Industrial Product Portfolio

Flash Purification, Metal Scavenging, Reagents & Scavengers

Biotage®

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About Biotage

Biotage offers equipment, knowledge and experience in the areas of analytical chemistry, medicinal chemistry, peptide synthesis, separation and purification. Customers include companies within the pharmaceutical, biotech, food, manufacturing, and fine chemicals industries, as well as leading academic institutes.

Vision

"Our vision is to be the first choice for our employees, customers and shareholders by creating smart and efficient solutions in the fields of chemical synthesis and separations science"

Who Are We?

Biotage is headquartered in Uppsala, Sweden and has offices in the US, UK, China and Japan. Biotage has approximately 290 employees and had sales of 490 MSEK in 2014. Biotage is listed on the NASDAQ OMX Nordic Stockholm stock exchange.

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Market & Application Areas

Our Products

Biotage provides versatile solutions, knowledge and experience in the areas of analytical, medicinal and scale-up chemistry. Our range of products and accessories meet the needs and standards of today's modern development laboratories, whilst ensuring a seamless transition to process development and larger scale activities.

The Industrial Product Portfolio

Our carefully selected portfolio of industrial scale products have a proven track record of successful applications and use in scale-up projects. Our strength lies in efficiency and value. From robust day-to-day methods to bespoke solutions, Biotage products are here to serve. We can support the discovery, development and manufacturing of customer pharmaceutical and biotechnology products, from pre-clinical, phase I, II and III to small scale commercial operations.

Our Customers

Biotage has a strong customer base of research and manufacturing partners, which include the world's top 20 pharmaceutical companies, multiple world class contract manufacturing organizations (CROs/CMOs) fine chemical manufacturers and prestigious academic institutes such as the US National Institutes of Health, the US Centers for Disease Control and Prevention, and the Karolinska Institute in Sweden.

Featured Technologies

Biotage® Flash 400 is a complete skid-mounted system designed for kilogram-scale separations. Built to last and engineered to perform, with materials that comply with FDA regulations and cGMP standards, Flash 400 is the first choice of pharmaceutical and contract manufacturing companies around the world for critical purification applications.

See Page 12.

A convenient metal scavenging kit is available to help determine optimal process conditions for metal mitigation. This kit comes will full instructions and protocols for screening, development and scale-up. All scavengers are supplied ready to use, straight out of the box.

See Page 22.

Typical Organic Chemical Synthesis or Development Work Flows

Compliance & Regulatory Information

Key to Icons

It is critical that products used in processes are reliable, reproducible, robust and fully traceable. Biotage has worked with a number of internationally recognized bodies to attain world class standards of quality and compliance in all Industrial products.

Quality Assurance and Environmental

ISO 9001:2008

Biotage is accredited to the world renowned British Standards Institute ISO 9001:2008 standard (registration number 31206), with the scope defined as “Design and manufacture of sorbent and resin materials for sample preparation and purification products. Manufacture of laboratory automation equipment.”

Quality is built into our everyday principles and practices. 2015 was a milestone in our commitment to quality as we have now held this ISO accreditation for 20 years.

All Biotage products are manufactured in controlled conditions. Consumables are lot controlled and traceable, and instruments carry full TÜV and CE registration.

Environmental Protection Policy

Preserving our shared environment is fundamental to Biotage, as it is to our employees, customers, and other stakeholders. Biotage has attained an environmental permit from Natural Resources Wales, under The Environmental Permitting (England & Wales) Regulations 2010. Our registration number is EPR/DP3832EF.

TSE/BSE statement

All Biotage polystyrene backbone resin materials and silica based products in the consumables range are produced from either petroleum based chemicals or inorganic salts. Raw materials are traceable and do not contain materials of animal or biological origin; nor do ancillary chemicals used in production processes.

ATEX

ATEX is the framework of legislation and guidance for controlling explosive atmospheres and the standards of equipment and protective systems used in them. This legislation will apply to filters when used in these potentially hazardous environments. Biotage® Flash 400 systems are ATEX compliant by design.

Built for cGMP Production

All industrial scale Biotage flash purification instruments come complete with an ASME “UM” stamp and are certified for usage in Japan, Europe and North America. Each system is accompanied by a full engineering documentation package, a certificate of performance and a certificate of compliance for validation filing.

Business Continuity

Biotage recognizes the impact of potential disasters or emergencies such as fire, flood, loss of utilities, or staffing disruptions can be reduced through a considered assessment of threat, vulnerability and risk. We have multiple inventory warehouse locations, two flexible chemical and manufacturing sites in different locations within the group and engage in multiple outsource and scale-up partnerships to ensure the continuity and stability of our supply chain.

Scalable

Biotage products are designed to solve problems, from small to large. Products may be used in research or manufacturing programs, where this icon is used.

Impurity and Chemical Control

REACH

Our suppliers have confirmed that the raw materials used to manufacture our products do not contain any substances that require registration. We will continue to monitor our suppliers to ensure that any changes in raw materials will be recorded and if required they will be registered as stated in the REACH Directive.

ICH Q3D

The final version of the Q3D guidelines by the International Conference on Harmonisation (ICH) were accepted by the ICH Steering Committee in December 2014. The implementation phase scheduled for January 2016 requires that the entire manufacturing industry and supply chain prioritize these considerations. The guidelines relate to impurities in new drugs and formulations, and affect a large number of pharmaceutical industries. Biotage metal scavengers have been specifically designed with this risk mitigation in mind.

Extractables

Biotage® Flash 75, Flash 150 and Flash 400 cartridges are constructed of medium-density polyethylene or polypropylene, and meet the FDA extractable requirement specified in 21 CFR 177.1520. Resin and silica products are extensively washed and tested during production phases to minimize any downstream contamination risk. Extractable data for all scavengers and stationary phases is available on request.

Shelf Life

Due to the nature of the components, shelf-life on all Biotage consumables products can be considered very long to indefinite for Quality Assurance/long term planning purposes. See individual product notes for further details.

Compliance and Quality

Biotage supported reagents and scavengers are made in an ISO9001:2008 compliant manufacturing facility. Each material is batch and lot controlled, with benefits of full traceability. The products are readily available in multi-kg quantities off-the-shelf and supported by a comprehensive regulatory qualification support package comprising certificate of analysis, extractables, chemical loading, lot information, batch identity and consistency, MSDS/SDS, and full instructions and suggestions for use. Further information in support of regulatory compliance is available on request and Biotage can provide extensive technical support relating to the efficient use of these products in various processes.


150
FLASH™
RADIAL
COMPRESSION
MODULE
U.S. Patent No. 4,250,035
Biotage

Industrial Purification

Flash Systems and Cartridges

Industrial Purification

Product Portfolio Overview

In 1994 Biotage was the first company to develop pre-packed cartridges for flash purification and has been the leader in quality, performance, and innovation ever since.

Biotage has a long history with purification instruments, pioneering innovation since the late 1970s. Our research scale purification instruments are the most technologically advanced and effective purification systems available. We have developed ACI™ Accelerated Chromatographic Isolation, a revolutionary advancement converting regular flash purification to the fastest, greenest, and most economical way to reliably isolate pure compounds. Our development systems enable you to leverage these value added features in silica choice and flow rate in method development, and apply them to larger scale purification, radically enhancing the efficiency of your production processes.

Many of the enhanced ACI silicas (which can accept twice a normal sample load, or give higher plates when packed into columns) are available as standard in our large scale process cartridge range.

ACI™ Accelerated Chromatographic Isolation

ACI™ - Accelerated Chromatographic Isolation radically improves the efficiency of the laboratory, embracing the latest developments in purification technology to guide chemists towards improved chromatography. Biotage has found a way to extract more value and productivity from purification processes that were previously assumed to be constant or non-negotiable. Many of these benefits are designed to be transferred to yield huge advantages on subsequent scale-up.

Engineered to Work – Built to Last

When considering larger, production scale purification, robustness and safety are key factors for any device. Biotage® Flash 75/150/400 systems need minimal maintenance and their design has proven to be extremely reliable over many years. These rugged systems safely operate at up to 100 psi enabling fast flow rates and the use of high viscosity solvents. They allow operators to save days of plant time compared to traditional methods. The philosophy is ease of use and simple, reliable scale-up from smaller scale research runs.

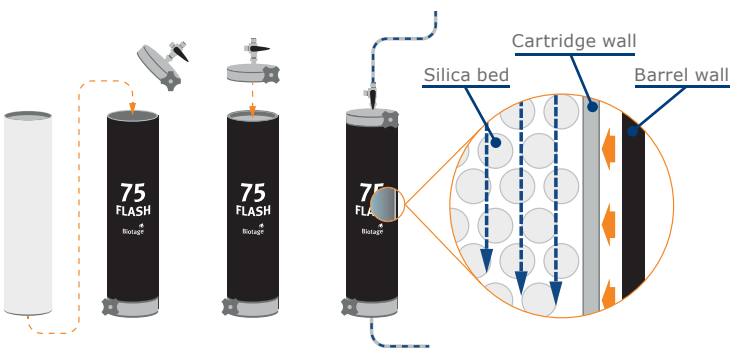
- Engineered for fast flows
- Fully grounded for safety
- No handling of loose silica
- Simple plug and play components
- Safer than glass columns
- Purify grams to kg of product quickly and effectively
- Confidence for your process
- Radial compression technology improves separation performance

Patented Radial Compression

Safer than glass columns; all Flash 75 and 150 cartridges are constructed of medium-density polyethylene to resist cracking and splitting and meet the FDA extractable requirement specified in 21 CFR 177.1520. There is no breakable glass, and all of the silica is completely self-contained, eliminating any exposure to silica dust or contaminants.

Our proven patented radial compression technology ensures near zero “wall effects” and prevents channeling inside each column. This maintains the bed’s stability, rendering cleaner, purer fractions in less time and higher overall product yield.

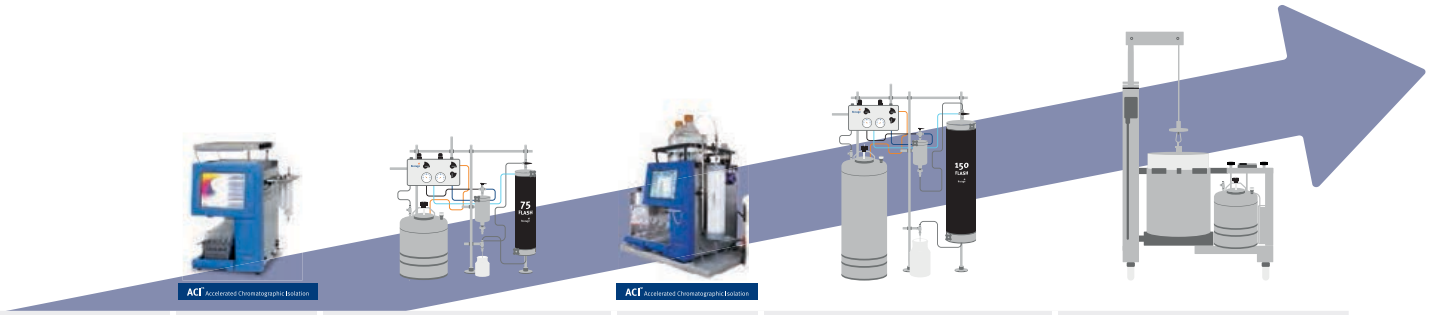
- Compression modules radially compress cartridges to maximize sample contact with silica and separation performance (higher sample load greater purity and recovery)
- Compression modules seal up to 100 psi, ensuring leak-free operation even with high flow rates and reversed-phase solvents



A pre-packed silica cartridge is loaded into the Biotage® Flash 75 radial compression barrel. External pressure from the barrel reduces wall effects and channeling inside the cartridge during purification.

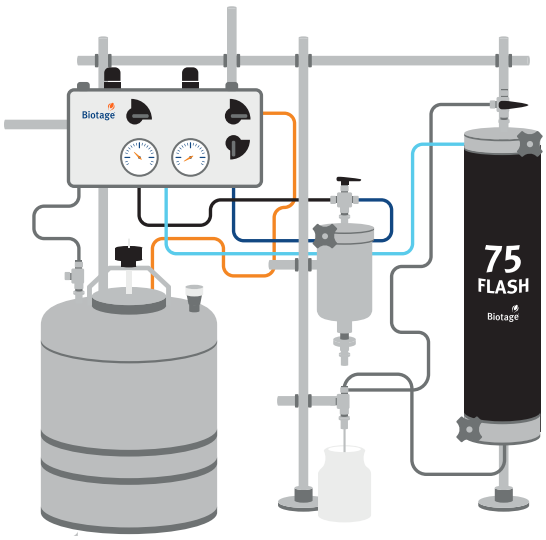
Meet the Family
Biotage® Flash 75/150/400 Systems

The Industries Preferred Process Scale Flash Purification



Flash System	Isolera™	Biotage® Flash 75		Isolera™ LS	Biotage® Flash 150		Biotage® Flash 400	
Format		M	L		M	L	M	L
Process/Scale	Development	Development & Production		Development & Production	Production		Production	
Input Sample Size (g)	35****	50	100	150	250	500	4000	8000
Flow Rate (mL/min)	200	250	250	500	1000	1000	6000	6000
Solvent Reservoir Volume (L)	-	12	12	-	37	60	-	-
Cartridge Volume (mL)	650	662	1325	2550	5300	10600	38000	75000
Column Volume (mL)*	470	500	1000	1980	4300	8600	28000	56000
Cartridge Size d x h (mm)	70 x 170	75 x 150	75 x 300	105 x 330	150 x 300	150 x 600	400 x 300	400 x 600
Cartridge Silica Mass (kg)*	0.34	0.4	0.8	1.5	2.5	5	20	40
Reversed Phase Cartridge Mass (kg)	0.4	0.5	1	1.9	3	6	24	48
SIM Volume (mL)	-	3	6	-	24	48	-	-
System Part Number	Several models available†	SF-022-19041	SF-022-19071	Several models available†	SF-022-25071	SF-022-25151	SF-521-50070	SF-521-50150
Accessories								
Additional Compression Modules**	-	FC-022-19041	FC-022-19071	-	FC-022-25071	FC-022-25151	FB-012-50070	FB-012-50150
Dry Loading 0–100 mL***	DLV-30, DLV-70	SIM-0102 (100 mL)		-	SIM-0102 (100 mL)		-	-
SIM Dry Loading 500 mL***	-	SIM-0502		DLV 500	SIM-0502		-	-
SIM Dry Loading 1000 mL***	-	SIM-1002		-	SIM-1002		-	-
SIM Dry Loading 2000 mL***	-	SIM-2002		-	SIM-2002		-	-

* Based on KP-Sil silica. For HP-Sphere multiply by 1.25
** Additionally available and interchangeable within the M/L format to extend the range of the systems. See ordering information section for more detail.
*** Sample injection modules, additionally available interchangeable units to support increased dry/viscous/poorly soluble sample addition
**** 750 g cartridge also available
† See "Biotage Flash Purification Systems - Pure Compounds in a Flash" (PPS319) or www.biotage.com



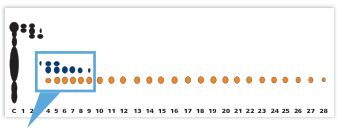
Biotage® Flash 75

Purify up to 100 g of product per run at up to 250 mL/min

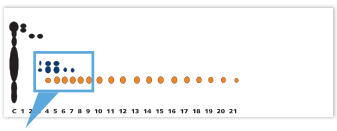
Biotage® Flash 75 is a simple, robust and reliable system that contains everything needed for separation and scale-up. Operating at a flow rate of 250 mL/min, supporting separations of up to 100 g per run, these flash systems and cartridges allow you to quickly develop scale-up and complete runs, saving hours – even days – of purification time. A variety of pre-packed cartridges are available depending on the purification goal and cartridges can also be custom packed with your preferred chromatography media (see page 14).

75% Time Saving

In a comparison between a Flash 75L cartridge (75 mm x 300 mm) and a 110 mm x 200 mm traditional glass column, fractions were collected in 2.5 hours using the glass column, while the Flash 75L cartridge required just 40 minutes. Additionally there were fewer mixed fractions, resulting in greater product purity.



More impure fractions from glass column.



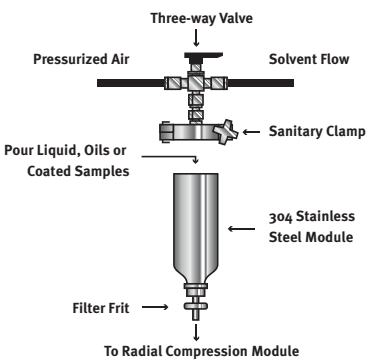
Faster and better purification with Biotage® Flash 75.

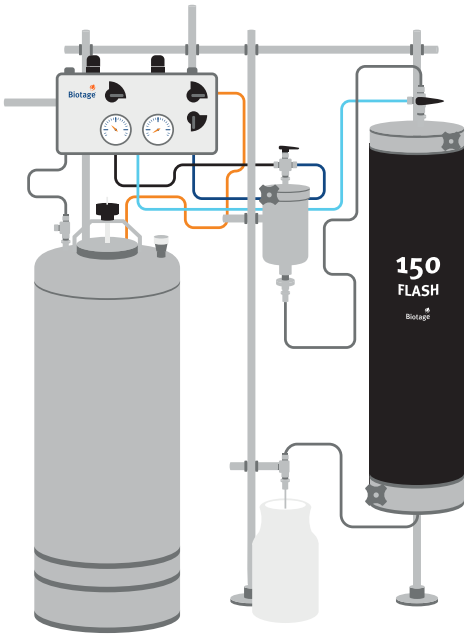
What's in the Box?

The system includes an easy-to-install radial compression module, a fully integrated air manifold, solvent reservoir, a start-up kit with all necessary tubing, grounding kit, and a user's manual. Flash 75 systems come with a sample injection module (SIM) as standard, which helps to bridge the gap from lab to large scale method development. The SIMs (available in 100 mL, 500 mL, 1000 mL and 2000 mL) facilitates the handling of routine samples as well as viscous oils and samples with poor solubility.

Optional Further Accessories

Sample injection modules, Solvent reservoirs, Compression module barrels (see "Ordering Information" on page 42).





Biotage® Flash 150

Fast Scale-up: Purify up to 500 g of product per run at up to 1 L/min

Like its little brother, the Biotage® Flash 150 system supports batch purification up to 80% faster than traditional glass columns. Flash 150 is a simple, robust and reliable system, containing everything needed for large or industrial scale separation or batch purification.

80% Time Saving

In a comparison between a Flash 150M cartridge (150 mm x 300 mm) and a 120 mm x 660 mm traditional glass column, fractions were collected in 7.2 hours using the glass column, while the Flash 150M cartridge required just 90 minutes. Additionally, the recovery ratio of product from the Flash 150M system was 4 times that of the glass column. This resulted in a plant saving nearly 4 weeks of development time.

	Flash 150M	Glass Column
Column Size (mm)	150 x 300	120 x 660
Silica Quantity (kg)	2.5	3
Sample Load Mass (g)	180	450
Flow Rate (mL/min)	500	70
Total # Fractions to Collect	45	30
Purification Time (min)	90	430
Pure Compound Per Run (g)	70.5	45
Recovery Ratio (%)	87	22
Purification Throughput (g/hr)	120	63

A variety of pre-packed cartridges are available depending on the purification goal, and cartridges can also be custom packed with your preferred chromatography media (see page 14).

What's in the Box?

The system includes an easy-to-install radial compression module, a fully integrated air manifold, solvent reservoir, sample injection module (SIM), a start-up kit with all necessary tubing, grounding kit and a user's manual. Flash 150 compression modules are mounted onto robust portable bases (included in the system package), which are fitted with casters for easy mobility. The SIMs (available in 100 mL, 500 mL, 1000 mL and 2000 mL) facilitates the handling of routine samples as well as viscous oils and samples with poor solubility.

Optional Further Accessories

Sample injection modules, Solvent reservoirs, Compression module barrels (see "Ordering Information" on page 42).

Biotage® Flash 400

The Industry Standard for Process-Scale Purification – Isolate up to 8 kg of product per run at 6 L/min

The Biotage® Flash 400 system is a complete skid-mounted system designed for kilogram-scale separations. Built to last and engineered to perform, with materials that comply with FDA regulations and cGMP standards, Flash 400 is the first choice of pharmaceutical and contract manufacturing companies around the world for critical purification applications.

Robust & Reliable

Robustness and safety are key factors for any scale up system. Biotage® Flash 400 needs minimal maintenance and its design has proven to be extremely reliable. With operating pressures up to 100 psi, this system supports flow rates up to 6 liters per minute, allowing operators to save days or even weeks of project time, resulting in substantial project cost savings.

The Flash 400 system uses pre-packed cartridges and radial compression, and supports two interchangeable barrels for use with either 400 mm x 300 mm (Flash 400M) or 400 mm x 600 mm (Flash 400L) cartridges. One of the compression module sizes is included in the system (the module of the other size can be ordered and is interchangeable as an option).

A variety of pre-packed cartridges are available depending on the purification goal and cartridges can be custom packed with the preferred chromatography media for your process (see page 14). The media in each cartridge is self-contained, improving handling and eliminating exposure to contamination and impurities or potentially high toxicity APIs.

Patented Radial Compression Technology

Our proprietary packing technique ensures that each cartridge is shipped with a tightly packed bed. The application of our proven, patented radial compression technology further maintains the bed's stability during use for higher purities and yield. Extra force from radial compression ensures near zero "wall effects" and channeling inside each column.

Built and Documented for cGMP Production

All systems come complete with an ASME "UM" stamp, CE certification, and are certified for usage in Japan, Europe and North America. A full engineering documentation package, certificate of performance and certificate of compliance for validation filing accompany each system. Professional Biotage service personnel train users on proper operation, and are available for project based or yearly training sessions.

Safety is Paramount

Safety is a key design criteria on all Biotage flash systems. Designed for use around large quantities of solvents Flash 400 systems can operate in an explosion proof, no sparking rated area. Air driven pump and hoists, proper grounding and pressure relief devices are some of the vital components included with every system. All systems comply with NEC Class 1, Division 1 and 2, Group C and D standards.

Pneumatic Control Panel

The pneumatic control panel located on the top of the Flash 400 system frame makes operation easy. The panel is divided into three sections that allow users to fully control the entire process.

Cartridges for Any Application

From routine normal phase flash chromatography to more difficult separations with reversed phase silica, activated carbon, low metal/acid washed silica, Mitsubishi Diaion™ HP20SS resins, ion exchange or other custom packed, client supplied media, Flash 400 systems are capable of addressing almost every purification need.

Scalable Results

Technologies such as crystallization and adsorption can be difficult and time consuming to scale up. Using the extensive cartridge range from Biotage, reliable results are verifiable and easy to achieve with any separation. A Biotage® SNAP 10 g column to purify 100 mg quantities can be used as a basis to purify multi gram and ultimately kg quantities of product using a 40 kg Flash 400 cartridge. Stepping up the cartridge range, purifications can be scaled up 4000 times.

Development Scale Purification Cartridges

Media and Size Options

Choosing the correct purification cartridge is crucial for maximizing efficiency. The following tables highlight application areas, silica types and part number options available for a wide variety of scale-up projects.

Selecting the Correct Media

Normal phase flash chromatography has been widely adopted as the method of choice for separation of product mixtures and reaction by-products. Whether standard silica or specially acid washed for low metals content, normal phase flash purification has proven itself to be incredibly powerful.

One of the most significant developments in purification is the separation of polar molecules by reversed phase purification. Reversed phase methods provide a great leap forward, but this has been a relatively under-used technique due to lack of information and supporting data. Polar, water soluble molecules are the focus of many pharmaceutical drug development programs and natural product research. These molecules make up the majority of the compounds involved in the fundamental chemistry of living organisms. Isolation of large quantities of such polar compounds has traditionally been carried out using expensive preparative HPLC (High Performance Liquid Chromatography) systems. These systems are typically dedicated to final product purification, and are not economically viable options for many chemists in day to day or smaller/flexible projects.

Application Selection Guide

Product	Examples	Normal Phase	Reversed Phase	Amino Phase
Alkaloids	Cocaine, morphine, nicotine, quinine	✓	✓	✓
Amino acids			✓	
Analgesics	Aspirin, acetaminophen, ibuprofen	✓	✓	
Aromatics		✓	✓	✓
Basic drugs			✓	✓
Carbohydrates	Sugars		✓	✓
Flavonoids			✓	
Glycosides			✓	✓
Lipids	Phospholipids	✓	✓	
Natural products	Terpenes, saponins, polyphenols	✓	✓	
(Oligo) nucleotides			✓	
Peptides (< 2k MW)		✓	✓	
Steroids		✓	✓	
Tannins			✓	
Vitamins	Tocopherols (vitamin E), retinol (vitamin A), vitamin D, vitamin K	✓	✓	✓

Cartridge Media Specifications

Phase	Media	Silica Type	Particle Size (µm)	Pore Volume (mL/g)	Surface Area (m2/g)	Pore Diameter (Å)
Normal Phase	KP-Sil		50	0.8	500	55
	KP-Sphere™ *		60	1.0	800	50
	HP-Sphere™ *		25	1.0	800	50
	KP-NH		55	0.6	220	-
Reversed Phase	KP-C18-HS		50	0.9	400	90
	Mitsubishi Diaion HP20		250–850	1.3	500	260
	Mitsubishi Diaion HP-20ss		75–150	1.3	500	260
Adsorption	Activated Carbon		60	-	1400–1800	-

*ACI™ compliant ACI™ Accelerated Chromatographic Isolation

How to Scale Up and Select an Industrial Purification System and Cartridge

Moving from lab scale to large scale comes with a number of additional considerations. Biotage® Flash 75, 150 and 400 systems are extremely tough, economically viable industrial purification systems that have been developed for this purpose.

Scaling up flash purification methods is easy and straightforward. Any method developed using a Biotage lab scale cartridge can be transferred to a larger cartridge using the scale-up factors in the table below. Once the development cartridge is determined, the lab scale method can be replayed, providing peak elution profiles for the scale up system consistent with the development process and suitable for final optimization.

Furthermore, all Biotage lab scale systems come with software that can automatically create linear gradients from TLC Rf spots; and then automatically convert those linear gradients into step gradients for application on a larger scale. Each system may be configured with either 'M' or 'L' cartridge capability to further increase its flexibility and range.

Example 1

A 25 g Biotage® SNAP cartridge was used to develop a 2.3 gram purification. The requirement is now to purify 125 g. The **scale-up factor is then 54.3**. We therefore move right in the chart on the 25 g row to the interval between 32 and 60. The appropriate large scale cartridge is in the 800–2500 g range, which corresponds to the Biotage® Flash 150M cartridge.

Example 2

A 100 g Biotage® SNAP cartridge was used to develop a 6.5 gram purification. The requirement is now to purify 900 g. The **scale-up factor is then 138**. We therefore move right in the chart on the 100 g row to the interval between 50 and 200. The appropriate large scale cartridge is in the 5–20 kg range, which corresponds to the Biotage® Flash 400M cartridge.

Cartridge Scale-up Conversion Table

Development Cartridge Size	4.6 x 250	5 g	10 g	25 g	30 g	45 g	50 g	80 g	100 g	120 g	200 g	340 g	400 g	750 g	800 g	1.5 kg	2.5 kg	5.0 kg	20 kg	40 kg
4.6 x 250	20	10	5	2	2	1.1														
5 g	32	16	8	3	3	1.8	1.6													
10 g	40	20	10	4	3.5	2.2	2	1.25												
25 g	48	24	12	5	4	3	2.4	1.5	1.2											
30 g	80	40	20	8	7	4.5	4	2.5	2	1.7										
45 g	136	68	34	14	12	7.5	6.8	4.3	3.4	2.8	1.7									
50 g	160	80	40	16	14	9	8	5	4	3.5	2	1.2								
80 g	300	150	75	30	25	17	15	9.5	7.5	6.5	3.8	2.2	1.9							
100 g	320	160	80	32	27	18	16	10	8	7	4	2.4	2	1.1						
120 g	600	300	150	60	50	33	30	19	15	12	7.5	4.4	3.8	2	1.9					
200 g	1000	500	250	100	83	56	50	31	25	21	13	7.4	6.3	3.5	3.1	1.7				
340 g	2000	1000	500	200	167	111	100	62	50	42	25	15	13	7	6.2	3.3	2			
400 g	8000	4000	2000	800	667	444	400	250	200	167	100	60	50	27	25	13.5	8	4		
750 g	16000	8000	4000	1600	1333	888	800	500	400	333	200	120	100	54	50	27	16	8	2	

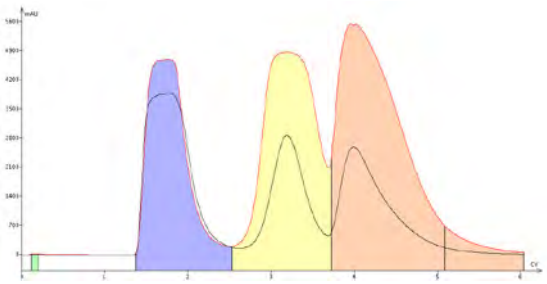
Scale-up factor from lab to large scale

Required Large Scale Media Mass	50 g – 80 g – 100 g – 120 g – 200 g – 340 g	400 g – 750 g	800 g – 1.5 kg	2.5 kg – 5 kg	5 kg – 20 kg	20 kg – 40 kg
Range	50–400 g	400–800 g	800–2500 g	2.5–5 kg	5–20 kg	20–40 kg
Cartridge Size	400 g	800 g	2.5 kg	5 kg	20 kg	40 kg
Available Cartridge Options	SNAP 340 g/75M	SNAP XL/75L	150M	150L	400M	400L

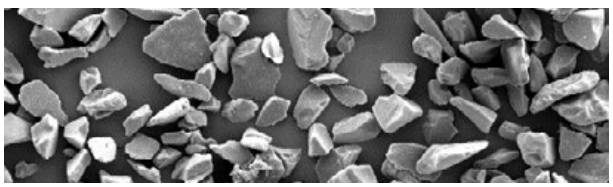
Reduce Purification Time and Cartridge Size With Higher Capacity Cartridges

Traditional process purification can benefit from advances in lab scale purification and materials science. Classic selection and predictor tables are based on a standard performance silica media for determining cartridge loading and sample size.

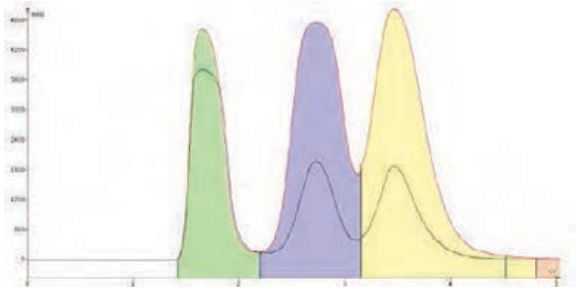
Biotage® HP-Sphere™ and KP-Sphere™ represent an innovative breakthrough in purification technology, leading to very high capacity and high resolution purification columns. With spherical beads, smaller particle size and a much higher surface area, these silica are more efficiently packed into columns, increasing the effective plate count whilst conferring approximately double the sample load capability. These revolutionary improvements result in a column that doubles the purification performance per run or allows a smaller column to be chosen for the same sample quantity, cutting the solvent use and run times in half.



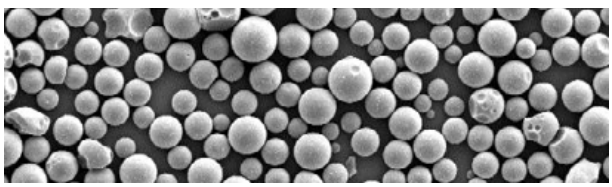
Irregular silica cartridge, 25 µm, 25 g, 25 mL/min, sample loading 2% wt/silica.



Better purification at 2 x the sample load



HP-Sphere™-silica in a Biotage® SNAP Ultra 25 g cartridge, 25 mL/min, sample loading 4% wt/silica.



Method development analysis: Comparison of a standard irregular 40–63 micron silica (left) with high capacity 25 micron HP-Sphere™ spherical silica (right).

Cartridge Part Number Options

	75M	75L	150M	150L	400M	400L
Media						
KP-Sil	FK0-1107-19045	FK0-1107-19075	FK0-1107-25075	FK0-1107-25155	FK0-1107-50070†	FK0-1107-50150†
KP-Sphere™*	F75M-0445-19045	F75L-0445-19075	F150M-0445-25075	F150L-0445-25155	F400M-0445-50070†	F400L-0445-50150†
HP-Sphere™*	F75M-0442-19045	F75L-0442-19075	F150M-0442-25075	F150L-0442-25155	F400M-0442-50070†	F400L-0442-50150†
KP-NH	FPNH-75M†	FPNH-75L†	FPNH-150M†	FPNH-150L†	FPNH-400M†	FPNH-400L†
KP-C18-HS	FL0-1118-19040†	FL0-1118-19070†	FL0-1118-25070†	FL0-1118-25150†	FL0-1118-50070†	FL0-1118-50150†
HP20	FT6-2030-19045	FT6-2030-19075	FT6-2030-25075	FT6-2030-25155	enquire	enquire
HP20ss	FT6-2530-19040†	FT6-2530-19070†	FT6-2530-25070†	FT6-2530-25150†	enquire	enquire
Carbon	C1YR-4021-19043‡	C1YR-4021-19073‡	C1YR-4021-25075	C1YR-4021-25155	C1YR-4021-50075	C1YR-4021-50155

■ Normal phase
■ Reversed Phase
■ Adsorption

All part numbers refer to a two-pack unless indicated. A custom packing service is available for other media. Please enquire for further details.

* ACI compliant ACI Accelerated Chromatographic Isolation
† 1 pack
‡ 10 pack

Case Study

Large Scale Purification of Glycosides for Alzheimer's Disease Therapy

Biotage® Flash 400 cartridges were used to purify large batches in a process for producing a drug candidate for Alzheimer's disease.

Gamma-secretase modulators (GSMs) are promising compounds for Alzheimer's disease therapy, due to their selective lowering of amyloid-β42 levels in the brain. An international team of researchers and development chemists have identified the GSM SPI-1865 as a candidate for a potential novel therapeutic agent.

Ruichao Shen, a leading scientist at Satori Pharmaceuticals Inc. explains: "In the production of a key intermediate for synthesis of our preclinical candidate compound, we need to purify 50 kg of crude extract obtained from biomass. The crude was divided into ten portions with 5.2 kg of solids per portion. Each portion was loaded on a preconditioned Biotage KP-Sil flash 400L cartridge and eluted with a gradient of 2–15% MeOH in DCM."

One of the key challenges related to workflow, Ruichao added, "The problem we faced was to find an efficient method to purify the crude mixture as fast as possible and maintain a good recovery at the same time. At that time Biotage had the largest pre-packed SiO_2 cartridge available in the industry. We chose the product and it helped us solve the problem well."

As part of the synthetic pathway to obtain SPI-1865, the group synthesized large quantities of two cycloartenol triterpenoid glycosides "... under an aggressive timeline" from roots of *Actaea racemosa* (known as black cohosh, a perennial herb containing many organic compounds with known biological activity). In doing so, no less than 147 kg of extract solution was purified by batch-wise purification using a Biotage® Flash 400L KP-Sil cartridge, installed on a Biotage® Flash 400 system. The fractions contained 11.44 kg of extracted product.

Read More

Ruichao Shen, Nathan O. Fuller, Gerd Osswald, Wesley F. Austin, Jed L. Hubbs, Dieter Haag, Janos Kovacs, Steffen P. Creaser, Mark A. Findeis, Jeffrey L. Ives, and Brian S. Bronk, **2014**. Multikilogram-Scale Production of Cycloartenol Triterpenoid Glycosides as Synthetic Intermediates for a γ-Secretase Modulator. *Organic Process Research & Development* 2014 18 (6), 676-682DOI: 10.1021/op5000732 - –

Metal Scavenging

Scavengers and Tool Kits

Metal Scavenging

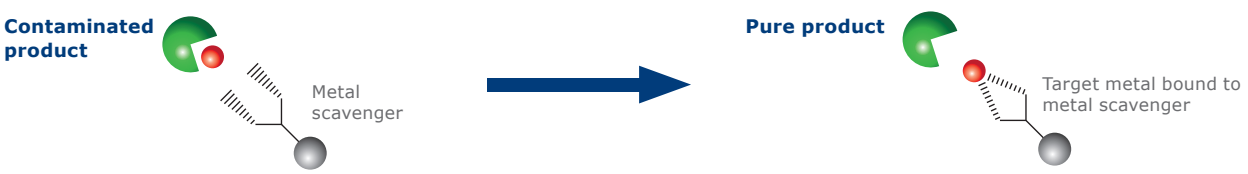
Dealing with Today's Impurity Challenges

Transition metal catalysts are powerful reagents that comply with principles of green chemistry. They are used sparingly, confer atom and economic efficiency, but may themselves be difficult to remove after the reactions.

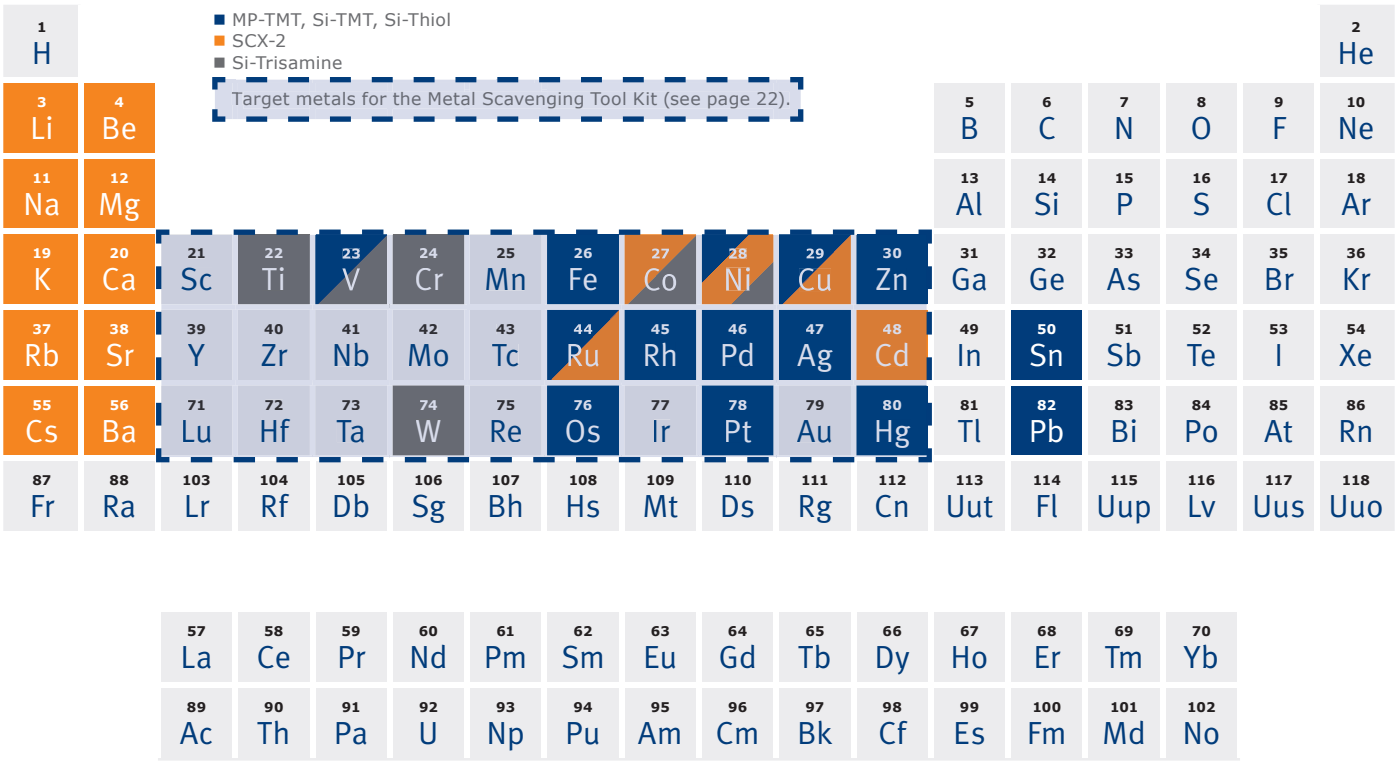
Traditional methods for removing metals include adsorption on carbon, distillation, precipitation or recrystallization. These techniques may be indiscriminate, energy intensive, non-reproducible or may actually increase the concentration of metal within an API crystal structure. Biotage metal scavengers are effective for the removal of a variety of metals (such as PGM's) from catalyzed reactions or final products such as APIs. This technology can be applied to a variety of different industries – from pharmaceutical to fine chemical, from flavors and fragrances to agrochemical, from water treatment to industrial waste management.

The mode of operation is very simple with wide solvent compatibility and specific reactivity, and metal scavengers impose very little constraint or stress on typical workflows. Biotage metal scavengers are designed to be added, stirred and filtered, leaving pure products in the solution.

This step-wise approach significantly reduces the traditional metal removal processing burden. The table below shows the wide variety of metals that can be removed by using metal scavengers.



Example Metal Scavenger Choices



This periodic table indicates the best metal scavenger choice for target metals. For more details please see "Metal Scavenger Overview" on page 23.

Built for Industry

In recent years, residual metal impurities have become a major issue in the pharmaceutical industry. The ICH Steering Committee in December 2014 finalized guidelines, requiring that the entire manufacturing industry and supply chain considers impurities more carefully in their processes. Biotage metal scavengers have been designed with this future compliance in mind.

In one metal scavenging case study, metal scavengers reduced Pd metal contamination in a Suzuki reaction product by 1000 fold, achieving the required <10 ppm limit effortlessly.

1. Crude Pd/mother liquors (1000 ppm Pd) is applied to Si-TMT.

2. Product passes through and palladium is efficiently retained.

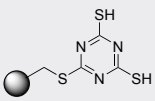
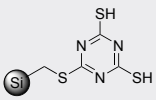
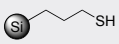
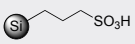
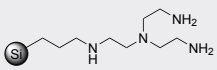
3. The clear product extract to the left and the original palladium catalyst to the right.

Metal Scavenging Tool Kit – an All in One Screening Kit

Biotage metal scavengers are available in loose powder form, which can be added and stirred into batch reactions. Alternatively they can be packed into column formats for flow through applications. In order to help determine optimal scavenging conditions, a convenient metal screening kit is available, featuring the market leading bound TMTs and the workhorse Si-Thiol metal scavengers, as well as some specific to basic and acidic products. This kit comes with full instructions and protocols for screening, development and scale-up, and all scavengers are supplied ready to use, straight out of the box.

It is always advisable to screen a variety of different scavengers in any early development program. For further details, case studies and example protocols, please see the Metal Scavenger User Guide (UI317).

Metal Scavenger Specifications

Scavenger	MP-TMT	Si-TMT	Si-Thiol	SCX-2	Si-Trisamine
Structure					
Type	Macroporous polystyrene	Silica	Silica	Silica	Silica
Name	Macroporous poly-styrene- 2,4,6-trimer-captotriazine	2,4,6-trimercaptotri-azine silica	Silica 1-propanethiol; 3-Mercaptopropyl silica	Silica Propylsulfonic Acid	Propyl tris-(2-amino-ethyl)amine silica
Particle size µm	150–355	40–63	40–63	40–63	40–63
Metals scavenged	Transition metals and group 1 or 2 alkali metals including Ag, Cd, Cr, Co, Cu, Fe, Hg, K, Li, Na, Ni, Ni, Pb, Pd, Pt, Rh, Ru, Sn, V, Zr, Z				
Typical scavenging conditions	Add 3–5 equiv. relative to Palladium to reaction and stir, RT, 5 minutes – 24 hours. Pass solution of metal through fixed bed/cartridge with scavenger, one pass or recirculate.				
Compatible solvents	Tetrahydrofuran (THF), Dichloromethane (DCM), Acetonitrile (MeCN), Toluene, Water, Methanol (MeOH), Ethyl Acetate (EtOAc), Dioxane, Dimethylsulfoxide (DMSO), N,N-Dimethylformamide (DMF)				
Storage	RT, (Long term, cool (4 °C)), dry location				
Shelf-life	Nominally 1 year but indefinitely stable when stored in original packaging under closed atmosphere conditions in a cool dark place.				
Part Numbers					
3 g	801506	n/a	n/a	n/a	n/a
10 g	801469	9538-0010	9180-0010	9536-0010	9495-0010
25 g	801470	9538-0025	9180-0025	9536-0025	9495-0025
100 g	801471	9538-0100	9180-0100	9536-0100	9495-0100
1000 g	801472	9538-1000	9180-1000	9536-1000	9495-1000

Each metal scavenger is supported by full QC analysis, lot traceability and a package of information designed to support use and registration at large scale.

Metal Scavenger Overview

Biotage® MP-TMT

Product Note: PPS371

Capacity: 0.66 mmol/g

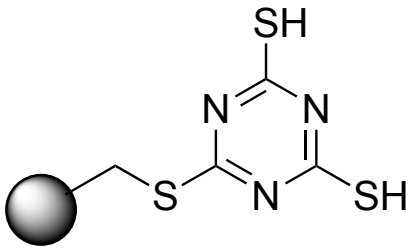
Bulk Density: 450 g/L

Target Metals: Ag Cu Ni Pd Rh Ru V Zn

Applications: Biotage® MP-TMT is a macroporous polystyrene-bound equivalent of 2,4,6-trimercaptotriazine (TMT).

MP-TMT scavenges residual palladium from palladium catalyzed reactions and has also shown to remove other metals.

MP-TMT is mechanically very robust, non-swelling and provides enhanced access to reactive sites resulting in optimal scavenging, higher recoveries and less solvent usage.



ISOLUTE® Si-Thiol

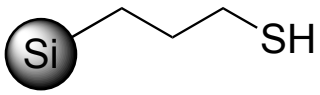
Product Note: PPS374

Capacity: 1.3 mmol/g

Bulk Density: 700 g/L

Target Metals: Ag Cu Fe Hg Pb Pd Pt Rh Sn V Zn

Applications: ISOLUTE® Si-Thiol is the silica-bound equivalent of 1-propanethiol, which is useful for scavenging a variety of metals used in organic chemistry including Pd, Pt, Cu, Hg, Ag and Pb. The versatility of this scavenger makes it a workhorse product for the industry.



ISOLUTE® Si-TMT

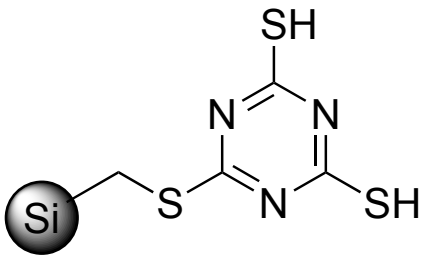
Product Note: PPS378

Capacity: 0.3 mmol/g

Bulk Density: 700 g/L

Target Metals: Ni Pd Pt St Rh Ru V Zn

Applications: ISOLUTE® SI-TMT is the silica bound equivalent of 2,4,6-trimercaptotriazine (TMT). Si-TMT has been shown to efficiently scavenge residual palladium from palladium-catalyzed reactions. The chemistry of Si-TMT is similar to that of the resin bound counterpart, however the silica is additionally amenable to being packed in column format, due to its smaller particle size.



ISOLUTE® SCX-2 (Si-Propylsulfonic Acid)

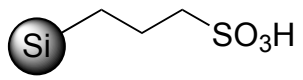
Product Note: PPS373

Capacity: 0.66 mmol/g

Bulk Density: 700 g/L

Target Metals: Cd Co Cu Fe Ni Rh Ru V Zn

Applications: ISOLUTE® SCX-2 is a strong cation exchanger, and thus can be used in the scavenging of many alkaline metals, typically in +I oxidation states but is also effective for transition metals such as ruthenium.



ISOLUTE® Si-Trisamine

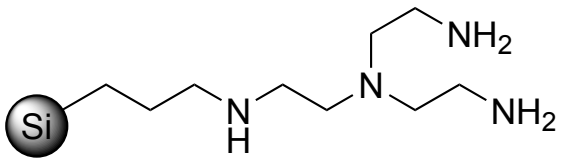
Product Note: PPS372

Capacity: 1.6 mmol/g

Bulk Density: 700 g/L

Target Metals: Cr Co Cu Fe Ni Pd Rh Ru V Zn

Applications: ISOLUTE® Si-Trisamine is a silica bound propyl-tris(2-aminoethyl)- amine. Si-Trisamine is a very powerful scavenger of transition metals (+II oxidation states) as well as electrophiles from aqueous or organic solutions.



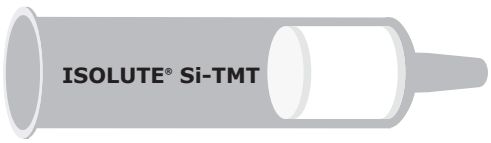
ISOLUTE® Si-TMT Cartridge

Product Note: PPS378

Capacity: 0.15 mmol

Target Metals: Ni Pd Pt St Rh Ru V Zn

Applications: We've added 500 mg/6 mL Si-TMT cartridges in the metal scavenging kit for maximum convenience. This small scale example cartridge can model a larger scale applications and will typically scavenge Pd from 1 mol% catalyzed reactions run at 1 mmol scale in one pass at RT under gravity flow. It is a great starting place for development studies.



	As	Cd	Co	Cr	Cu	Hg	Li	Mo	Ni	Sb	Sn	V
MP-TMT	0	0.5	0	2	2.2	0	0	2	2	0	9	0
Si-Thiol	0 (13)*	1.1	0	2	1.5	0 (4)*	0	4	0	0	0	1 (13)**
Si-TMT	0	1.3	0	4	2.4	3	0	1	0	0	0	2
SCX-2	0	0.6	0	2	1.2	3	0	2	0	0	0	0
Si-Trisamine	0	0.7	0	2	1.2	0	0	0	0	0	0	1

* Competitor S
** Competitor P

Trace element/native metal scavengers (ppm by ICP). Biotage metal scavengers are clean and consistently contain the lowest native trace metal content.

User Study: Metal Scavenger Supporting GLP/GMP Compliant API Manufacturing

Mr. Toshio Fujiwara is head of Process Chemistry at CMC Research & Development Department, Discovery Research Laboratories. Nippon Shinyaku Co., Ltd use Biotage metal scavengers to archive metals mitigation management according to GLP and GMP. The purpose of the metal scavenger is to control residual metals such as palladium, which are difficult to remove from the API by other methods.

We had an opportunity to talk with Mr Fujiwara about his work and company. He added "Primarily, my role is to develop a synthetic process for pipeline compounds from exploratory studies. We are aiming to establish an efficient, inexpensive and safe synthetic approach in accordance with the production scale. I also supply drug samples for GLP studies and clinical studies, which are required for drug development. After elucidation of the chemical structure of the candidate compound, I participate in a project that involves GLP studies, clinical studies and finally registration application over a long period of time."

— So what is the role of metal scavenging in your work?
"In supplying samples for clinical studies, its production should be done according to the GMP Guide for APIs and a quality level as prescribed by the Guide should be attained. This is especially important for medicinal products that are produced by a coupling reaction (i.e. Suzuki-Miyaura coupling) using such metals as palladium. Therefore, residual metals should be strictly controlled in the final drug substance. Metal scavengers are considered to be one of the removal methods for this purpose."

— Are there any other removal methods?
"We usually use removal methods involving extraction or crystallization. However, the characteristics of the target chemical may prevent its removal. In such cases, we need to use a reagent such as metal scavenger."

— I see. So, can you tell me how you have employed Biotage's metal scavenger?
"Actually, the candidate compound contains a nitrogen heterocyclic ring and the ring is coordinated with nitrogen and palladium, thus making removal difficult. We could not remove the residual metals with extraction or crystallization. In addition, we have searched for an effective method to remove the residual metals because a coupling reaction using palladium is performed before the final purification process due to the synthetic approach of this chemical compound."

— That sounds like a real technical challenge?
"Surely it was, but then, I heard about the metal scavenger kit of Biotage AB. Since this kit shows specificities for compounds, various evaluations were performed for each of the 5 types of scavengers included in the kit under a wide variety of solvents and temperature conditions. Of course, we tested other makers' products, but Si-Thiol of Biotage AB gave the best results in terms of removal rate. Furthermore, we can place a large order in bulk to respond to demands for a larger scale production. That was the deciding factor. Recently, the speed in developing new drugs has been emphasized; therefore, a response to a scale-up in production is important."

— You considered the adoption of Si-Thiol for the first time around 2009.
"Yes. After considering and choosing Si-Thiol, we have proceeded with GLP/GMP productions and the API process is going well. A production scale of tens of kg gave the same results as the smaller production scale. There is no problem."

— What do you feel is the advantage of metal scavengers after using it in real situations?
"When we first considered palladium removal methods, we bought the screening kit first. There was a moderate number of scavengers packaged in this kit. Too many scavengers would make finding optimal conditions difficult because we must consider solvent conditions among other factors. Moreover, for those working in the process chemistry field, it is a great advantage that these metal scavengers can be supplied at a bulk scale."

— Lastly, we would be grateful if you could provide us with your future plan.
"Since we achieved satisfactory results in this research project, I am sure the metal scavenger of Biotage will be our first choice when working on a future project in which palladium removal can be problematic. Of course, for any future production involving the candidate compounds used in this project, we will continue to use the product as well."

Read More

The full article "Metal Scavenger Supporting GLP/GMP-compliant API Manufacturing" is available on www.biotage.com.

Supported Reagents and Scavengers

Enhancing Chemistry

Supported Reagents and Scavengers

An Introduction

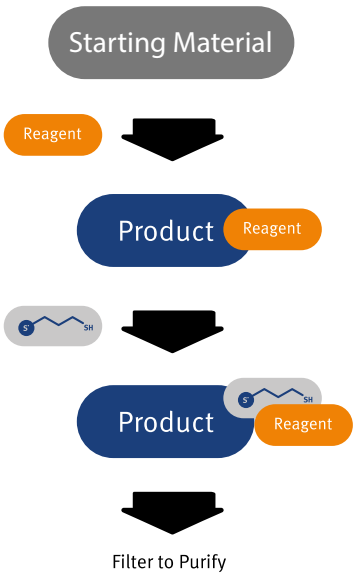
Polymer supported chemistry is well documented in the literature and has been used widely in industrial applications for over fifty years. Biotage supported reagents and scavengers are based on functionalized polystyrene or silica polymers. They are inert, specifically-reactive and clean additives deployed to achieve a specific purpose.

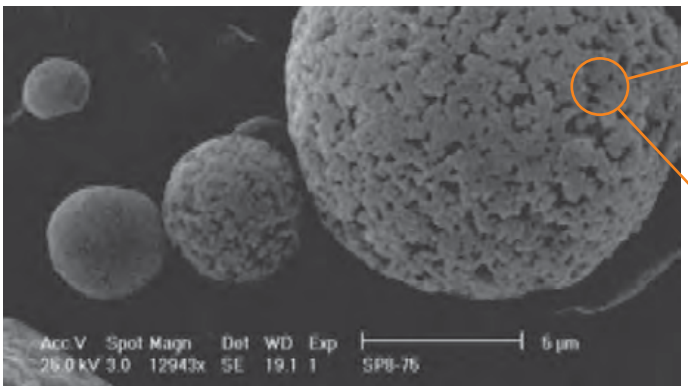
Their application is very simple:

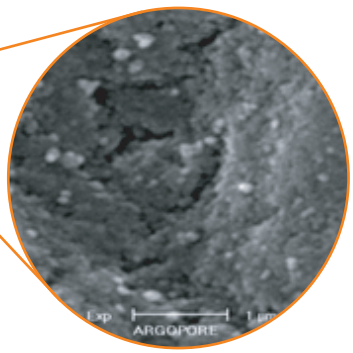
1. Add resin/silica to reaction
2. Stir for desired time
3. Filter as usual to purify

... or pack them into columns and flow through for fixed-bed applications.

There are numerous applications – from reaction clean-up to catalysis, from catch and release purification to solvent switching, or from reagent delivery to trace transition metal removal from APIs.

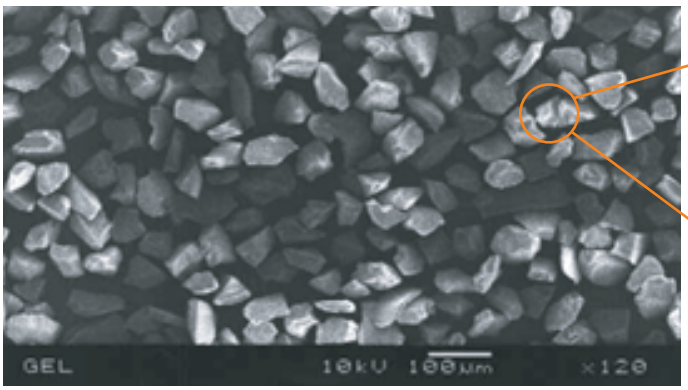


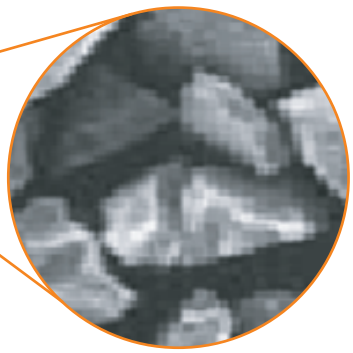




Electron micrograph of MP-TMT resin particle.

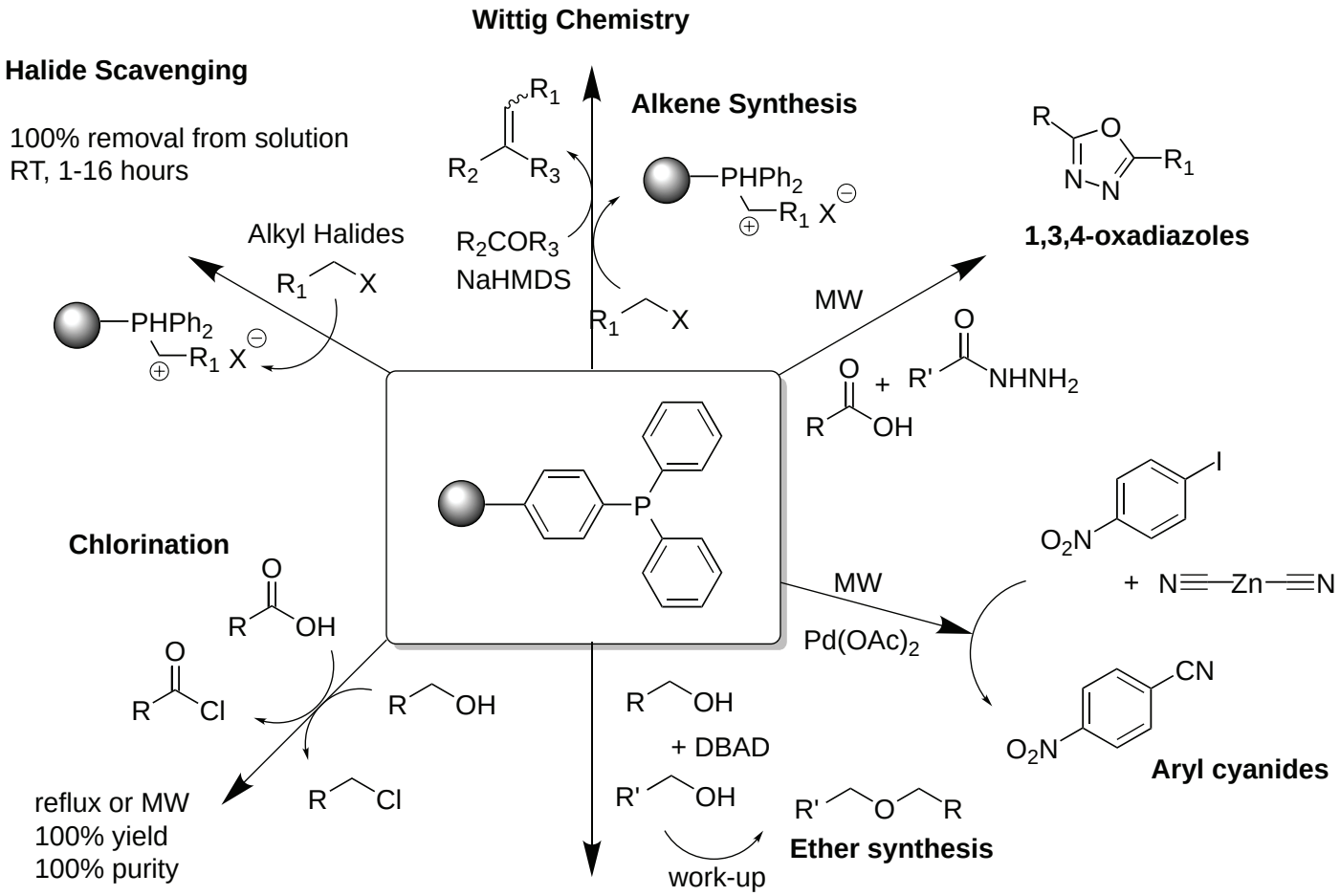
- Insoluble, cross-linked polystyrene
- Spherical 50–1000 µm diameter
- Formal pore structure
- Excellent diffusion and mass transport properties





Electron micrograph of Si-TMT particle.

- Surface orientated chemistry
- Robust 60 µm particles
- Insoluble



Difficult by-product triphenylphosphine oxide stays 100% resin bound and now can be removed by simple more convenient low-tech filtration methods.

Efficient Delivery to Reactions

Polymer supported reagents are functionalized polymers that perform synthetic transformations in a similar manner to their small molecule, non-bound counterparts, however, they provide the added advantage of heterogeneity, meaning that they are very easy to remove from reactions afterwards for example by simple filtration techniques.

Non-Toxic, No Smells and Easier To Handle

Once bound to the resin (or silica) there vapor pressure of volatile or toxic reaction components is virtually eliminated so bound resins and silica scavengers are especially good for capturing compounds such as isocyanates, or nucleophilic amines/anilines.

Reduce Processing Steps and Mitigate Impurity Risks

Even if by-products are not toxic or do not have a stench, they may still be difficult to separate, co-elute, or mask other target products in a mixture. PS-Triphenylphosphine resin for example performs the chemistry you would expect, but the PS-Triphenylphosphine oxide by-product is 100% resin bound, and is thus easily removed by filtration afterwards. No more issues with large UV signals masking the intended product, giving false reaction performance indicators.

Similarly the dicyclohexylurea urea by-product from PS-Carbodiimide resin coupling reactions is also 100% resin bound and can never interfere with products in solution and further downstream reactions.

Drive Reactions With Excess Reagent/Scavenger

Adding more reagents will drive a reaction to completion, but the excess reagents will need to be separated afterwards, involving additional purification steps. With a resin bound strategy, the resin (or silica) supported reagent is heterogeneous, it does 'see' the solution, but it is completely insoluble, so removing excess after the reaction is just a case of filtering using simple and inexpensive laboratory items.

Re-cycle and Re-use

Being easy to recover after a reaction, many resins and supported products are also additionally compliant with the principles of green chemistry, by being recyclable or operating in a catalytic mode. While many resins are used once, for reasons of industry preference or regulation, Biotage can support clients who need guidance on how to re-use, by providing technical guidance.

Making the Impossible – Possible

Resins and silicas are heterogeneous, meaning that we can lock away products and completely selectively release them later (or lock away by-products, and only let product through). Processes that are energy and labor intensive, such as solvent switching, can be achieved in a matter of seconds at room temperature and at normal atmospheric pressure. High boiling point solvents such as DMF and DMSO can be removed from amine mixtures and replaced with more volatile solvents.

Thermally and Mechanically Stable

Resin reagents or scavengers work well with overhead stirring or mechanical shaking. They withstand temperatures up to approx. 150 °C (i.e. microwave chemistry heating conditions). Silica supported reagents and scavengers are mechanically stable, and may also be stirred but are more often packed into fixed bed formats for flow through applications. Silicas can withstand 150–200 °C temperatures, so as long as the intended chemistry is compatible, the resin or silica option is an efficient delivery vehicle for the chemistry of the project.

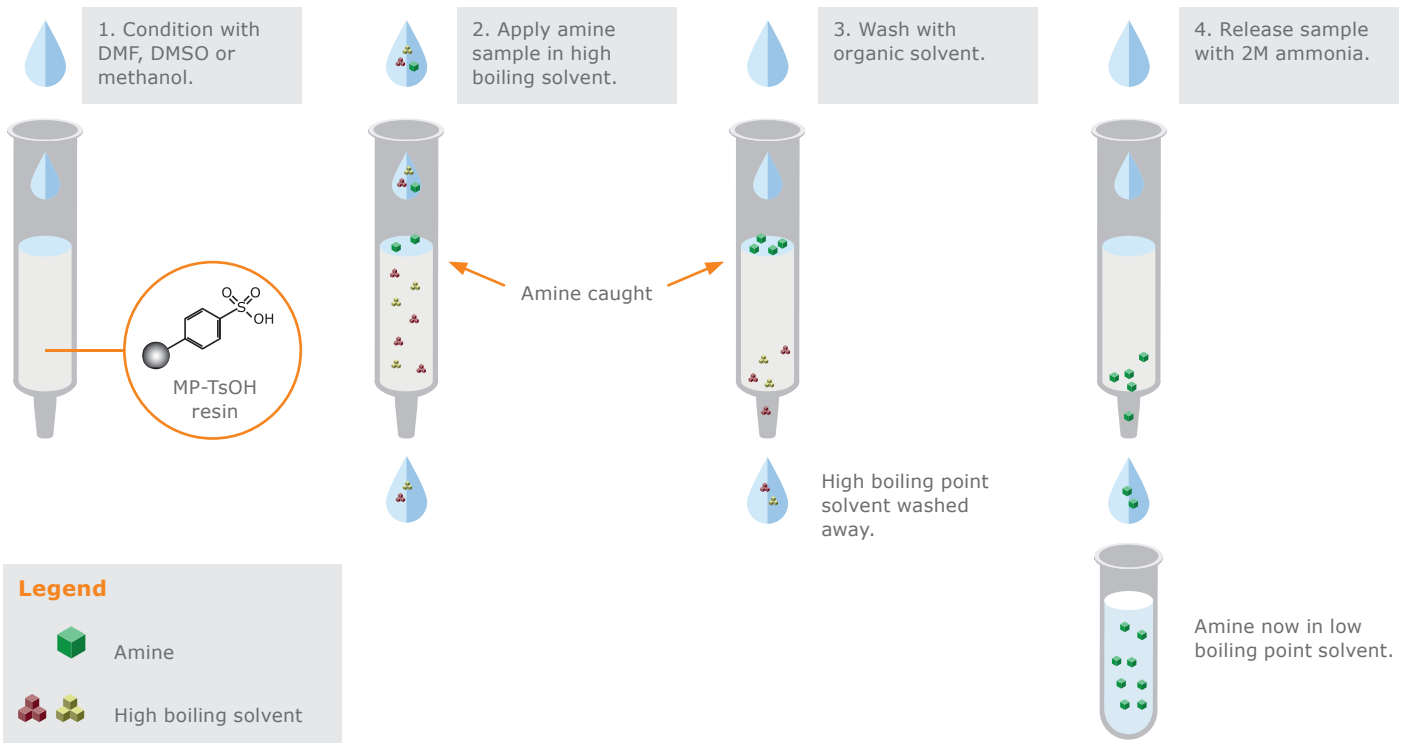
Scale-Up and Formats

Additionally, Biotage has a flexible cartridge packing facility to accommodate many scale-up paths and options, from grams to multi-kg and in a variety of formats for processing.

Long Shelf Life

Polymer supported reagents and scavengers are stable. By definition they only take part in the reactions they were designed for, so side reactions and degradation is much less of an issue compared to small molecule chemistry. In real terms the shelf-life of a functionalized polymer may be indefinite, so we recommend a nominal 1 year expiry when the product is stored in cool dry conditions.

High Boiling Point Removal



Application Guide

	Scavengers						Reagents								
	MP-Carbonate	MP-TsOH/SCX 2	MP-Trisamine	PS-Isocyanate/ MP-Isocyanate	PS-Benzaldehyde	PS-$TsNHNH_2$	PS-Carbodiimide	PS-HOBt	PS-PPh_3-Pd	PS-TEMPO	PS-PPh_3	PS-TBD	MP-Borohydride	MP-Cyano-borohydride	MP-Triacetoxy borohydride
Amide Synthesis							✓	✓							
C-C Bond Formation: Suzuki, Still, Sonagashira									✓						
Reaction Quenching: Removing Nucleophiles				✓	✓										
Reaction Quenching: Removing Electrophiles			✓			✓									
Wittig, Mitsunobu, Alkylation											✓				
Oxidation							✓			✓					
Solvent Switching/Acid Base	✓	✓													
Reduction/Reductive Amination													✓	✓	✓
Halogenation											✓				
Etherification												✓			

Summary of applications for Biotage supported reagents and scavengers. Each resin is supported by full instructions for use and a technical application note. For highlights, please first refer to the summary overview at the end of this section on page 32.

Detailed Scavenger Selection Guide

	Suggested Scavenger						
What to remove	**MP/PS-Isocyanate**	**MP-Carbonate**	**PS-Benz-aldehyde**	**PS-$TsNHNH_2$**	**Si/MP-Trisamine**	**SCX-2/ MP-TsOH**	**PS-TBD**
Acids		✓✓		✓✓	✓		✓
Acid Chlorides				✓	✓✓		
Acidic Phenols		✓		✓✓	✓		✓
Alcohols*	✓✓						
Aldehydes				✓	✓		
Alkoxides	✓						
Amino Acids		✓			✓✓	✓	✓✓
Anhydrides				✓	✓		
Anilines	✓✓		✓✓			✓	
Boronic Acids		✓		✓✓	✓		✓
Carboxylic Acids		✓✓		✓✓	✓		✓
Chloroformates				✓	✓		
Heterocycles			✓✓			✓	
Hydrazines	✓✓		✓			✓	
Isocyanates				✓	✓		
Isothiocyanates				✓	✓✓		
ketones				✓	✓		
Organometallics	✓		✓✓				✓✓
Sulfonyl Chlorides				✓	✓		
Thionyl Chlorides				✓	✓		
Thiolates	✓✓						

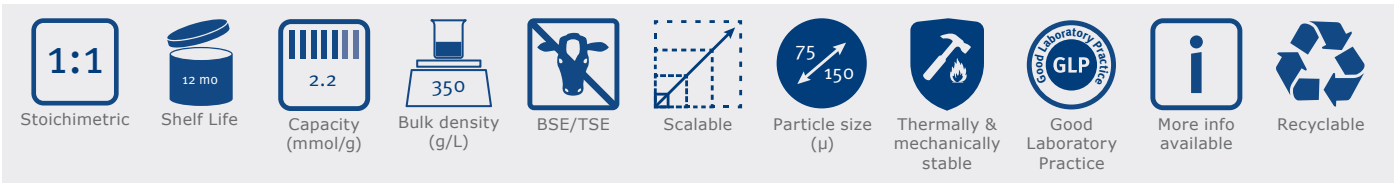
✓✓ Best choice ✓ Secondary choice
* Requires 1 equivalent of soluble base.

Examples of application areas and uses for Biotage scavengers, with primary suggestions.

Supported Reagents and Scavengers Overview

For Full Details Please See Individual Product Technical Notes

Legend



Supported Reagents

Biotage® PS-Carbodiimide

Technical Note: PPS402

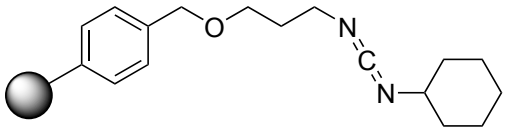
Applications: Coupling agent for amide and ester synthesis, formation of pentafluorophenyl (PFP) and other activated esters.

Typical Conditions: Add 2 equiv. (equivalents) of resin, 1.5 equiv. of acid, 1.0 equiv. of amine in DCM at RT.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DCM (7.0 mL/g), DCE (6.9 mL/g), THF (6.5 mL/g), DMF (4 mL/g) and other organic aprotic solvents that swell polystyrenes

Part Numbers: 800369 (10 g); 800370 (25 g); 800371 (100 g); 800372 (1000 g); 800508 (3 g sample)



Biotage® PS-HOBt(HL)

Technical Note: PPS393

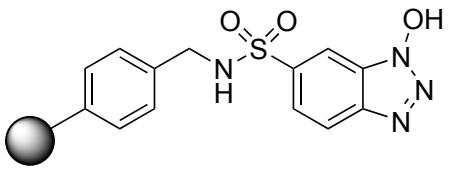
Applications: Active ester formation, coupling of acids and amides, protecting group (Fmoc, CBz, Boc) transfer.

Typical Conditions: 1.5 equiv. of carboxylic acid, 4.5 equiv. of DIC, 0.6 equiv. of DMAP in a 4:1 DCM/DMF solvent mixture for 2 hours, catalytic HOBt.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DMF (7.5 mL/g), THF (4.8 mL/g), DCM (3.0 mL/g)

Part Numbers: 800417 (10 g); 800418 (25 g); 800419 (100 g); 800420 (1000 g); 800509 (3 g sample)



Biotage® RGT PS-PPh_3-Pd

Technical Note: PPS401

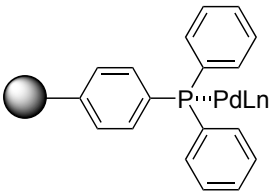
Applications: Catalyst for Suzuki, Sonogashira, Stille, Buchwald-Hartwig, Negishi.

Typical Conditions: Various, for example 0.5 mol% catalyst, 16 hours, 75 °C.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DMF (3.5 mL/g), THF (4.1 mL/g), DCM (4.9 mL/g)

Part Numbers: 800473 (1 g sample); 800474 (10 g); 800475 (25 g); 800476 (100 g)



Biotage® PS-TEMPO

Technical Note: PPS388

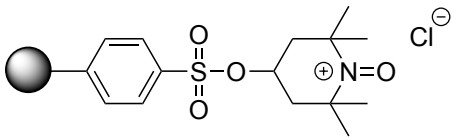
Applications: Catalytic or stoichiometric oxidation of a variety of alcohols.

Typical Conditions: 3 equiv. N-Chloro-succinimide and 3 equiv. HCl/dioxane swirled with 0.5 g PS-TEMPO for 10 min. The resin is filtered, washed and used directly. Add 2.5 equiv. of activated PS-TEMPO to alcohol.

Polymer Type: PS (Gel)

Compatible Solvents: Dichloromethane (DCM), Dichloroethane (DCE), THF, N,N-Dimethylformamide (DMF), Dioxane, Toluene, nonalcoholic solvents

Part Numbers: 800520 (10 g); 800521 (25 g); 800522 (100 g); 800523 (1000 g); 800524 (3 g sample)



Biotage® PS-Triphenylphosphine

Technical Note: PPS389

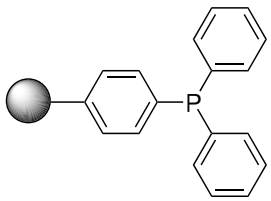
Applications: Wittig, Mitsunobu, chlorination of acids and alcohols, scavenging of alkyl halides.

Typical Conditions: Mitsunobu – 1.0 equiv. of alcohol, 1.5 equiv. of phenol, 2.2 equiv. of resin, 1.5–2 equiv. of DEAD or DIAD, stir at RT. Wittig – 2 equiv. of ylide resin, 8 equiv. of NaHMDS/THF, wash resin with THF, add 1.0 equiv. carbonyl compound in THF at RT.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DMF (3.5 mL/g), THF (4.1 mL/g), DCM (4.9 mL/g), benzene (3.1 mL/g)

Part Numbers: 800378 (10 g); 800379 (25 g); 800380 (100 g); 800381 (1000 g); 800510 (3 g sample)



Biotage® PS-TBD

Technical Note: PPS382

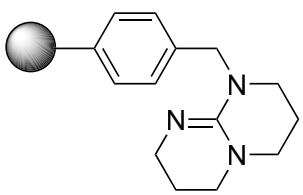
Applications: Alkylation of phenols and amines; esterification of carboxylic acids, alkylation of active methylene compounds, dehalogenation of organic halides, Williamson ether synthesis.

Typical Conditions: Add 2–3 equiv. of resin relative to the limiting reagent or acid species. Form on resin enolate, wash resin and add sub stoichiometric electrophile to complete the high purity displacement of product form the resin. Can be heated to accelerate.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DCM (7.6 mL/g), DMF (3.5 mL/g), THF (6.6 mL/g), MeOH (6.6 mL/g), MeCN (2.5 mL/g)

Part Numbers: 800421 (10 g); 800422 (25 g); 800423 (100 g); 800424 (1000 g); 800513 (3 g sample)



Biotage® MP-Borohydride

Technical Note: PPS390

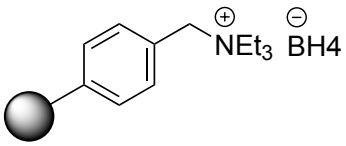
Applications: Reduction of carbonyl compounds, azides and oximes, reductive amination, reduction of conjugated enones to unsaturated alcohols.

Typical Conditions: 1.0 mmol carbonyl compound in EtOH or MeOH plus 0.5mmol of MP-BH_4 resin stirred at RT for 1–16 hours. Products isolated by filtration to remove the resin.

Polymer Type: MP (macroporous) resin

Compatible Solvents (Swelling Data): THF (2.9 mL/g), DCM (3.4 mL/g), MeOH (3.4 mL/g), DMF (2.9 mL/g)

Part Numbers: 800401 (10 g); 800402 (25 g); 800403 (100 g); 800404 (1000 g); 800512 (3 g sample)



Biotage® MP-Cyanoborohydride

Technical Note: PPS392

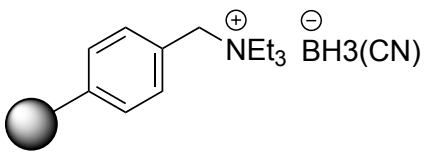
Applications: Reductive amination, reductive methylation of primary and secondary amines, reduction of imines, reduction of conjugated enones to unsaturated alcohols.

Typical Conditions: Add 2–3 equiv. of the scavenger relative to the acid chloride, 1–4 hours, 20 °C. If there is an additional resin bound base present (i.e. cocktail methodology), the number of equiv. can be decreased 50%. Can be heated to accelerate scavenging.

Polymer Type: MP (Macroporous) resin

Compatible Solvents (Swelling Data): THF (2.9 mL/g), DCM (3.4 mL/g), MeOH (3.4 mL/g), DMF (2.9 mL/g)

Part Numbers: 800405 (10 g); 800406 (25 g); 800407 (100 g); 800408 (1000 g); 800511 (3 g sample)



Biotage® MP-Triacetoxyborohydride

Technical Note: PPS391

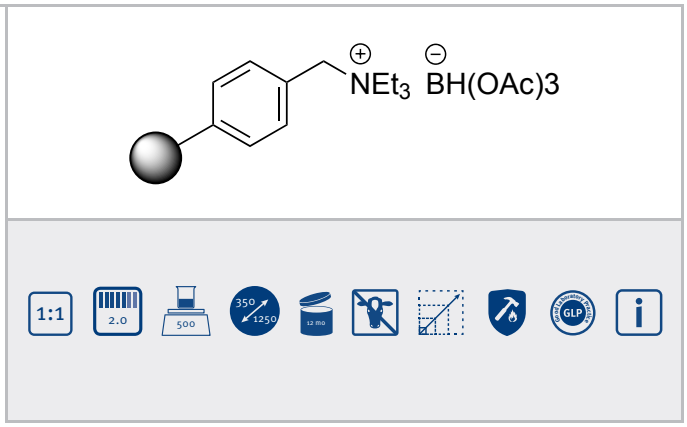
Applications: Reductive amination with primary or secondary amines.

Typical Conditions: 1.0 mmol of carbonyl compound, 1.2 mmol of amine in THF, 2.5 mmol of resin, stir 1–16 hours at RT. PS-Benzaldehyde or PS/MP-Isocyanate can be added afterwards to scavenge amine. Filter to remove resin.

Polymer Type: MP (Macroporous) resin

Compatible Solvents (Swelling Data): THF (2mL/g), DMF (2mL/g), NMP (2mL/g)

Part Numbers: 800413 (10 g); 800414 (25 g); 800415 (100 g); 800416 (1000 g); 800517 (3 g sample)



Supported Scavengers

Biotage® MP-TsOH

Technical Note: PPS398

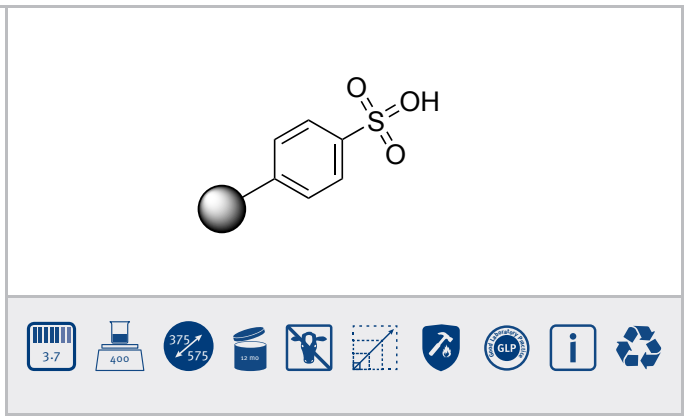
Applications: Catch and release purification of amines, solvent switch, acid catalysis.

Typical Conditions: 2–3 equiv. of resin compared to amine, wash, release with 2M methanolic ammonia. The silica form can also be packed into a column and used in a flow through format.

Polymer Type: MP (Macroporous) resin

Compatible Solvents (Swelling Data): DCM (3.0 mL/g), THF (3.1 mL/g), DMF (3.1 mL/g), MeOH (3.1 mL/g)

Part Numbers: 800461 (10 g); 800462 (25 g); 800463 (100 g); 800464 (1000 g); 800498 (3 g sample)



Biotage® MP-Carbonate

Technical Note: PPS386

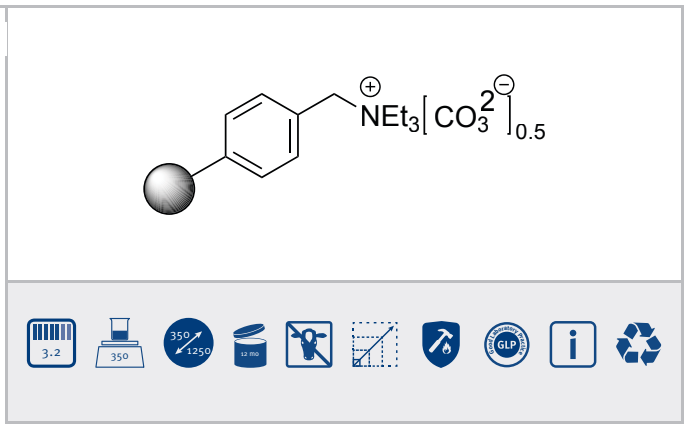
Applications: General base, ammonium or TFA salt neutralization, scavenging acids and acidic phenols.

Typical Conditions: 3 equiv relative to substrate, 0.5–2 h, 20 °C ammonia. The silica form can also be packed into a column and used in a flow through format.

Polymer Type: MP (Macroporous) resin

Compatible Solvents (Swelling Data): DCM (3.0 mL/g), DCE (3.0 mL/g), THF (3.0 mL/g), THF (2.8 mL/g), DMF (2.9 mL/g), EtOH

Part Numbers: 800267 (10 g); 800268 (25 g); 800269 (100 g); 800314 (1000 g); 800493 (3 g sample)



Biotage® MP-Trisamine

Technical Note: PPS405

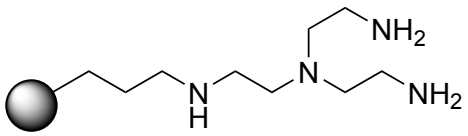
Applications: Scavenging of acid chlorides, sulfonyl chlorides isocyanates and other electrophiles. May also be used as a transition metal scavenger.

Typical Conditions: Add 2–3 equiv. of the scavenger relative to the acid chloride, 1–4 hours, 20 °C. If there is an additional resin bound base present (i.e. cocktail methodology), the number of equiv. can be decreased 50%. Can be heated to accelerate scavenging.

Polymer Type: MP (Macroporous) resin

Compatible Solvents (Swelling Data): DCM (3.9 mL/g), DMF (‹4.5 mL/g), THF (3.7 mL/g), MeOH (3.8 mL/g), water (4.0 mL/g)

Part Numbers: 801397 (10 g); 801398 (25 g); 801399 (100 g); 801400 (1000 g); 801505 (3 g sample)



Biotage® PS-TsNHNH$_2$

Technical Note: PPS403

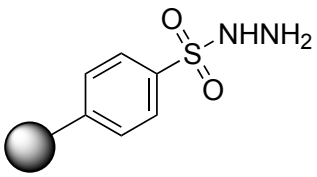
Applications: Scavenging aldehydes and ketones

Typical Conditions: Add 2–3 equiv. relative to the excess electrophile. Organic solvents, 1–16 hours at RT. May be heated to accelerate.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DCM (7mL/g), DCE (7mL/g), THF (6.5mL/g), DMF (7.2mL/g)

Part Numbers: 800270 (10 g); 800271 (25 g); 800272 (100 g); 800317 (1000 g); 800497 (3 g sample)



Biotage® PS-Benzaldehyde

Technical Note: PPS404

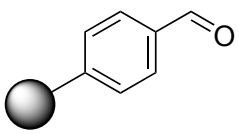
Applications: Scavenging nucleophiles including primary amines, hydrazines and reducing agents. Scavenging primary amines in the presence of secondary amines.

Typical Conditions: Add 2–3 equiv. relative to the excess nucleophile. Organic solvents, 1–16 hours at RT. May be heated to accelerate.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DCM (8.1 mL/g), DCE (7.4 mL/g), THF (7.3 mL/g), toluene (7.0 mL/g)

Part Numbers: 800360 (10 g); 800361 (25 g); 800362 (100 g); 800363 (1000 g); 800502 (3 g sample)



Biotage® PS-Isocyanate

Technical Note: PPS400

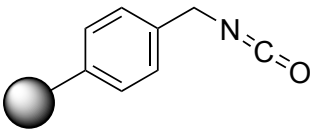
Applications: Scavenging nucleophiles including primary amines, hydrazines and reducing agents.

Typical Conditions: Add 2–3 equiv. relative to the excess nucleophile. Organic solvents, 1–16 hours at RT. May be heated to accelerate.

Polymer Type: PS (Gel)

Compatible Solvents (Swelling Data): DCM (4.5 mL/g), DMF (‹4.5 mL/g), THF (4.7 mL/g), MeOH (3.9 mL/g), water (4.7 mL/g)

Part Numbers: 800495 (3 g sample), 800260 (10 g); 800261 (25 g); 800262 (100 g); 800311 (1000 g)



Biotage® MP-Isocyanate

Technical Note: PPS399

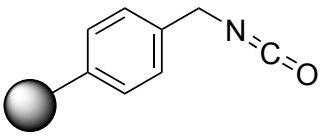
Applications: Scavenging nucleophiles including primary amines, hydrazines and reducing agents.

Typical Conditions: Add 2–3 equiv. relative to the excess nucleophile. Organic solvents, 1–16 hours at RT. May be heated to accelerate.

Polymer Type: MP (macroporous) resin

Compatible Solvents (Swelling Data): DCM (4.5 mL/g), DMF (‹4.5 mL/g), THF (4.7 mL/g), MeOH (3.9 mL/g), water (4.7 mL/g)

Part Numbers: 801504 (3 g sample), 801409 (10 g); 801410 (25 g); 801411 (100 g); 801412 (1000 g)



MIPs

Molecularly Imprinted Polymers

Resin Development Service

Development of Custom Designed Selective Resins

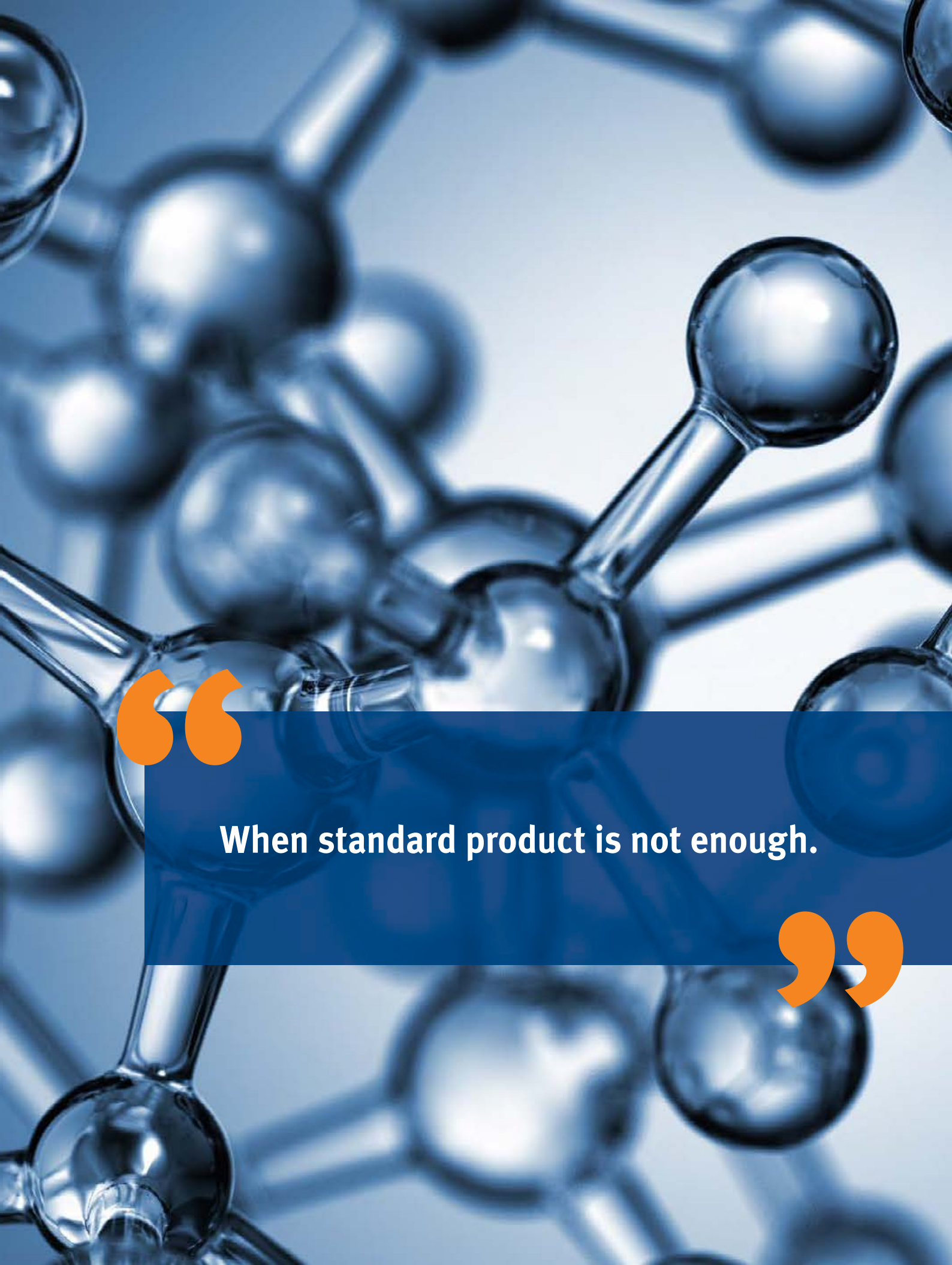
For more demanding applications or when off the shelf scavenging solutions won't work, MIP Technologies (a subsidiary of Biotage) – a high-tech company specializing in novel and tailor-made polymeric resins for targeted separation may hold the answer.

MIP Technologies has a large library of polymers which can be screened for specific activities, and has the capacity to develop custom resins for individual applications. Using powerful screening and identification methods, a candidate often emerges from our resin bank. The matching procedure is a three-step approach:

1. Screening MIP internal library of resins (chosen from >2500 candidates)
2. Optimize found resin hits from screening
3. Scale-up and transfer methods to customer

For further details of this service please see "Development of Custom Designed Selective Resins By MIP Technologies" (PPS346).

MIP Technologies also offers a series of unique RENSA® polymeric resins. For more information please refer to the the brochure "RENSA, Polymeric Resin Guide" (PPS396) at www.biotage.com


When standard product is not enough.

Ordering Information

Large Scale Flash Systems

Description	Part Number	Qty.
Package, Flash 75Mi	SF-022-19041	1
Package, Flash 75Li	SF-022-19071	1
Package, Flash 150Mi	SF-022-25071	1
Package, Flash 150Li	SF-022-25151	1
Final Assembly Flash 400 M with Hoist System	SF-521-50070	1
Final Assembly Flash 400 L with Hoist System	SF-521-50150	1

Large Scale Cartridges

Description	Part Number	Qty.
Normal Phase - KP-Sil		
Cartridge KP-Sil Flash 75M	FK0-1107-19045	2
Cartridge KP-Sil Flash 75L	FK0-1107-19075	2
Cartridge KP-Sil Flash 150M	FK0-1107-25075	2
Cartridge KP-Sil Flash 150L	FK0-1107-25155	2
Cartridge KP-Sil Flash 400M	FK0-1107-50070†	1
Cartridge KP-Sil Flash 400L	FK0-1107-50150†	1
Normal Phase - KP-Sphere™		
Flash 75M with KP-Sphere	F75M-0445-19045	2
Flash 75L with KP-Sphere	F75L-0445-19075	2
Flash 150M with KP-Sphere	F150M-0445-25075	2
Flash 150L with KP-Sphere	F150L-0445-25155	2
Flash 400M with KP-Sphere	F400M-0445-50070	1
Flash 400L with KP-Sphere	F400L-0445-50150	1
Normal Phase - HP-Sphere™		
Flash 75M Ultra	F75M-0442-19045	2
Flash 75L Ultra	F75L-0442-19075	2
Flash 150M Ultra	F150M-0442-25075	2
Flash 150L Ultra	F150L-0442-25155	2
Flash 400M with HP-Sphere	F400M-0442-50070	1
Flash 400L with HP-Sphere	F400L-0442-50150	1
Normal Phase - KP-NH		
Cartridge KP-NH Assembly Flash 75M	FPNH-75M	1
Cartridge KP-NH Assembly Flash 75L	FPNH-75L	1
Cartridge KP-NH Assembly Flash 150M	FPNH-150M	1
Cartridge KP-NH Assembly Flash 150L	FPNH-150L	1
Cartridge KP-NH Assembly Flash 400M	FPNH-400M	1
Cartridge KP-NH Assembly Flash 400L	FPNH-400L	1
Reversed Phase - KP-C18-HS		
Cartridge, KP-C18-HS Flash 75M	FL0-1118-19040	1
Cartridge, KP-C18-HS Flash 75	FL0-1118-19070	1
Cartridge, KP-C18-HS Flash 150M	FL0-1118-25070	1
Cartridge Assembly, KP-C18-HS Flash 150L	FL0-1118-25150	1
Cartridge KP-C18-HS FLASH 400M	FL0-1118-50070	1
Cartridge Assembly, KP-C18-HS Flash 400L	FL0-1118-50150	1
Reversed Phase/Other - HP20		
Cartridge HP-20 Flash 75M	FT6-2030-19045	2
Cartridge HP-20 Flash 75L	FT6-2030-19075	2
Cartridge HP-20 Flash 150M	FT6-2030-25075	2
Cartridge HP-20 Flash 150L	FT6-2030-25155	2
Reversed Phase/Other - HP20ss		
Cartridge HP-20-SS Flash 75	FT6-2530-19040	1
Cartridge HP-20-SS Flash 75L	FT6-2530-19070	1
Cartridge HP-20-SS Flash 150M	FT6-2530-25070	1
Cartridge HP-20-SS Flash 150L	FT6-2530-25150	1
Adsorbtion - Carbon		
FLASH-WAC 75M	C1YR-4021-19043	10
FLASH-WAC 75L	C1YR-4021-19073	10
FLASH-WAC 150M	C1YR-4021-25075	2
FLASH-WAC 150L	C1YR-4021-25155	2
FLASH-WAC 400M 13 kg WAC Cartridge	C1YR-4021-50075	2
FLASH-WAC 400L 26 kg WAC Cartridge	C1YR-4021-50155	2

Accessories

Description	Part Number	Qty.
Compression Modules		
FLASH 75Mi Radial Compression Module	FC-022-19041	1
FLASH 75Li Radial Compression Module	FC-022-19071	1
FLASH 150Mi Radial Compression Module	FC-022-25071	1
FLASH 150Li Radial Compression Module	FC-022-25151	1
FLASH 75M Radial Compression Barrel	FB-012-19040	1
FLASH 75L Radial Compression Barrel	FB-012-19070	1
FLASH 150M Radial Compression Barrel	FB-012-25070	1
FLASH 150L Radial Compression Barrel	FB-012-25150	1
Barrel, Option Flash 400M	FB-012-50070	1
Barrel, Option Flash 400L	FB-012-50150	1
4 Litre Solvent Reservoir	FN-004-41201	1
12 Litre Solvent Reservoir	FN-012-41201	1
37 Litre Solvent Reservoir	FN-037-41200	1
60 Litre Solvent Reservoir	FN-060-41200	1
Valve, 3-Way injection valve for Flash 75/150 systems	FIV-VLV-1000	1
Grounding Kit	FGD-15075	1
Dry Loading Vessels		
Dry load vessel kit with holder and frits, 30 g	DLV-030	1
Dry load vessel kit with holder and frits, 70 g	DLV-070	1
Dry Load Vessel for Isolera LS with holder and frits	DLV-500	1
Dry load vessel cartridges with frits, 30 g	DLV-035	20
Dry load vessel cartridges with frits, 70 g	DLV-075	20
Empty dry load cartridges and frits	DLV-505	4

Description	Part Number	Qty.
Stainless steel Biotage SIM for Flash 75, 100 mL	SIM-0102	1
Stainless steel Biotage SIM for Flash 75, 500 mL	SIM-0502	1
Stainless steel Biotage SIM for Flash 150, 1000 mL	SIM-1002	1
Stainless steel Biotage SIM for Flash 150, 2000 mL	SIM-2002	1

Bulk Media

Description	Part Number	Qty.
KP-Sil BULK	K0-1107-05000	5 kg
KP-C18-HS BULK	L0-1118-00100	100 g
KP-C18-HS BULK	L0-1118-01000	1 kg
KP-C18-HS BULK	L0-1118-05000	5 kg
ISOLUTE FLASH NH2 BULK	9454-1000	1 kg
ISOLUTE HM-N, BULK	9800-1000	1 kg
ISOLUTE HM-N, BULK	9800-5000	5 kg

Metal Scavengers

Screening Kit

Metal Scavenging Toolkit - Resins	K-MS-2	1

MP-TMT

MP-TMT	801506	3 g
MP-TMT	801469	10 g
MP-TMT	801470	25 g
MP-TMT	801471	100 g
MP-TMT	801472	1 kg

Si-TMT

ISOLUTE Si-TMT	9538-0003	3 g
ISOLUTE Si-TMT	9538-0010	10 g
ISOLUTE Si-TMT	9538-0025	25 g
ISOLUTE Si-TMT	9538-0100	100 g
ISOLUTE Si-TMT	9538-1000	1 kg

Si-Thiol

ISOLUTE Si-Thiol	9180-0010	10 g
ISOLUTE Si-Thiol	9180-0025	25 g
ISOLUTE Si-Thiol	9180-0100	100 g
ISOLUTE Si-Thiol	9180-0500	500 g
ISOLUTE Si-Thiol	9180-1000	1 kg
ISOLUTE Si-Thiol	9180-5000	5 kg
ISOLUTE Si-Thiol	9180-10000	10 kg

Si-Trisamine

ISOLUTE Si-Trisamine	9495-0010	10 g
ISOLUTE Si-Trisamine	9495-0025	25 g
ISOLUTE Si-Trisamine	9495-0100	100 g
ISOLUTE Si-Trisamine	9495-0500	500 g
ISOLUTE Si-Trisamine	9495-1000	1 kg

SCX-2

ISOLUTE Si-Propylsulfonic Acid (SCX-2)	9536-0010	10 g
ISOLUTE Si-Propylsulfonic Acid (SCX-2)	9536-0025	25 g
ISOLUTE Si-Propylsulfonic Acid (SCX-2)	9536-0100	100 g
ISOLUTE Si-Propylsulfonic Acid (SCX-2)	9536-0500	500 g
ISOLUTE Si-Propylsulfonic Acid (SCX-2)	9536-1000	1 kg

Supported Catalysts

PS-TEMPO

PS-Tempo	800524	3 g
PS-Tempo	800520	10 g
PS-Tempo	800521	25 g
PS-Tempo	800522	100 g
PS-Tempo	800523	1 kg

PS-PPh3-Pd

PS-PPh3-Pd	800473	1 g
PS-PPh3-Pd	800474	10 g
PS-PPh3-Pd	800475	25 g
PS-PPh3-Pd	800476	100 g

Supported Reagents

PS-Carbodiimide

PS-Carbodiimide	800508	3 g
PS-Carbodiimide	800369	10 g
PS-Carbodiimide	800370	25 g
PS-Carbodiimide	800371	100 g
PS-Carbodiimide	800372	1 kg

PS-HOBT(HL)

PS-HOBT(HL)	800509	3 g
PS-HOBT(HL)	800417	10 g
PS-HOBT(HL)	800418	25 g
PS-HOBT(HL)	800419	100 g
PS-HOBT(HL)	800420	1 kg

PS-Triphenylphosphine

PS-Triphenylphosphine	800510	3 g
PS-Triphenylphosphine	800378	10 g
PS-Triphenylphosphine	800379	25 g
PS-Triphenylphosphine	800380	100 g
PS-Triphenylphosphine	800381	1 kg

PS-TBD

PS-TBD	800513	3 g
PS-TBD	800421	10 g
PS-TBD	800422	25 g
PS-TBD	800423	100 g
PS-TBD	800424	1 kg

Description	Part Number	Qty.
MP-Borohydride		
MP-Borohydride	800512	3 g
MP-Borohydride	800401	10 g
MP-Borohydride	800402	25 g
MP-Borohydride	800403	100 g
MP-Borohydride	800404	1 kg
MP-Cyanoborohydride		
MP-Cyanoborohydride	800511	3 g
MP-Cyanoborohydride	800405	10 g
MP-Cyanoborohydride	800406	25 g
MP-Cyanoborohydride	800407	100 g
MP-Cyanoborohydride	800408	1 kg
MP-Triacetoxyborohydride		
MP-Triacetoxyborohydride	800517	3 g
MP-Triacetoxyborohydride	800413	10 g
MP-Triacetoxyborohydride	800414	25 g
MP-Triacetoxyborohydride	800415	100 g
MP-Triacetoxyborohydride	800416	1 kg
MP-TsOH		
MP-TsOH	800498	3 g
MP-TsOH	800461	10 g
MP-TsOH	800462	25 g
MP-TsOH	800463	100 g
MP-TsOH	800464	1 kg
MP-Carbonate		
MP-Carbonate	800493	3 g
MP-Carbonate	800267	10 g
MP-Carbonate	800268	25 g
MP-Carbonate	800269	100 g
MP-Carbonate	800314	1 kg

Description	Part Number	Qty.
MP-Trisamine		
MP-Trisamine	801505	3 g
MP-Trisamine	801397	10 g
MP-Trisamine	801398	25 g
MP-Trisamine	801399	100 g
MP-Trisamine	801400	1 kg
PS-TS-NHNH$_2$		
PS-TS-NHNH$_2$	800497	3 g
PS-TS-NHNH$_2$	800270	10 g
PS-TS-NHNH$_2$	800271	25 g
PS-TS-NHNH$_2$	800272	100 g
PS-TS-NHNH$_2$	800317	1 kg
PS-Benzaldehyde		
PS-Benzaldehyde	800502	3 g
PS-Benzaldehyde	800360	10 g
PS-Benzaldehyde	800361	25 g
PS-Benzaldehyde	800362	100 g
PS-Benzaldehyde	800363	1 kg
PS-Isocyanate		
PS-Isocyanate	800495	3 g
PS-Isocyanate	800260	10 g
PS-Isocyanate	800261	25 g
PS-Isocyanate	800262	100 g
PS-Isocyanate	800311	1 kg
MP-Isocyanate		
MP-Isocyanate	801504	3 g
MP-Isocyanate	801409	10 g
MP-Isocyanate	801410	25 g
MP-Isocyanate	801411	100 g
MP-Isocyanate	801412	1 kg

Notes

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