-to-column reproducibility.

SiliCycle has been manufacturing and packing HPLC columns for many years and offer more than 40 different phases. Raw materials and HPLC columns go through our ISO 9001-2008 registered manufacturing facility, under strict SOP's and standard QC column performance testing, assuring column performance, peak symmetry and lot-to-lot reproducibility.

The Silia*Chrom* portfolio ranges from reversed-phase to normal phase columns, columns for large proteins and peptide analysis and SFC compatible solutions. An incredibly range of column dimensions and particle sizes are available to accommodate the vast majority of your applications.

Whether you need a column to use in a wide range of pH, with 100 % aqueous or organic mobile phases, or a low bleed sorbent for LC-MS applications, we have the solution for you:

- **Silia*Chrom* Plus**: for everyday separations, most versatile family
- **Silia*Chrom* dt**: 100 % aqueous compatible
- **Silia*Chrom* XT & XT Fidelity**: for high pH conditions (*up to 12*)
- **Silia*Chrom* SB**: for extremely low pH conditions (*from 0.5 - 1*)
- **Silia*Chrom* XDB**: for large hydrophobic molecules
- **Silia*Chrom* XDB1 & XDB2**: for QC analysis
- **Silia*Chrom* HILIC**: for highly polar analytes (*urea phase*)
- **Silia*Chrom* GF**: for biomolecules separation

With a broad range of family phases available, using SiliCycle HPLC columns ensures flexibility and scalability. The next page will help you select the right column characteristics for your project.

SiliaChrom HPLC Column Characteristics

	Main Characteristics	SiliaChrom Phases	Particle Size (µm)	Pore Size (Å)	Specific Surface Area (m^2/g)	Carbon Load (%)	Endcapping (Yes / No)	pH Range	USP Code	T Limit (°C)*	Pressure Limit (psi)
SiliaChrom Plus	Wide range of selectivities Ultra-pure metal-free silica (*99.9999% purity*) High column performance and resolution Enhanced batch-to-batch reproducibility Extended column lifetime Reduced silanol activity, better peak symmetry Extremely low bleeding for LC-MS applications Easy scale-up to preparative formats	Plus C18	3, 5, 10	100	370 - 430	15	PI	2.0 - 8.0	L1	60	5,500
		Plus C18-300	3, 5, 10	300	80 - 120	8	PI	2.0 - 8.0	L1	60	4,000
		Plus C8	3, 5, 10	100	370 - 430	8	PI	2.0 - 8.0	L7	60	5,500
		Plus C8-300	3, 5, 10	300	80 - 120	5	PI	2.0 - 8.0	L7	60	4,000
		Plus C4	3, 5, 10	100	370 - 430	6	PI	2.0 - 8.0	L26	60	5,500
		Plus C4-300	3, 5, 10	300	80 - 120	3	PI	2.0 - 8.0	L26	60	4,000
		Plus PFP	3, 5, 10	120	320 - 360	9	PI	2.0 - 8.0	L43	60	5,500
		Plus Phenyl	3, 5, 10	100	370 - 430	11	PI	2.0 - 8.0	L11	60	5,500
		Plus Cyano	3, 5, 10	100	370 - 430	7	PI	2.0 - 8.0	L10	60	5,500
		Plus Amino	3, 5, 10	100	370 - 430	8	PI	2.0 - 8.0	L8	60	5,500
		Plus Diol	3, 5, 10	100	370 - 430	7	PI	2.0 - 8.0	L20	60	5,500
		Plus Silica	3, 5, 10	100	370 - 430	-	PI	2.0 - 8.0	L3	60	5,500
		Plus SAX	3, 5, 10	PI (*Proprietary Information*)			PI	2.0 - 8.0	L14	60	PI
		Plus SCX	3, 5				PI	2.0 - 8.0	L9	60	
SiliaChrom dt	Stable from 100% aqueous to 100% organic Enhanced retention of hydrophilic molecules Inertness for acidic and basic analytes	dt C18	2.5, 3, 5, 10	100	410 - 440	18	Y	1.5 - 9.0	L1	60	5,000
		dt C8	3, 5, 10	100	410 - 440	14	Y	1.5 - 9.0	L7	60	5,000
		dt Silica	3, 5, 10	100	410 - 440	-	Y	1.5 - 9.0	L3	60	5,000
SiliaChrom XT	Coated with a monomeric prepolymer for excellent durability at high pH Ideal for basic compounds and metabolic studies	XT C18	3, 5, 10	150	200	15	Y	1.5 - 12.0	L1	60	5,000
		XT Fidelity C18	3, 5, 10	100	380	21	Y	1.5 - 12.0	L1	60	5,000
SiliaChrom SB	Protecting group that shields the silica surface for extremely low pH stability Extremely low bleeding for LC-MS applications under acidic conditions	SB C18	3, 5, 10	150	200	12	N	0.5 - 7.5	L1	60	4,500
		SB C18-300	5	300	80	5	N	0.5 - 7.5	L1	60	4,500
		SB C8	5	150	200	7	N	1.0 - 7.5	L7	60	4,500
		SB C8-300	5	300	80	3	N	1.0 - 7.5	L7	60	4,500
SiliaChrom XDB	High loading capacity Low surface area, allowing shorter retention times for large hydrophobic molecules	XDB C18	5	150	200	15	Y	1.5 - 9.0	L1	60	5,500
		XDB C8	5	150	200	8	Y	1.5 - 9.0	L7	60	5,500
		XDB Silica	5	150	200	-	Y	1.5 - 9.0	L3	60	5,000
SiliaChrom XDB1 & XDB2	High loading capacity Great column-to-column and batch-to-batch reproducibility Good peak shape for acidic, neutral and basic analytes Stronger separation power for isomers	XDB1 C18	3, 5	100	380 - 400	22	Y	1.5 - 10.0	L1	60	5,500
		XDB1 C18-300	5, 10	300	80	8	Y	1.5 - 9.0	L1	60	5,500
		XDB1 C8	5, 10	100	380 - 400	14	Y	1.5 - 8.5	L7	60	5,500
		XDB1 C8-300	5	300	80	4	Y	1.5 - 8.5	L7	60	5,500
		XDB1 C1	5	100	380 - 400	3	Y	1.5 - 8.5	L13	60	5,500
		XDB1 C1-300	5	300	80	1	Y	1.5 - 8.5	L13	60	5,500
		XDB2 C18	3, 5, 10	100	380	18	Y	1.5 - 9.0	L1	60	5,500
SiliaChrom HILIC	Unique chemistry (*urea*) Compatible with reversed and normal-phase conditions Enhanced sensitivity in MS Approved phase for SFC	HILIC	3, 5, 10	100	380	8	N	2.0 - 8.0	-	60	5,000
		HILIC-300	5	300	80	2.5	N	2.0 - 8.0	-	60	5,000
SiliaChrom GF	Separation of peptides, proteins and nucleic acids Two exclusion ranges: 5 - 100 kDa (*100 Å*) 50 - 1,000 kDa (*300 Å*)	GF	5, 10	100	340	5	Y	2.0 - 8.0	-	45	4,000
		GF-300	5, 10	300	80	1	Y	2.0 - 8.0	-	45	4,000
		GF AMIDE	5, 10	100	340	5	Y	2.0 - 8.0	-	60	4,000
		GF AMIDE-300	5, 10	300	80	1	Y	2.0 - 8.0	-	60	4,000

*At pH range 5.0 - 7.5. Other phases could be available on a custom basis. Contact us.

Contact & Ordering Information

Photo: Stéphane Groleau

Terms and Conditions

General

Unless otherwise stated, all transactions are expressly subject to these Terms and Conditions. Modifications or additions will be recognized only if accepted in writing by an officer of SiliCycle Inc. (*hereinafter named SiliCycle*), or an officially designated representative. Provisions of Buyer's Purchase Order or other documents that add to or differ from these Terms and Conditions are expressly rejected. No waiver of these Terms and Conditions or acceptance of others shall be construed as failure of the Company to raise objections.

Privacy Policy

Because your clientele is our most valuable asset, we take privacy very seriously and won't share your personal information with anyone. Your information is used only to personalize your profile and to facilitate the transaction. You can change or update your information at any time.

Quotation and Published Prices

Quotations automatically expire 30 calendar days from the date issued unless otherwise stated. Quotes are subject to withdrawal with notice within that period. Prices shown on the published price lists and other published literature issued by SiliCycle are not unconditional offers to sell and are subject to change without notice.

Warranty

SiliCycle guarantees to the original Buyer that the products sold conform to the composition and purity described therein at the time of their shipment. The Buyer's sole remedy in the event that SiliCycle fails to meet said warranty shall be the replacement of the unused portion of the product(*s*), or if approved by SiliCycle, a refund (*at the purchase price*) provided that the Buyer returns the alleged non-conforming product(*s*) within 30 days after reception of product(*s*). SiliCycle makes no other guarantee of suitability for a particular purpose or of the merchantability in the use or handling of the product, and does not accept any liability for consequential, special, indirect or incidental damages resulting therefrom.

Changes

The Buyer may, with the express written consent of SiliCycle, make changes in the specifications for products or work covered by the contract. In such an event, the contract price and delivery dates shall be equitably adjusted. SiliCycle shall be entitled to payment for reasonable profit plus costs and expenses incurred by work and materials rendered unnecessary as a result of such changes and for work and materials required to effect said changes.

If the Buyer has made a mistake on his / her purchase order and the material has already been shipped and received, SiliCycle may approve the exchange of said material (*if price is identical*); however the Buyer will be responsible for all shipping costs. See return authorization policy section on the next page to obtain a return merchandize authorization form prior to returning goods.

Cancellation

Undelivered parts of any order may be cancelled by the Buyer only with the written approval of SiliCycle. If the Buyer makes an assignment for benefit of creditors, or in the event that SiliCycle, for any reason feels insecure about Buyer's willingness or ability to perform, SiliCycle shall have the unconditional right to cancel the sales transaction or demand full or partial payment.

In the event of any cancellation of this order by either party, the Buyer shall pay SiliCycle for reasonable costs and expenses incurred by the SiliCycle prior to receipt of the cancellation notice, plus SiliCycle's usual rate of profit for similar work.

Taxes

The Company's prices do not include any applicable sales, goods and services, use, excise or similar taxes and the amount of any such tax SiliCycle may be required to pay or collect will be added to each invoice and paid by the Buyer.

Terms of Payment

All merchandise purchased remains the property of SiliCycle until such time as all invoices for the merchandise have been paid in full. Except for purchases paid online, or unless explicitly stated elsewhere in writing, terms are cash net 30 days from date of invoice. Additional fees of 2 % per month (*26.8 % per year*) will accrue on all accounts past due. If any payment is in default and it becomes necessary to hire a recovery agency or lawyer, the client accepts to pay, in addition to the outstanding balance, recovery fees equal to 20 % of the balance in capital and interests. By reason of the financial condition of Buyer or otherwise, SiliCycle may require full or partial payment in advance.

Certain orders may require a deposit or progressive payments as referenced in the quote. Such deposits may be increased upon receipt of purchase order based upon the Buyer's most current credit rating. Subject to the warranties stated in this policy, all sales are final without right of return.

Return Policy

Our Customer Service Department is available to assist you at any time should a problem arise with your order. Please make sure to inspect your packages immediately upon receipt and notify us within the next two (*2*) business days of any damage and / or discrepancies. Should a product be sent to you incorrectly, as the result of an error on our part, we will take quick and appropriate action to correct the problem at no charge to you.
In order to maintain the quality of our products and continue to provide competitive prices, some products may not be returned for credit. SiliCycle will not grant credit for:

(i) Shelf-worn, used or defaced products;
(ii) Scavengers, reagents, catalysts, or any other bounded silica whose containers have been opened;
(iii) Products that are personalized or customized;
(iv) Refrigerated or temperature-controlled products;
(v) Products that have been discontinued;
(vi) Products not directly purchased from SiliCycle

Products sold in distribution by SiliCycle will be subject to the Terms and Conditions Policy of the respective manufacturer.
Prior to any return, an authorization and a return material authorization (*RMA*) number must be obtained from our Customer Service Department. Shipping instructions will also be provided at this point. The RMA will ensure the safe and proper handling of material; it should therefore be referenced on all shipping labels.

The Buyer has 30 days from the issuance of the RMA to return the goods. Returns made without an authorization number will not be accepted and will be returned to the Buyer.

Returns are subject to a 50 % restocking and / or disposal fee.

Shipping Policy

SiliCycle uses a two-day or five-day delivery (*or equivalent*) depending on weight and availability of product. Standard overnight delivery can also be arranged. Freight charges are prepaid and added to the invoice unless special instructions are requested by the customer. These conditions apply to all North American shipments. International delivery delays will vary according to orders and destination countries.

Delivery

Delivery dates indicated in the contract documents are approximate and based on prompt receipt of all necessary information regarding the product covered by the contract. SiliCycle will use reasonable efforts to meet the indicated delivery dates, but cannot be held responsible for its failure to do so.

In the event of any delivery delay caused by the Buyer, SiliCycle will store and handle all items ordered at Buyer's risk and will invoice Buyer for the unpaid portion of the contract price, plus storage, insurance and handling charges on or after the date on which the product is ready for delivery. The invoice will be payable in full within 30 days from the invoice date, unless otherwise expressly agreed to in writing by SiliCycle.

SiliCycle will not hold orders unless specifically approved. SiliCycle has the right to make partial shipments and bill for those shipments; the buyer will make payment in accordance with the terms mentioned in this policy.

Shipping and Handling Charges

Shipping charges plus the applicable company handling charges will be prepaid and billed as a separate item on the product invoice. Title to the product and risk of loss shall pass to Buyer upon delivery to a carrier.

Application

All products are sold for laboratory or manufacturing uses. Only professional laboratory staff should handle the chemicals.

Ordering Information

How to order

You can order any SiliCycle product on-line through the SiliCycle e-commerce website: www.silicycle.com.

Orders can also be placed by:

- phone: +1 418.874.0054 or toll free for North America only: +1 877.745.4292
- fax: +1 418.874.0355
- mail: SiliCycle headquarters address at the bottom of this page
- e-mail: info@silicycle.com

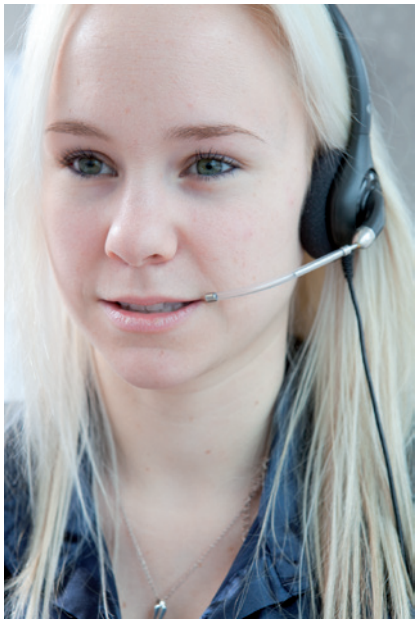
Please have the following information on hand:

- Your name
- Company name, billing and shipping address
- Purchase order number
- Credit card information
- Catalog number and product description
- Size, quantity and unit of measure
- E.I.N. or F.I.N .for United States clients

SiliCycle headquarters address:

2500, Parc-Technologique Blvd
Quebec City, Quebec
G1P 4S6, CANADA

Technical Support



At SiliCycle, we are committed to providing the best technical support possible. Our worldwide Technical Support Group is comprised of a team of highly qualified M. Sc., Engineers and Ph. D. Chemists, Technical Support Professionals and Service Coordinators who are prepared to troubleshoot, answer questions and provide solutions for your service and applications needs.

In order to better respond to your technical inquiries, feel free to contact us in three different ways:

- E-mail: support@silicycle.com
- Phone: International +1 418.874.0054
- USA and Canada +1 877.745.4292 (*Toll-Free*)

SILICYCLE Inc.®
UltraPure SILICA GELS

SiliaMetS® Metal Scavengers

Your Partner of Choice for Metal Scavenging!

Group of metals removed by SiliaMetS® Metal Scavengers (data available!)

1 (IA)	2 (IIA)	3 (IIIB)	4 (IVB)	5 (VB)	6 (VIB)	7 (VIIB)	8 (VIII)	9 (VIII)	10 (VIII)	11 (IB)	12 (IIB)	13 (IIIA)	14 (IVA)	15 (VA)	16 (VIA)	17 (VIIA)	18 (VIIIA)
Hydrogen																	Helium
1 1.0079																	2 4.0026
H -259.14 -252.87 2.2 0.089 -1,1																	He <-272.2 -268.93 0.17
Lithium	Beryllium											Boron	Carbon	Nitrogen	Oxygen	Fluorine	Neon
3 6.941	4 9.0122											5 10.811	6 12.011	7 14.007	8 15.999	9 18.998	10 20.18
Li 180.54 1347 1.0 0.534 1	Be 1278 2970 1.5 1.85 2											B 2079 2550 2.0 2.34 3	C 3367 4827 2.5 2.25 -4,2,4	N -209.86 -195.8 3.1 1.25 -3,2,3,4,5	O -218.4 -182.96 3.5 1.43 -2,-1	F -219.62 -188.14 4.1 1.69 -1	Ne -248.67 -246.05 0.90
Sodium	Magnesium											Aluminum	Silicon	Phosphorus	Sulfur	Chlorine	Argon
11 22.990	12 24.305											13 26.982	14 28.086	15 30.974	16 32.066	17 35.453	18 39.948
Na 97.81 882.9 1.0 0.971 1	Mg 648.8 1090 1.2 1.738 2											Al 660.37 2467 1.5 2.699 3	Si 1410 2355 1.7 2.33 4	P 44.1 280 2.1 1.82 -3,3,5	S 112.8 444.67 2.4 2.07 -2,2,4,6	Cl -100.98 -34.6 2.8 3.21 -1,1,3,5,7	Ar -189.2 -185.7 1.78
Potassium	Calcium	Scandium	Titanium	Vanadium	Chromium	Manganese	Iron	Cobalt	Nickel	Copper	Zinc	Gallium	Germanium	Arsenic	Selenium	Bromine	Krypton
19 39.098	20 40.078	21 44.956	22 47.88	23 50.942	24 51.996	25 54.938	26 55.845	27 58.933	28 58.693	29 63.546	30 65.39	31 69.723	32 72.61	33 74.922	34 78.96	35 79.904	36 83.80
K 63.35 774 0.9 0.86 1	Ca 839 1484 1.0 1.55 2	Sc 1541 2831 1.2 2.99 3	Ti 1660 3287 1.3 4.54 3,4	V 1890 3380 1.5 6.11 2,3,4,5	Cr 1857 2672 1.6 7.19 2,3,6	Mn 1244 1962 1.6 7.43 2,3,4,6,7	Fe 1535 2750 1.6 7.86 2,3,6	Co 1495 2870 1.6 8.9 2,3	Ni 1453 2732 1.8 8.90 2,3	Cu 1083 2567 1.8 8.96 1,2	Zn 419.6 907 1.7 7.13 2	Ga 29.78 2403 1.8 5.904 3	Ge 937.4 2830 2.0 5.32 4	As 817 613 2.2 5.73 -3,3,5	Se 217 684.9 2.5 4.79 -2,4,6	Br -7.2 58.78 2.7 3.12 -1,1,3,5,7	Kr -156.6 -152.3 3.71
Rubidium	Strontium	Yttrium	Zirconium	Niobium	Molybdenum	Technetium	Ruthenium	Rhodium	Palladium	Silver	Cadmium	Indium	Tin	Antimony	Tellurium	Iodine	Xenon
37 85.468	38 87.62	39 88.906	40 91.224	41 92.906	42 95.94	43 98.906	44 101.07	45 102.91	46 106.42	47 107.87	48 112.41	49 114.82	50 118.71	51 121.76	52 127.60	53 126.90	54 131.29
Rb 38.89 688 0.9 1.532 1	Sr 769 1384 1.0 2.54 2	Y 1522 3338 1.1 4.47 3	Zr 1852 4377 1.2 6.51 4	Nb 2468 4742 1.2 8.57 3,5	Mo 2617 4612 1.3 10.2 2,3,4,5,6	Tc 2172 4877 1.4 11.5 7	Ru 2310 3900 1.4 12.4 3,4,8	Rh 1966 3697 1.5 12.4 1,2,3,4	Pd 1552 3140 1.4 12.0 2,4	Ag 961.9 2212 1.4 10.5 1,2	Cd 320.9 765 1.5 8.65 2	In 156.5 2080 1.5 7.31 3	Sn 232.0 2270 1.7 7.31 2,4	Sb 630.7 1750 1.8 6.69 -3,3,5	Te 449.5 990 2.0 6.24 -2,4,6	I 113.5 184.4 2.2 4.93 -1,1,3,5,7	Xe -111.9 -107.1 5.85
Cesium	Barium	Lanthanides	Hafnium	Tantalum	Tungsten	Rhenium	Osmium	Iridium	Platinum	Gold	Mercury	Thallium	Lead	Bismuth	Polonium	Astatine	Radon
55 132.91	56 137.33	*	72 178.49	73 180.95	74 183.84	75 186.21	76 190.23	77 192.22	78 195.08	79 196.97	80 200.59	81 204.38	82 207.2	83 208.98	84 209.98	85 209.99	86 222.02
Cs 28.40 678.4 0.9 1.873 1	Ba 725 1640 1.0 3.5 2	57-71	Hf 2227 4602 1.2 13.3 4	Ta 2996 5425 1.3 16.6 5	W 3410 5660 1.4 19.3 2,3,4,5,6	Re 3180 5627 1.5 21.0 2,4,7	Os 3045 5027 1.5 22.6 2,3,4,6,8	Ir 2430 4430 1.6 22.4 1,2,3,4,6	Pt 1772 3827 1.4 21.4 2,4	Au 1064 2807 1.4 19.3 1,3	Hg -38.841 356.6 1.5 13.5 1,2	Tl 303.5 1457 1.4 11.85 1,3	Pb 327.5 1740 1.6 11.4 2,4	Bi 271.3 1560 1.7 9.75 3,5	Po 254 962 1.8 9.32 2,4,6	At 302 337 2.0 11.3 -1,1,3,5,7	Rn -71 -61.8 9.73
Francium	Radium	Actinides	Rutherfordium	Dubnium	Seaborgium	Bohrium	Hassium	Meitnerium	Darmstadtium	Roentgenium	Copernicium	Ununtrium	Ununquadium	Ununpentium	Ununhexium	Ununseptium	Ununoctium
87 223.02	88 226.03	**	104 261.11	105 262.11	106 266.12	107 264.12	108 269.13	109 268.14	110 271.15	111 272.15	112 285	113 287	114 289	115 291	116 289	117 293	118 293
Fr 27 677 0.9 1	Ra 700 1140 1.0 5.0 2	89-103	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Uuo	Uuq	Uup	Uuh	Uus	Uuo

Atomic Number - 46 — Palladium - Element Name
106.42 - Atomic Weight
Symbol - Pd
1552 - Melting Point (°C)
3140 - Boiling Point (°C)
1.4 - Electronegativity (Allred, Rochow)
Density - 12.0 (solids, g/cm³ at 20°C; liquids, g/mL at 20°C; gases, g/L at 0°C, 1 atm)
2,4 - Oxidation States

*Lanthanides

Lanthanum	Cerium	Praseodymium	Neodymium	Promethium	Samarium	Europium	Gadolinium	Terbium	Dysprosium	Holmium	Erbium	Thulium	Ytterbium	Lutetium
57 138.91	58 140.12	59 140.91	60 144.24	61 146.92	62 150.36	63 151.96	64 157.25	65 158.93	66 162.50	67 164.93	68 167.26	69 168.93	70 173.04	71 174.97
La 921 3457 1.1 6.145 3	Ce 799 3426 1.1 6.66 3,4	Pr 931 3512 1.1 6.77 3,4	Nd 1021 3068 1.1 7.00 3	Pm 1168 2460 1.1 7.26 3	Sm 1077 1791 1.1 7.52 2,3	Eu 822 1597 1.0 5.24 2,3	Gd 1313 3266 1.1 7.90 3	Tb 1356 3123 1.1 8.23 3,4	Dy 1412 2562 1.1 8.55 3	Ho 1474 2695 1.1 8.80 3	Er 1497 2900 1.1 9.07 3	Tm 1545 1947 1.1 9.32 2,3	Yb 819 1094 1.1 6.97 2,3	Lu 1663 3395 1.1 9.84 3

**Actinides

Actinium	Thorium	Protactinium	Uranium	Neptunium	Plutonium	Americium	Curium	Berkelium	Californium	Einsteinium	Fermium	Mendelevium	Nobelium	Lawrencium
89 227.03	90 232.04	91 231.04	92 238.03	93 237.05	94 244.06	95 243.06	96 247.07	97 247.07	98 251.08	99 252.08	100 257.18	101 258.01	102 259.10	103 262.11
Ac 1050 3200 1.0 10.1 3	Th 1750 4790 1.1 11.7 4	Pa 1600 1.1 15.4 4,5	U 1132 3818 1.2 19.0 3,4,5,6	Np 640 3902 1.2 20.2 3,4,5,6	Pu 641 3232 1.2 19.8 3,4,5,6	Am 994 2607 1.2 13.7 3,4,5,6	Cm 1340 1.2 13.5 3,4	Bk 1.2 14 3,4	Cf 1.2 3,4	Es 1.2 3	Fm 1.2 3	Md 1.2 3	No 2,3	Lr 3

Element Categories in the Periodic Table

METALS						Metalloids	NONMETALS				Group of metals removed by SiliaMetS® Metal Scavengers (to date)
Alkali metals	Alkaline earth metals	Inner transition elements: Lanthanides	Inner transition elements: Actinides	Transition metals	Poor metals		Other nonmetals	Halogens	Noble gases	Unknown	

Element name colors show state at 0°C and 1 atm: **SOLIDS** in white, **LIQUIDS** in black and **GASES** in red.

TEL.: 1 418 874.0054 FAX: 1 418 874.0355 TOLL-FREE: 1 877.SILICYCLE (*NORTH AMERICA ONLY*) INFO@SILICYCLE.COM SILICYCLE.COM

As a recognized industry leader in the development, manufacturing and commercialization of innovative silica gel products, and with multi-ton manufacturing capability, SiliCycle® is your partner of choice for all your METAL REMOVAL, CATALYSIS, SYNTHESIS, and PURIFICATION requirements.

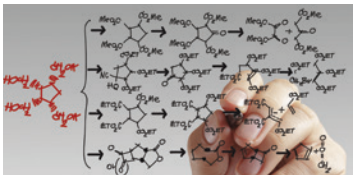
METAL & ORGANIC SCAVENGING

Removal of:
- Metals
- Electrophiles & Nucleophiles
- Potential Genotoxic Impurities (*PGI*)

CATALYSIS & SYNTHESIS

- Couplings (*Suzuki, Stille, Heck, ...*)
- Debenzylation & Hydrogenation
- Oxidation
- And Many More Reactions

ACIDS, BASES & REAGENTS



- Acids & Bases
- Amide Couplings
- Reductive Aminations
- Other Reactions

LOW PRESSURE CHROMATOGRAPHY

- Bulk Silica Gels (*Irregular & Spherical*)
- Bonded Phases
- TLC Plates
- Prepacked Flash Cartridges

SAMPLE PREPARATION

- SPE & Well Plates
- Micro-SPE Tips
- QuEChERS
- SPE Hardware & Manifold

HIGH PRESSURE CHROMATOGRAPHY

- Bulk Sorbents
- HPLC & UPLC Columns
- SEC & SFC Columns
- Guard Cartridges & Accessories

CONSUMABLES

- Vials & Caps
- Syringe Filters
- Membrane Filters

EQUIPMENTS

- Parallel Synthesis Synthesizer - MiniBlock & MiniBlock XT
- TLC Scanner
- Vacuum Manifold

DESICCANTS & OTHER BULK ABSORBENTS

- Desiccant
- Activated Alumina
- Molecular Sieve

R&D SERVICES

- Scavenging Screening
- Method Development & Optimization
- Impurities Determination
- Custom Column Packing

CONTACT INFORMATION:

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UltraPure SILICA GELS

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