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28041-Madrid
tel.: 91 500 2060
e-mail: info@symta.com

Synthesis & Purification

CATALOG

Solid-bound Reagents

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Initiator Microwave Synthesis Systems

Biotage PathFinder

Scavenger Resins

ISOLUTE Columns and 96-Well Plates

Work-up Equipment

FLASH Purification Cartridges

FLASH-AC Activated-Carbon Cartridges

Isolera FLASH Purification Systems

FlashMaster II Purification System

V-10 Evaporation System

Discovery-scale FLASH Systems and Modules

Development-Scale FLASH Chromatography Systems

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Consumables and Accessories for Analytical Sample Preparation

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2008/09 Synthesis and Purification Product Catalog

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Blending Technology

Working together

Today pharmaceutical chemists throughout the world rely on Biotage products as part of their daily workflow. As the innovators of microwave synthesis technology and cartridge based flash purification, we have set the industry standard for speed, safety and ease-of-use. Data shows that chemists have performed more than 900,000 microwave syntheses and 1.7 million flash purifications using Biotage products.

As part of the Argonaut Business acquisition in June 2005, Biotage also acquired the International Sorbent Technology (IST) products, Argo resins and Jones Flash Chromatography instruments. This adds complimentary tools such as solid-bound reagents used in synthesis and work-up. International Sorbent Technology (IST) has long been a leading supplier of Sample Preparation Products. With a variety of sorbent chemistries and formats, IST sorbents deliver higher recoveries and purity.

Microwave synthesis, solid-bound scavengers and reagents along with cartridge based automated flash purification have significantly reduced the discovery-cycle time for new chemical entities (NCEs). From synthesis to purification Biotage offers a complete suite of synthetic organic tools that improve purity, yield and reproducibility.

Biotage products range from discovery through clinical trials and large-scale production. We offer application expertise and personal customer support, customizing solutions to meet the needs of customers. Biotage will continue providing new and innovative tools to meet today’s research and development challenges.

Customer Support and Service

1-Point Support™, The Answer to All Your Questions

Support and Service

Biotage technical engineers and application specialists, with years of preparative chromatography and synthesis experience, are fully prepared to assist you. Our customer support teams frequently work with industry and academic experts and attend conferences to continually develop their skills and knowledge, giving Biotage the unique ability to offer customized solutions in the following areas.

Training and Workshops

Biotage offers courses and seminars on improving synthesis, work-up, purification, evaporation, sample preparation and scale-up using Biotage systems and products. Course levels range from beginner to advanced and include hands-on training with samples supplied by the customer.

Application Support

We can assist you with difficult reactions and in converting traditional methods to microwave synthesis or scale-up protocols. Our work-up, purification and sample prep experts can help you maximize productivity and cost savings with tools and knowledge that speed and improve results. Our mission at Biotage is to offer superior products and service. Our broad support superstructure is available through a single point of contact, our 1-Point Support team.

Products and Plan Coverage

Biotage offers a comprehensive annual service plan that covers all parts, on-site labor and recommended preventative maintenance. Receive priority status on all service calls from specialized Biotage Field Service Engineers using genuine Biotage parts (essential for maintaining the instrument's highest performance).

Platinum Coverage

- Priority status (preferred response time of 3 days or less)
- On-site service (reduces instrument downtime)
- Unlimited labor, travel and parts
- 1 PM per instrument, which includes all PM parts designated for each individual systems
- Authorized Biotage service engineers and genuine Biotage parts
- In-house training seminars

Gold Coverage

- Unlimited labor and travel
- On-site service (reduces instrument downtime)
- 1 PM per instrument, which includes all PM* parts designated for each individual systems
- 25% Discount on all parts needed to complete a repair
- Authorized Biotage service engineers and genuine Biotage parts
- Preferred Response time of 3 days or less

*Parts outside the PM parts are NOT included with Gold Coverage

Customer Satisfaction and Convenience

Independent research consistently shows greater than 98% customer satisfaction with Biotage Service. By purchasing a Biotage Service contract you can lock-in and cap annual service costs to avoid any unexpected budget expenses and eliminate the "red tape" associated with generating a separate order for an "on-demand" service visit. Biotage systems with active service contracts get repaired 50% faster than units scheduled for "on-demand" service.

Great Value for your Investment with Multiple Biotage Systems

In addition to the standard 1-Point Support™ plan supplied with each Biotage system, we offer the option of further support designed to match the increased requirements at sites with numerous system and application demands.

Repair and Return Policy

Repair and Return Policy
Visit www.biotage.com to request service online

Before requesting service please have available:
1) Company Name
2) Contact Name
3) Contact Information
4) Product Type
5) Serial Number (if available)
6) A brief description of the symptoms or technical problems you are experiencing

Warranty Repair*
Units covered under warranty will be repaired for any fabrication failure at no charge. If you have any questions about the applicability, please contact your local 1-Point Support team.

Non-Warranty Repair
For out-of-warranty repairs, contact your local 1-Point Support team. A team member will discuss service options with you and assist in arranging the return of the equipment for repair or an on-site visit, if necessary. Biotage may utilize refurbished components when repairing units.

Return Procedure**
1. Contact your local Biotage 1-Point Support team to obtain a Return Material Authorization (RMA) number before returning any Biotage system.
2. Carefully pack the system to prevent damage in transit
3. Check with Biotage regarding proper method of shipment
4. Indicate the RMA number on the carton and on the packing slip

Always insure shipment for the replacement value of the system. Include a description of symptoms, your name, address, and telephone number, and a purchase order to cover repair costs, return and shipping charges, if your company requires it.

*See Terms and Conditions page 322

**Biotage assumes no responsibility for damage caused by improperly packaged units.

Contact Biotage
1-Point Support™

www.biotage.com
The Biotage Web site offers our customers easy access to current information on new products, applications, and events.

Europe
Service and Support
Telephone: +46 18 56 59 11
E-mail:
1-pointsupport@eu.biotage.com

Ship to: Biotage
RMA Number:
Kungsgatan 76
SE-753 18 Uppsala, Sweden

United States
Service and Support
Telephone: 1 800 446 4752
press (3) at the auto attendant
E-mail:
1-pointsupport@biotage.com

Ship to: Biotage
RMA Number:
1725 Discovery Drive
Charlottesville, VA 22911

Japan
Service and Support
Telephone: +81 422 28 1233
E-mail:
1-pointsupport@biotage.co.jp

Ship to: Biotage
RMA Number:
Medi Coop BLDG. 8 5F
2-4-14 Kichijojihoncho,
Musashinoshi
Tokyo, Japan 180-0004

All returns must include RMA number

Instrument Plans

Instrument Service Plans (Platinum)

Part Number	Type	Instrument	Labor	Travel	Parts	PathFinder	PMs
SER-SYN-PL	Platinum	Synthesizer	Y	Y	Y	Y	1
SER-LIB-PL	Platinum	Liberator	Y	Y	Y	Y	1
SER-CRE-PL	Platinum	Creator / EXP	Y	Y	Y	Y	1
SER-OPT-PL	Platinum	Optimizer / EXP	Y	Y	Y	Y	1
SER-IN1-PL	Platinum	Initiator / EXP	Y	Y	Y	Y	1
SER-IN8-PL	Platinum	Initiator 8 / 8 EXP	Y	Y	Y	Y	1
SER-I60-PL	Platinum	Initiator 60 / 60 EXP	Y	Y	Y	Y	1
SER-ADV-PL	Platinum	Advancer	Y	Y	Y	Y	1
SER-QU3-PL	Platinum	Quad 3	Y	Y	Y	N	1
SER-QUV-PL	Platinum	Quad UV	Y	Y	Y	N	1
SER-PIO-PL	Platinum	Pioneer	Y	Y	Y	N	1
SER-HOR-PL	Platinum	Horizon	Y	Y	Y	N	1
SER-FX2-PL	Platinum	2 Channel Flex	Y	Y	Y	N	1
SER-FX4-PL	Platinum	4 Channel Flex	Y	Y	Y	N	1
SER-FMX-PL	Platinum	4 Channel Flex MUX	Y	Y	Y	N	1
SER-PAR-PL	Platinum	Parallex	Y	Y	Y	N	1
SER-PMX-PL	Platinum	Parallex MUX	Y	Y	Y	N	1
SER-SP1-PL	Platinum	SP1	Y	Y	Y	N	1
SER-S4N-PL	Platinum	SP4 New	Y	Y	Y	N	1
SER-ACS-PL	Platinum	Advantage 3400 Complete System	Y	Y	Y	N	1
SER-ABS-PL	Platinum	Advantage 3400 Basic System	Y	Y	Y	N	1
SER-END-PL	Platinum	Endeavor	Y	Y	Y	N	1
SER-SUR-PL	Platinum	Surveyor	Y	Y	Y	N	1
SER-TRI-PL	Platinum	Trident	Y	Y	Y	N	1
SER-TWO-PL	Platinum	T-Workstation	Y	Y	Y	N	1
SER-FM2-PL	Platinum	FlashMaster II	Y	Y	Y	N	1
SER-FMS-PL	Platinum	FlashMaster Solo	Y	Y	Y	N	1
SER-Q05-PL	Platinum	Quest 205	Y	Y	Y	N	1
SER-Q05-PL	Platinum	Quest 210	Y	Y	Y	N	1
SER-AT2-PL	Platinum	Atlantis 2 Reactor System	Y	Y	Y	N	1
SER-AT4-PL	Platinum	Atlantis 4 Reactor System	Y	Y	Y	N	1
SER-AT5-PL	Platinum	Atlantis 5 Reactor System	Y	Y	Y	N	1
SER-AT6-PL	Platinum	Atlantis 6 Reactor System	Y	Y	Y	N	1
SER-V10-PL	Platinum	V-10	Y	Y	Y	N	1
SER-IS1-PL	Platinum	Isolera One	Y	Y	Y	N	1
SER-IS4-PL	Platinum	Isolera Four	Y	Y	Y	N	1

Instrument Plans & Ordering

Instrument Service Plans (Gold)

Part Number	Type	Instrument	Labor	Travel	Parts	PathFinder	PMs
SER-ACS-GLD	Gold	Advantage 3400 Complete System	Y	Y	N	N	1
SER-ABS-GLD	Gold	Advantage 3400 Basic System	Y	Y	N	N	1
SER-FM2-GLD	Gold	FlashMaster II	Y	Y	N	N	1
SER-FMS-GLD	Gold	FlashMaster Solo	Y	Y	N	N	1
SER-END-GLD	Gold	Endeavor	Y	Y	N	N	1
SER-SYN-GLD	Gold	Synthesizer	Y	Y	N	N	1
SER-CRE-GLD	Gold	Creator / EXP	Y	Y	N	N	1
SER-OPT-GLD	Gold	Optimizer / EXP	Y	Y	N	N	1
SER-IN1-GLD	Gold	Initiator / EXP	Y	Y	N	N	1
SER-IN8-GLD	Gold	Initiator 8 / 8 EXP	Y	Y	N	N	1
SER-I60-GLD	Gold	Initiator 60 / 60 EXP	Y	Y	N	N	1
SER-QU3-GLD	Gold	Quad 3	Y	Y	N	N	1
SER-QUV-GLD	Gold	Quad UV	Y	Y	N	N	1
SER-HOR-GLD	Gold	Horizon	Y	Y	N	N	1
SER-FX2-GLD	Gold	2 Channel Flex	Y	Y	N	N	1
SER-FX4-GLD	Gold	4 Channel Flex	Y	Y	N	N	1
SER-SP1-GLD	Gold	SP1	Y	Y	N	N	1
SER-SP4-GLD	Gold	SP4 New	Y	Y	N	N	1
SER-V10-GLD	Gold	V10	Y	Y	N	N	1
SER-IS1-GLD	Gold	Isolera One	Y	Y	N	N	1
SER-IS4-GLD	Gold	Isolera Four	Y	Y	N	N	1

How to Place Your Order

When placing your order please have available:

- Your purchase order number
- Biotage part number(s)
- Product description(s)
- Shipping address
- Billing address
- Contact person, including telephone number
- Product user name and department

Orders can also be placed using your VISA, Mastercard, or American Express account IN THE US ONLY.

North America
Main Office: +1 434 979 2319
Toll Free: +1 800 446 4752
Fax: +1 434 979 4743
Order Tel: +1 434 220 2687
Order Fax: +1 434 296 8217
ordermailbox@biotage.com

Europe
Main Office: +46 18 56 59 00
Fax: +46 18 59 19 22
Order Tel: +46 18 56 57 10
Order Fax: +46 18 56 57 05
order@eu.biotage.com

Spain - SYMTA, S.A.L.
Tel: +34 91 500 2060
Fax: +34 91 500 0045
info@symta.com

Prices and Specifications

Prices in the Biotage catalog are suggested list prices and are current at the time of the book's printing and are subject to change without notice. Specifications not listed in this catalog can be obtained by contacting Biotage Customer Service or your local distributor.

Published Microwave Reactions

Biotage Application Notes

Applications Corner

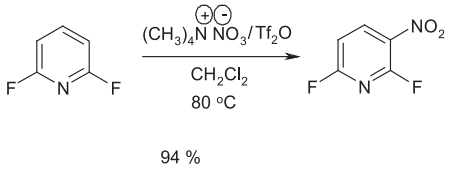
Application Notes and Index of Published Microwave Reactions

Applications Corner

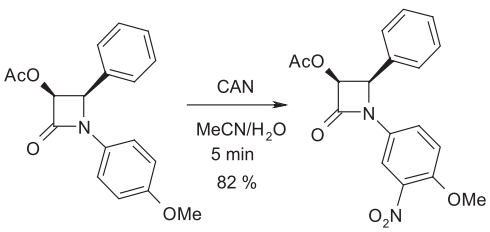
In this section, Biotage has hand selected published microwave reactions for your quick and easy reference. All chemistries listed were created using Biotage systems.

Solution-Phase Microwave Reactions

Nitration

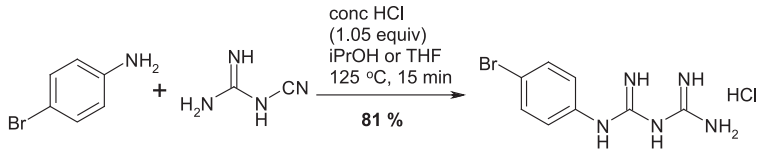


Shackelford, S. A. *et al. J. Org. Chem.* **2003**, 68, 267-275.



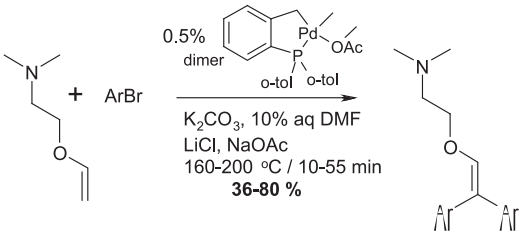
Bose, A. K. *et al. Synthesis*, **2002**, 1578-1591.

Amination

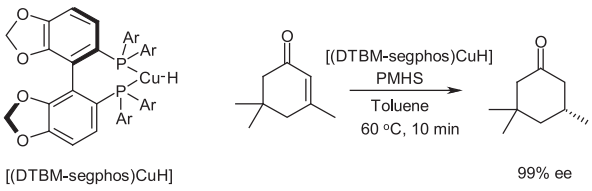


Organ, M.G. *et al. J. Combi. Chem.*, **2004**, 6, 776-782.

Coupling

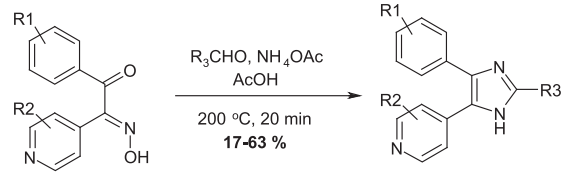


Larhed, M. *et al. J. Org. Chem.* **2004**, 69, 3345-3349.

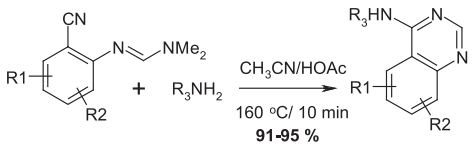


Lipshutz, B. H. *et al. Can. J. Chem.* **2005**, 83, 606-614.

Heterocycles

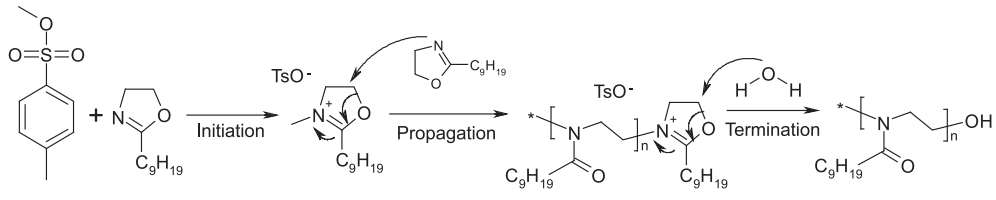


Combs, A. P.; Sparks, R. B. *Org. Lett.*; **2004**, 6 (14), 2473-2475.



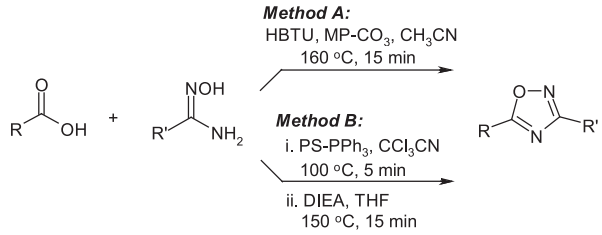
Han Y. *et al. Org. Lett.* **2004**, 6 (25), 4775-4778.

Polymerization

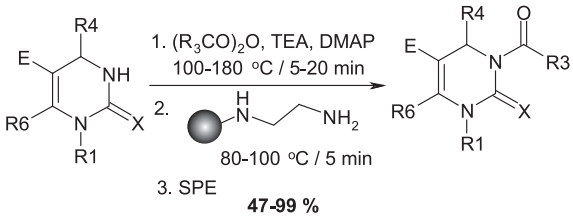


Schubert, U. S. *et al. J. Comb.Chem.* **2005**, 7, 10-13.

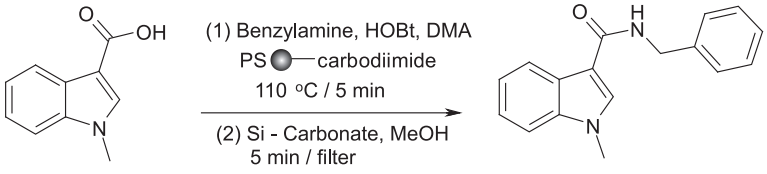
Solid-Supported Reagents



Wang, Y. *et al. Org. Lett.* **2005**, 7, 925-928.

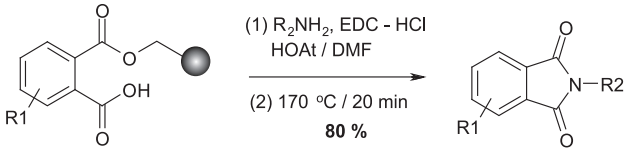


Kappe, O. C. *et al. Org. Lett.* **2003**, 5 (8), 1205-1208.

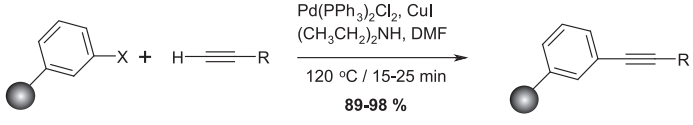


Sauer, D. R. *et al. Org. Lett.* **2003**, 5 (24), 4721-4724.

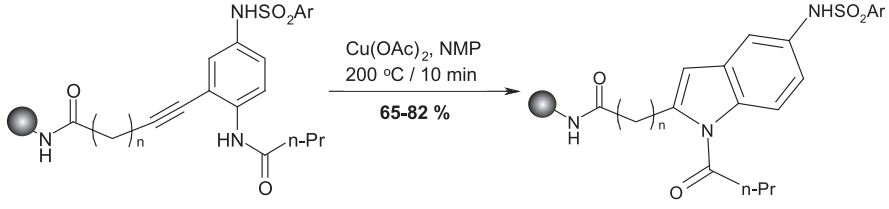
Polymer-Supported Microwave Reactions



Chassaing C. *et al. Org. Lett.* **2003**, 5 (11), 1851-1853



Gogoll, A., Erdelyi, M., *J. Org. Chem.* **2003**, 68, 6431-6434



Dai, W-M. *et al. Org. Lett.* **2003**, 5 (16), 2919-2922

References

1. Mavandadi, F.; Lidstrom, *P. Current Topics in Med. Chem.* **2004**, 4, 773-792.
2. Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, 6, 314-320.
3. Lew, A, Krutzik, P.O.; Hart, M.E.; Chamberlain, A. R. *J. Combi. Chem.* **2002**, 4, 95-105.
4. Larhed, M; Hallberg, A. *Drug Discovery Today*, **2001**, 6, 406-416.
5. Lidstrom, P.; Tierney, J. *Tetrahedron* **2001**, 57, 9225-9283.
6. Kappe, C.O. *Am. Lab.* **2001**, 33, 13-19.

Application Note 48

Microwave-Assisted Friedel Crafts Reaction in the Presence of Ionic Liquids

Shahnaz Ghassemi, Jeff Dishman, Rebecca Previs

The applications group at Biotage uses the products we build, just as our customers do. We have a group of chemists who study the science of microwave synthesis and flash purification and apply it to synthetic organic reaction mixtures, natural product extracts, and biochemicals such as peptides and nucleotides. In this section, we highlight the most popular of the application notes published on our Website, www.biotage.com.

Abstract

The Friedel-Crafts reaction is one of the most fundamental reactions from a synthetic, industrial, and pharmacological point of view and has been widely utilized in the production of pharmaceuticals and fine chemicals. Friedel-Crafts reactions proceed through electrophilic aromatic substitution (EAS) to generate carbon-carbon bonds. In general, the reaction requires a volatile and hazardous halogenated solvent, Lewis acids such as $AlCl_3$, HF or H_2SO_4, long reaction times followed by difficult recovery and purification. In order to eliminate the use of volatile hazardous solvents and shorten reaction times, microwave-assisted Friedel-Crafts reactions using $AlCl_3$-ionic liquid (Al-IL) as solvent and Lewis acid were explored. Ionic liquids (ILs) are molten salts whose physical properties make them ideal as a nonvolatile solvent and catalyst in both conventional and microwave-assisted organic synthesis. Due to their ionic nature ILs are excellent absorbers of microwave irradiation. Moreover the mixture of these salts and Lewis acids (e.g., aluminum trichloride) are liquid at room temperature.

Solid at RT

Al-IL
Liquid at RT

The acidity of the Al-IL depends on the ratio of $AlCl_3$ to butyl-3-methyl imidazolium chloride [bmim]Cl. The acid-base properties of this system are described by this equilibrium:

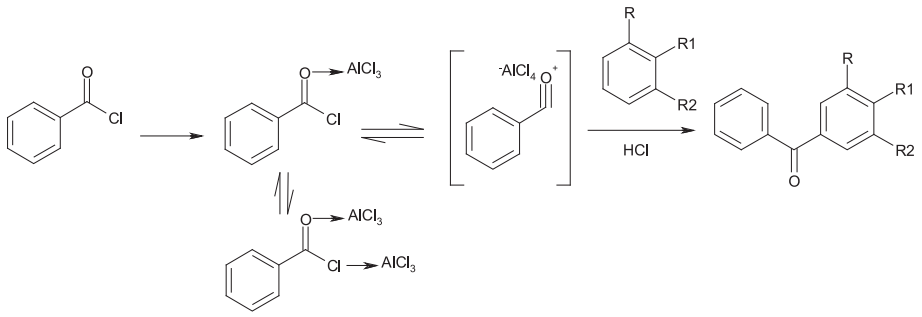
$$2\ AlCl_4^- \rightleftharpoons Al_2Cl_7^- + Cl^-$$

$Al_2Cl_7^-$ is the Lewis acid and Cl- the Lewis base. The higher ratio of $AlCl_3$ to [bmim]Cl provides higher concentration of $Al_2Cl_7^-$. This ratio is defined as (N):

$$\mathbf{N = [AlCl_3/(AlCl_3 + [bmim]Cl)]}$$

In a 1:1 ratio of Al to [bmim]Cl (N = 0.5), aluminum is present entirely in the tetrachloroaluminate form (natural melts) and in the 2:1 ratio (N = 0.6), only the heptachloroaluminate form (acidic melts) exists.

In this application note, we report the use of Al-[bmim]Cl (N = 0.6) in microwave-assisted Friedel-Crafts acylation of aromatic compounds. The proposed mechanism for this reaction is the formation of several intermediates including the complex of acid chloride with one or two $AlCl_3$ and formation of benzylium cation, which is the key intermediate in these electrophilic aromatic substitutions, followed by release of HCl gas to form the final product.



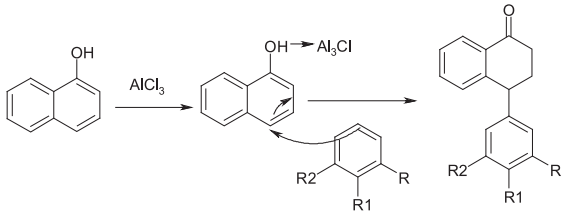
This application note also describes the synthesis of 4-(3',4'-chlorophenyl)-3,4-dihydro-1(2H)-naphthalenone and its analogs, a starting material in the synthesis of the antidepressant medication Zoloft, via Friedel-Crafts alkylation. The literature-reported synthesis requires 1,2-dichloroethane in 10 times excess solvent, long reaction times (6 h), and a multi-step purification process. A cost-effective and safe synthetic and purification route for this material is reported herein.

Procedures

General procedure for microwave-assisted Friedel-Crafts acylation in presence of ionic liquids: 1.2 eq. of Al-[bmim]Cl was added to a mixture of 1 eq. of benzoyl chloride and 1.2 eq. of aromatic compounds. These mixtures were heated in a controlled microwave synthesizer for 3 minutes at 150 °C. The final products were isolated by absorbing the reaction mixture into silica gel and purifying it by automated flash chromatography using ethyl acetate/hexane gradient. This procedure was used to acylate activated and deactivated aromatic compounds using benzoyl chloride (Table 1).

Synthesis of 4-(3', 4', 5'-substituted phenyl)-3,4-dihydro-1(2H)-naphthalenone:

General procedure for microwave-assisted Friedel-Crafts alkylation in presence of ionic liquids:



Procedure A:

A mixture of 1 eq. naphthol to 1.2 eq. 1,2,3-substituted phenyl and 2.0 eq. of $AlCl_3$ was heated via microwave for 3 min at 80 °C. In all cases the isolated yields of the desired products were >70% (Table 2).

Procedure B:

A mixture of 1 eq. naphthol to 1.2 eq. 1,2,3-substituted phenyl and 1.5 eq. of Al-[bmim]Cl (N = 0.65) was heated via microwave for 3-8 min at 80-150 °C. In all cases the isolated yields of the desired products were ~97%. The products were isolated without any liquid-liquid extraction. The reaction mixture was simply pre-absorbed onto silica and transferred on top of a silica cartridge followed by flash chromatography using ethyl acetate:hexane as the mobile phase (Figure 1).

Results

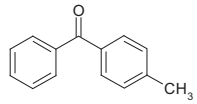
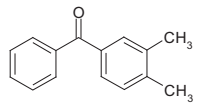
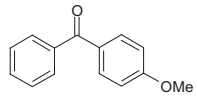
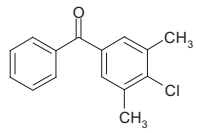
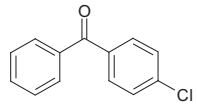
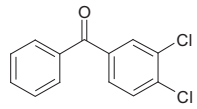
No	Product %	Isolated Yield	% HPLC Purity
1		85.9	94.8
2		88.3	95.4
3		90.5	87.2
4		87.4	89.3
5		83.3	91.2
6		84.3	88.7

Table 1. The results of Microwave-Assisted Friedel-Crafts Acylation of substituted phenyl with benzoyl chloride using Al-[bmim]Cl (N = 0.6) at 150 °C for 3 min

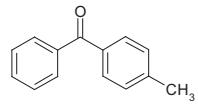
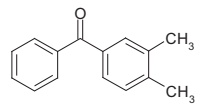
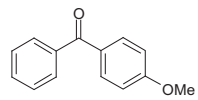
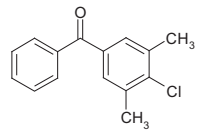
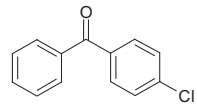
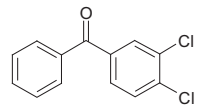
No	Product %	Isolated Yield	% HPLC Purity
7		73.6	89.9
8		78.3	90.3
9		69.5	92.5
10		78.4	85.8
11		83.3	91.2
12		84.3	88.7

Table 2. The results of Microwave-Assisted Friedel-Crafts alkylation using 1.2 : 1 equivalent. Substituted phenyl : 1-naphthol and 2 equivalent. $AlCl_3$ at 80 °C for 3 min.

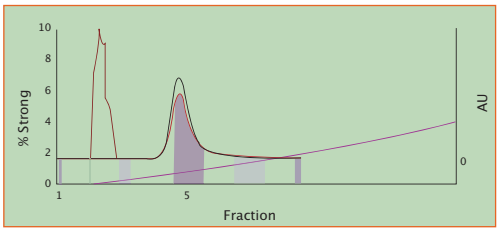


Figure 1. Flash Chromatography Separation of compound 12

The heterogenous reaction mixture of these reactions appeared yellow. After heating in the microwave for 3 min at 80 °C, the reaction mixtures changed to a green to dark-brown liquid (Figure 2).

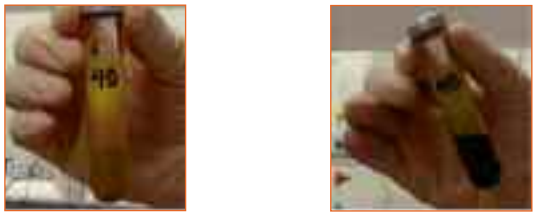


Figure 2. Change in color of reaction before and after microwave heating at 80 °C for 3 min.

Conclusion

Ionic liquids prepared from $AlCl_3$ and [bmim]Cl with different Lewis acid strength can be used as a catalyst and a solvent in microwave-assisted Friedel-Crafts acylation and alkylation of phenols. The use of these salts in microwave-assisted syntheses eliminated the need to use a volatile and hazardous halogenated solvent and also shortened the reaction times from hours to minutes. Products could be isolated in a short time without any liquid-liquid extraction, in high yield and purity, by absorbing the reaction mixture onto silica followed by normal phase flash chromatography.

References

1. Boon, J.A, Levisky, J.; Pflug, L.; Wilks, J.S. *J. Org. Chem.*, **1986**, 51, 480-483.
2. Csihony, S.; Mehdi, H.; Homonny, Z.; Vertes, A.; Farka, O.; Horvavth, I.T. *J. Chem. Soc., Dalton Trans.*, **2003**, 680-685.

Application Note 47

Single-system FLASH Purification Scale-up— From Milligrams to Multigrams

J. Robert Bickler, M.S.

Introduction

Medicinal chemistry groups synthesize starting materials, intermediates, and final compounds at different scales – from milligram to multigram. In the past, purification at all these scales required more than one flash system – one for milligram to gram scale (10 grams) and another for multigram scale (>10 grams).

The Biotage automated gradient flash purification system is designed to provide purification from milligram to multigram levels just by changing cartridge size.

Application

Sample load is typically determined from ΔCV calculations using TLC Rf values. From this information, sample loading levels can be determined. Scale-up factors (see Table 1) are determined by using the ratio of crude sample to media weight. Although scale-up factors can also be used to set flow rate on the larger cartridges, most chemists find comfort in setting flow rate to the cartridge diameter.

	FLASH 12+S	FLASH 12+M	FLASH 25+S	FLASH 25+M	FLASH 40+S	FLASH 40+M	FLASH 65M	FLASH 75S	FLASH 75M	FLASH 75L
FLASH 12+S	1	2	5	10	11	22	78	47	78	156
FLASH 12+M	-------	1	2	5	6	11	39	23	39	78
FLASH 25+S	-------	-------	1	2	3	5	18	11	18	36
FLASH 25+M	-------	-------	-------	1	1	3	9	5	9	18
FLASH 40+S	-------	-------	-------	-------	1	2	7	4	7	14
FLASH 40+M	-------	-------	-------	-------	-------	1	4	2	4	7
FLASH 65M	-------	-------	-------	-------	-------	-------	1	-------	1	2
FLASH 75S	-------	-------	-------	-------	-------	-------	-------	1	2	3
FLASH 75M	-------	-------	-------	-------	-------	-------	-------	-------	1	2
FLASH 75L	-------	-------	-------	-------	-------	-------	-------	-------	-------	1

Table 1. Scale-up factor table. Find starting cartridge (top) and locate the scale-up factor and corresponding cartridge required for that sample load (left).

In this application, we show how the direct scale-up of a sample purification from 320 mg to 25 g using a single gradient profile, (see Figure 1).

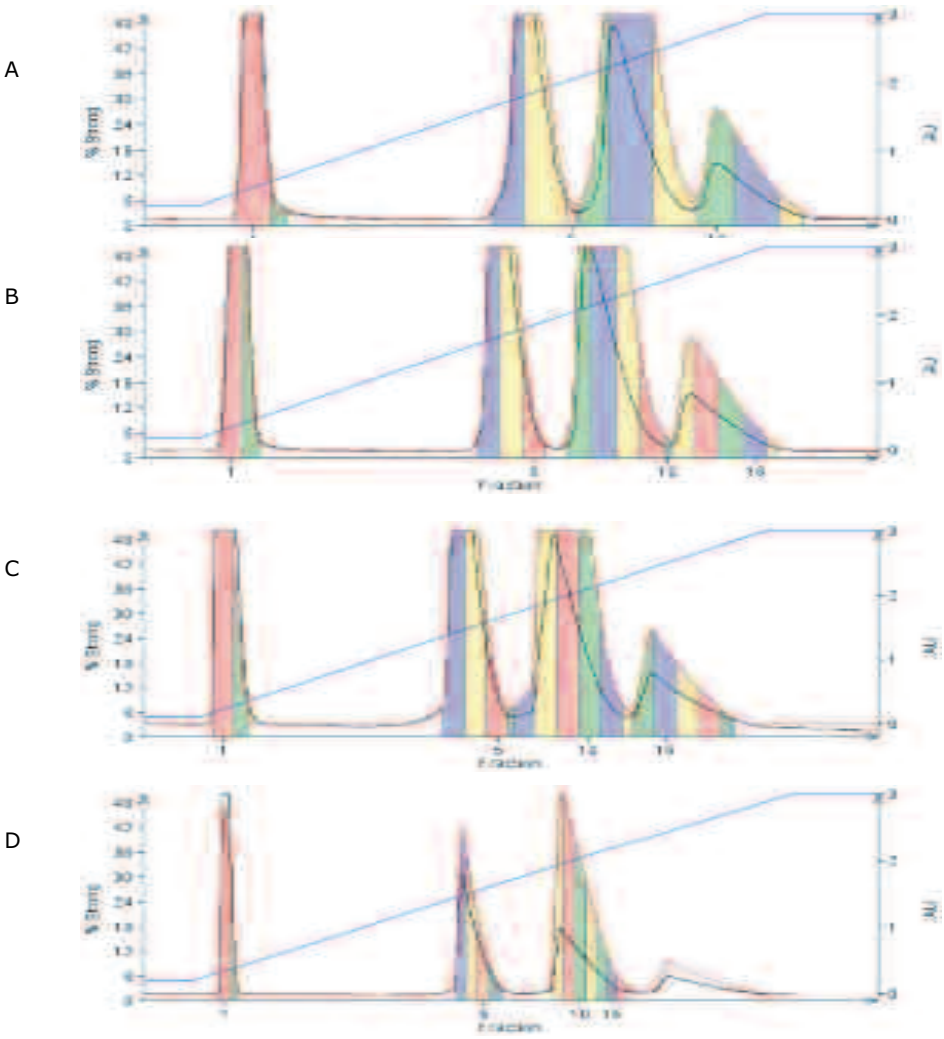


Figure 1. Scale-up of a 4-component sample from 320 mg to 25 g while maintaining the separation. A) 320 mg on a FLASH 12+M at 12 mL/min, B) 1.28 g on a FLASH 25+M at 25 mL/min, C) 3.57 g on a FLASH 40+M at 40 mL/min, D) 25 g on a FLASH 75L at 95 mL/min. The flow cell was reduced to a 0.1 mm path length with the FLASH 75 cartridge to show impact of smaller flow cell. Solvent gradient 5% EtOAc in hexane to 50% EtOAc/hexane over 10 CV.

Conclusion

FLASH purification scale-up above 20 grams per injection is now possible on a single flash system, while maintaining full separation. Determining scale-up factors is simplified using a look up table. No longer are two different flash systems required when purification of milligram and multi-gram samples is required.

Application Note 1

Purification of a Protected Peptide by FLASH Chromatography

Shahnaz Ghassemi, Ph.D.

Abstract

Medical research involving peptides as pharmaceutical actives has increased over the last decade. Peptide synthesis requires the coupling of several different amino acids in sequential steps to obtain the desired product. The efficacy and biological activity of peptides are dependent on their final purity. Purity and yield are dramatically increased when purification is performed on smaller synthetic segments prior to segment coupling.

Historically, peptide segments have been blocked from coupling using any number of bulky, hydrophobic, removable reagents such as Fmoc (9-fluorenylmethoxycarbonyl), Boc (tert-butyloxy carbonyl), trityl, etc., which bond to the peptide N-terminus and C-terminus. The resulting protected peptides, however, are very hydrophobic and have been difficult to purify by reversed-phase techniques.

In this application, a solution containing 300 mg of a crude peptide protected with trityl and dimethylcyclopropyl amide groups was purified using normal-phase chromatography with both a Biotage FLASH 12+™ system and a self-packed glass column (containing the same silica mass) for comparison. The results in the table below clearly show higher yield and purity of the target peptide in 1/24 the time with the FLASH 12+ system.

Column	Dimensions (mm)	Separation Time (min)	Solvent Consumed (mL)	Crude Load (mg)	Peptide Mass Recovered (mg)	Peptide Yield (%)	Peptide Purity (%)
Open Glass	12 x 150	240	236	300	154	60	78
FLASH 12+	12 x 150	10	50	300	192	95	99

Application Note 21

Effects of Solvent Type and Strength in FLASH Separations

J. Robert Bickler, M.S.

Abstract

Isolation of desired compounds from reaction mixtures and natural products by flash chromatography is not always a straightforward process. A product and its analogs may not be separable without performing some type of method development and optimization.

Application 21 discusses the role of TLC (thin-layer chromatography) as a flash purification method-development and optimization tool, in relation to the impact of solvent choice on compound retention and selectivity. In this application, a mixture of four dyes (three hydrazine dye analogs and an anthraquinone dye) was used as an example.

TLC was used to evaluate five solvent mixtures for selectivity: ethyl acetate/heptane, acetone/heptane, isopropanol/heptane, toluene, and methylene chloride. TLC was also used to evaluate the solvent strength of these mixtures by varying the polar component percentage. A total of 12 solvent systems were transferred and simultaneously run on a 12-channel, Quad3™ Parallel FLASH Purification system to show how TLC separations translate to flash separations.

TLC results show that the three hydrazine dye analogs (fat red 7B, methyl yellow, and Sudan IV) cannot be separated when an oxygen-containing solvent is used, regardless of concentration; only methylene chloride, or toluene efficiently separate all four dyes (Figures 1 and 2). Without using TLC for method development and optimization, successful FLASH purification would not have been possible.

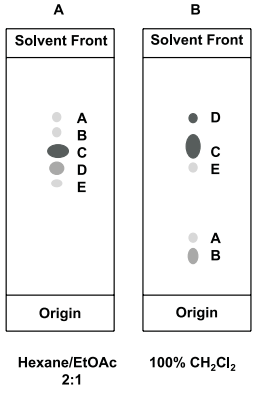


Figure 1.
TLC separations showing the effect of different solvents on elution profile (selectivity). A) A mixture of hexane (group) and ethyl acetate (group VIa), B) same sample separated with methylene chloride (group V). Note how the elution order of the five spots has changed.

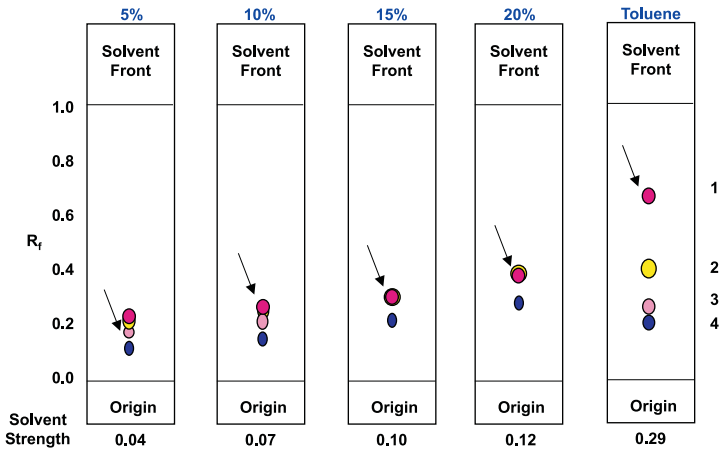


Figure 2. TLC separation of dyes using ethyl acetate/heptane mixtures and toluene. Note the difference in selectivity (⟶) compared to toluene. Elution order: 1. fat red 7B, 2. methyl yellow, 3. Sudan IV, 4. Sudan blue.

Application Note 49

A Study on Flash Chromatography Performance Using Different Sample Loading Methods

Jack Liu, Ph.D.

Introduction

The purification efficiency is a function of loading mass and sample volume in flash chromatography. Excessive sample mass and dissolving solvents have a direct impact on the quality of the purification. Sample resolution degrades as column becomes overloaded. When a column is overloaded with dissolving solvent, sample peak broadens significantly causing the loss of resolution. This paper demonstrates a new sample loading technology that allows dry-loading to minimize the dilution effect of the dissolving solvent while the sample mass is maximized. The study showed that in the 'dry' loading method, dissolving solvent was first removed under vacuum and then separation was performed that significantly improves peak resolution while the 'wet' loading separation resulted in collapsed resolution with sample carry-over and peak fronting. Removal of dissolving solvent also minimizes the disruption of elution process when a stronger solvent is required to dissolve the sample.

Materials and Methods

A Biotage automated flash purification system was used for the flash chromatography. The system is configured with dual variable UV detector allowing flexible tuning of absorbance for high sample loading. Cartridges used for the purification included FLASH 12+™M Si and FLASH 25+™M C18. Sample loading with Biotage Samplet™ was compared to other methods. Collected individual fractions as were analyzed with a reversed phase HPLC system. Purity data collected by HPLC analysis are used to illustrate purity and mass distribution of the purification.

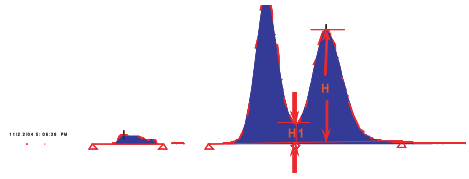


Figure 1. Description of peak resolution

To investigate the effect of band broadening on purification, peak resolution is focused in this study. To illustrate the peak resolution of two adjacent components, a relative resolution factor is used. The relative resolution factor is defined as: Resolution (%) = (1 – H1/H) x 100, where H is peak height and H1 is the depth of overlapped region (Figure 1).

Results and Discussion

The impact of dissolving solvent upon sample resolution is illustrated in Figures 2 and 3. When sample is dissolved in the same solvent as the mobile phase, band broadening is worsened as the loading volume increase (Figure 2). The resolution is maintained when the volume of dissolving solvent is kept less than 5% of the column volume (lower panel of Figure 2).

Strong dissolving solvent causes the degradation of resolution characterized with sample co-elution and carry-over (Figure 3). Even small amount of strong solvent can collapse the resolution due to its interruption to the eluting process. A detailed fraction analysis is shown in (Figure 4). Both retained components were carried over even at the void of column and the purity of less retained component A is significantly affected as a result of the carry over of component B (Figure 4). Although using strong solvent to increase mass load is desired for low solubility samples, removing the extra strong solvent is necessary to maximize the resolution.

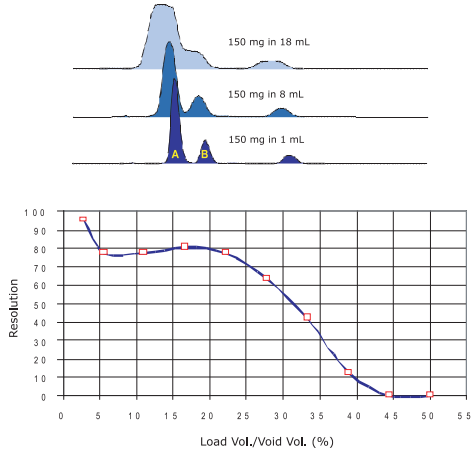


Figure 2. Volume loading effect. Sample, a crude oxazoline derivative; dissolving solvent, 80/20 methanol-water; cartridge, FLASH 25+™M C18; flow, 25 mL/min; mobile phase 80:20 (v/v) methanol-water; detection, UV 254 nm

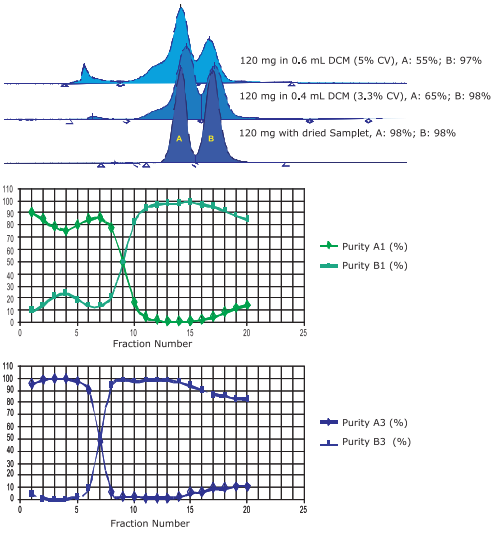


Figure 3. Impact of strong dissolving solvent upon resolution. Sample, 2-Component mixture; cartridge: FLASH 12+M Si, flow, 12 mL/min, mobile phase, 95:5 Hexane/Ethyl acetate

Purification profiles of dry sample loading are shown in (Figure 5). The strong dissolving solvent (DCM) in the samplet was removed under vacuum to eliminate sample co-elution and carry-over. The separation shows excellent sample resolution with high purity fractions while the sample mass was maximized.

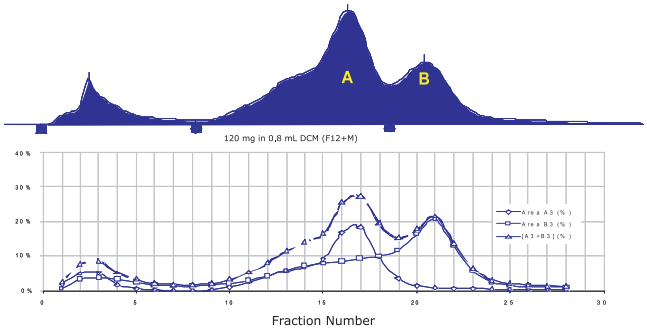


Figure 4. Collapsed resolution as a result of strong loading solvent

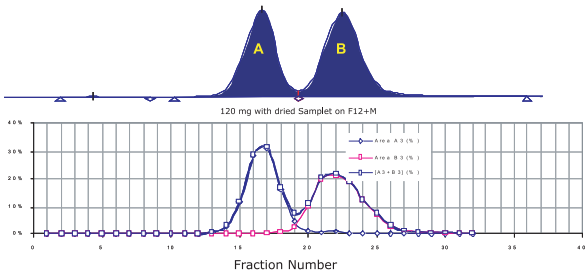


Figure 5. Preserved resolution of 'dry' sample loading

Separation profiles with traditional liquid injection method (Figure 6) and with the samplet dry loading were compared. In the liquid injection method, a weak solvent (hexane) was used to dissolve the sample. No co-elution and carry-over were observed, however, band-broadening still occurs. On the other hand, dry loading method using samplet improves resolution (82% versus 48%) as shown (Figure 6).

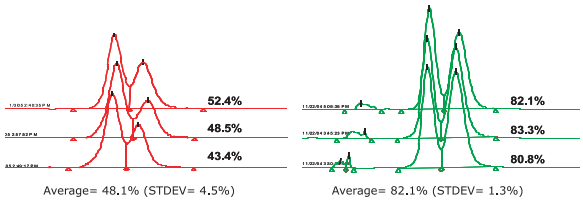


Figure 6. Traditional liquid loading (right) versus the 'dry' samplet loading.

Conclusion

Mass and volume overloading is very common in flash chromatography to obtain maximum throughput and to reduce overall purification costs. However, solvent effects needs to be taken into consideration as shown in this study. Volume overloading causes significant band-broadening, degrading sample resolution. Judicious choice of dissolution solvents is critical to resolution: stronger dissolution solvents can disrupt separation process by causing unwanted sample co-elution and carry over as well as band broadening. It is shown that 'dry' sample loading is advantageous over liquid loading methods. Use of the Biotage Samplet™ technology combined with the Biotage purification system allows chemists to maximize resolution and loading capacity without sacrificing purity. It is hoped that the results illustrated in this paper will be useful to chemists for better practice of flash chromatography.

Application Note 40

Purification of Heterocyclic Amines on a New FLASH Media—KP-NH Silica

MarthaJoy M. Spano and J. Robert Bickler, M.S.

Abstract

Much of pharmaceutical research is centered on nitrogen heterocycle chemistry. These basic amines are difficult to purify using traditional silica chromatography because of strong interactions between acidic silica and the molecules' basic amine groups. These interactions cause band spreading and poor compound recovery.

Biotage developed KP-NH, an alternative to amine-modified solvents and reversed-phase chromatography, for organic amine purification. KP-NH has a slightly alkaline nitrogenous surface chemistry that provides an "organic amine-friendly" environment capable of high-sample loads, improved selectivity, and recovery compared to silica. This application note shows the comparison of silica to KP-NH for the purification of basic pharmaceuticals tolperisone, verapamil, and nifedipine.

Results

KP-Sil strongly binds most organic amines used in this study, only nifedipine (contains a nitroaromatic ring) was recovered from silica at high yield. In Figure 1, the selectivity difference between the KP-Sil and KP-NH for sample three is shown. KP-NH separates and elutes each individual component with tolperisone eluting first, verapamil second, and nifedipine third. KP-Sil binds tolperisone and does not separate verapamil from nifedipine.

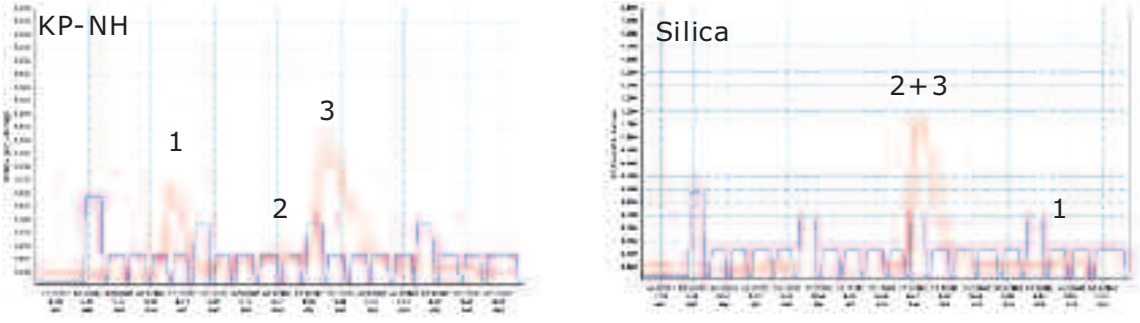


Figure 1. Comparison of KP-NH (left) and silica purification results using a hexane–ethyl acetate (0-100%) gradient. KP-NH is able to separate and elute all three compounds, tolperisone (1), verapamil (2), and nifedipine (3). Using silica, tolperisone elutes last with lower yield, while verapamil and nifedipine co-elute. Sample load was 300 mg. Cartridge size 12 x 150 mm. Purification system, Biotage Horizon™.

Conclusion

Biotage KP-NH cartridges offer definite benefits as an alternative to plain silica in medicinal chemistry FLASH purification applications. Specifically, nitrogen heterocycles and tertiary organic amines are purified with better purity and yield on KP-NH than on plain silica using simple hexane-ethyl acetate gradients.

Application Note 41

Improving Reversed-Phase FLASH Purification Throughput

Sjaan Armentrout, John Gu, J. Robert Bickler, M.S.

Abstract

Normal-phase flash purification is commonly used by organic chemists in pharmaceutical drug discovery and process development labs. However, for many synthesized products (e.g. peptides, nucleotides and basic drug candidates) purification on standard flash silica is not an option due to irreversible adsorption, chemical interaction and/or solubility issues. Reversed-phase FLASH purification is an excellent solution for these applications. Yet, this technique has been used sparingly because of perceived lower loading capacity, higher operating pressures, and a scarcity of publications addressing reversed-phase flash chromatography.

Samples dissolved in organic solvents, when injected into highly aqueous reversed-phase solvent systems, are typically not well retained by C-18 columns. The injection solvent competes with the sample for access to the stationary phase, causing early compound elution (breakthrough) and peak broadening. The higher operating pressures required for reversed-phase purification preclude the use of glass columns and cause leaks in many commercially available flash systems. Research shows that system backpressure (in psig) when using reversed-phased solvents is roughly four times the flow rate (in mL/min) for 50:50 methanol/water (Figure 1).

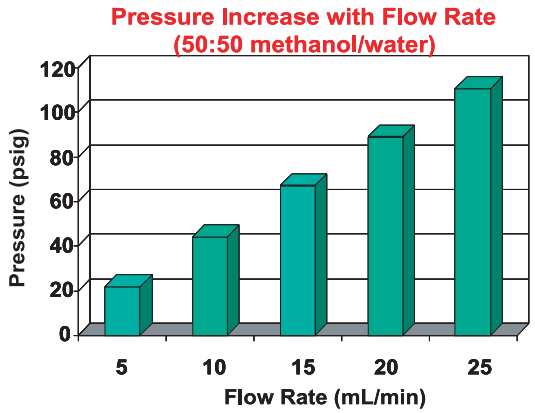


Figure 1. Pressure increase with flow rate

In recent years, Biotage has developed High Performance FLASH Chromatography (HPFC™) systems capable of operation at 100 mL/min and an operating pressure of up to 100 psig. HPFC systems utilize Biotage FLASH+™ cartridges and Samplets™ for sample purification. Samplets are pre-made sample pre-concentration cartridges designed to adsorb samples dissolved in strong solvents. Once the majority of strong solvent has been removed from the Samplet, solvent effects are dramatically reduced, improving sample load and purification. Samplet-based HPFC products simplify reversed-phase FLASH purification and reduce user error.

A comparison of Samplet and direct-liquid-injection loading techniques is made in this application note. Each of these techniques is used to separate and purify several basic pharmaceutical compounds by reversed-phase HPFC. Effects of injection mass and flow rate on reversed-phase FLASH purification cartridges are shown.

Procedure

The experiments were conducted using three samples. Samples one and two consisted of a three-component equal weight mixture of 1-methylbenzimidazole, brucine, and promethazine dissolved in methanol at 150 mg/mL and 300 mg/mL, respectively. Sample three contained 100 mg/mL of promethazine in methanol, which oxidized rapidly to produce a deep blue color. Each solution was adsorbed onto C18 Samplets and air-dried in a fume hood until no solvent was organoleptically detected.

All three samples were separated on KP-C18-HS cartridges using a Horizon™ automated HPFC system. Separation performance and loading capacity were compared using a direct-liquid-injection (through a valve) and the Samplet injection technique. The promethazine solution was purified using a FLASH 12+S cartridge, and the three-component mixtures were separated using a FLASH 12+M cartridge. In all instances, 1 mL of sample was applied. Compound retention and peak shape were compared for each injection technique. Promethazine fractions were analyzed for peak purity by HPLC.

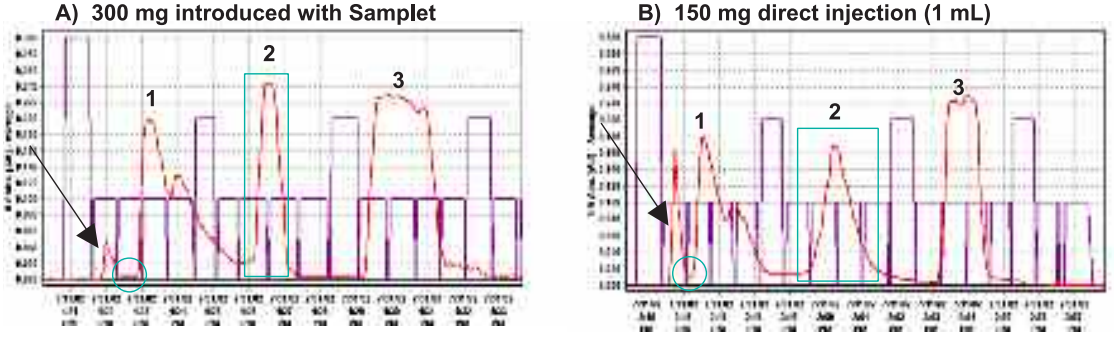


Figure 2. FLASH elution conditions

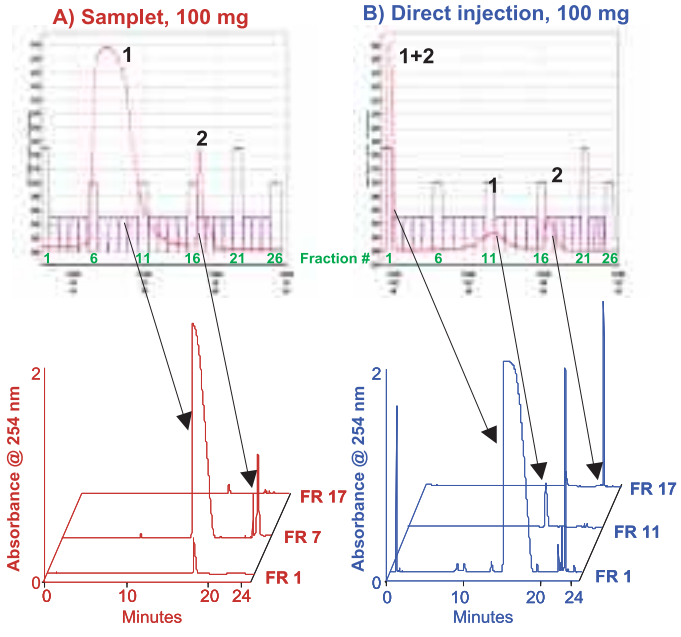
Cartridge:	FLASH 12+M C18
Solvents:	A = DI H2O with 0.1% NH4COOH
	B = 90% methanol in H_2O with 0.1% NH4COOH
Gradient:	Equilibrate 12 mL at 0% B
	Linear gradient 0–100% B in 90 mL
	Hold 100% B for 24 mL, step to 0% B for 60 mL
Flow rate:	13 mL/min
Detection:	254 nm
Compounds:	1. 1-Methylbenzimidazole
	2. Brucine
	3. Promethazine

Results

In each case the Samplet increased compound retention and loading capacity by eliminating solvent effects. Drying the Samplets prior to purification increased compound retention (Figures 2 and 3) because the dissolution solvent, removed by evaporation, no longer competed with the compounds' interaction with the cartridge media. Also, compounds eluted with narrower peak width (Figure 2), higher purity (no mixed peak containing both promethazine and its degradant), and greater yield (Figure 3) when the sample was introduced onto the cartridge using the Samplet.

Higher loading capacity is also evident when using a Samplet. In Figure 2, sample A (300 mg/mL) was injected using a Samplet and sample B (150 mg/mL) was directly injected using a syringe. The data shows the three components, 1-methylbenzimidazole, brucine, and promethazine, having a similar separation profile, even though twice as much sample was loaded and purified using the Samplet.

The increased pressure capability of the Horizon HPFC system enabled a separation to occur in 12 minutes at a flow rate of 13 mL/min. A similar separation would take nearly an hour to complete using glass column technology.



HPLC conditions

Column:	YMC Pro C18 (4.6 x 100 mm)
Solvents:	A = Methanol/ 0.1% NH4COOH (aq) 10:90
	B = Methanol/ 0.1% NH4COOH (aq) 90:10
Gradient:	Equilibrate 2 min at 0% B
	Linear gradient 0-50% B in 20 min
	Step to 100% B, hold for 2 min
Flow rate:	2 mL/min
Injection vol.:	50 µL
Detection:	254 nm
Compounds:	1) Promethazine (100 mg/mL in methanol)
	2) Blue degradation product

Figure 3. Samplet (A) and direct injection (B) impact on degraded promethazine purification using FLASH 12+S C18 cartridges and gradient elution. Samplet injection of promethazine sample provides complete compound (1) and degradation product (2) retention and purification while a direct liquid sample injection (1 mL) inhibits retention and purification. Collected fractions were analyzed by HPLC to verify fraction composition and compound purity.

Conclusion

Reversed-phase purifications using KP-C18-HS cartridges with the Horizon HPFC system demonstrate high loading capacity and throughput. Because of ruggedly constructed cartridges and the Horizon's high-flow/high-pressure pump, flow-rate limitations are eliminated, reducing overall sample run time. Use of Samplet technology further increases purification throughput by increasing the loading capacity of the cartridge.

Samplet use greatly reduces the solvent effects seen with direct injections, increasing compound retention, purity, and yield. Additionally, co-elution or breakthrough in the void volume is reduced, elevating recovery of the compound of interest.

Application 42

Using TLC to Accurately Predict FLASH Purification Results

J. Robert Bickler, M.S.

Abstract

Although many TLC and flash-grade silicas have the same physical specifications (surface area, porosity, etc.), differences in their qualities exist. These differences manifest themselves as gross errors in the calculated CV, variable selectivity, and unreliable loading capacity calculations. Because of these real-method transfer problems, it is very important that the TLC silica and the flash silica be identical and from the same vendor. When TLC and flash silicas are identical, the equation 1/Rf = CV holds, where Rf is the retention factor of a compound separated by TLC, and CV is the number of column volumes required to elute a compound in flash. Cartridge-loading capacity is based on the difference in CV (ΔCV) between two adjacent compounds.

Discussion

A test of Biotage and a competitor's TLC plates using a five-dye test mix with identical elution conditions highlights the performance differences. Although Rf values are similar for most compounds (red, orange, black, and blue), the yellow dye shows a remarkably different Rf value, 0.18 (5.56 CV) on a Biotage TLC plate, but an Rf of 0.25 (4.00 CV) on the competitor's plate; Table 1. When this dye mix was purified on a Biotage FLASH 12+M cartridge, the yellow dye eluted in 5.50 CV, as predicted by the Biotage TLC plate; Table 1.

TLC Rf to Flash CV Correlation

	Biotage FLASH TLC Rf	Calc. CV	ΔCV	Biotage FLASH CV	% Relative Error	Comp. TLC Rf	Calc. CV	ΔCV	Biotage FLASH CV	% Relative Error
Red	0.84	1.19		1.25	4.76	0.82	1.22		1.25	2.44
Orange	0.34	2.94	1.75	3.00	1.96	0.33	3.03	1.81	3.00	-1.01
Black	0.30	3.33	0.39	3.25	-2.56	0.28	3.57	0.54	3.25	-9.89
Yellow	0.18	5.56	2.23	5.50	-1.01	0.25	4.00	0.43	5.50	27.27
Blue	0.10	10.00	4.44	9.25	-8.11	0.09	11.11	7.11	9.25	-20.12

Table 1. Shows improved flash purification predictability when the TLC silica and flash silica are the same. Much greater reliability in calculated elution volumes (solvent consumption) is possible. In this example, the yellow dye has an Rf of 0.18 (5.56 CV) on the Biotage FLASH TLC plate but an Rf of 0.25 (4.00 CV) on the competitive plate. With more accurate CV calculations, better throughput, purity, yield, and solvent, cost savings will be realized.

Conclusion

TLC to flash method transfer accuracy is improved when TLC plates and flash cartridges made with identical silica from the same vendor are used. In the example cited above, the Biotage FLASH TLC plate Rf data correlate to flash CV with greater accuracy than a competitive plate with the same silica specifications. For synthetic chemists, the benefits of matched TLC plates and flash cartridges are better purification throughput, increased compound purity and yield, and reduced solvent cost.

Application Note 43

Eliminating Aqueous Work-Up in Multiple-Step Solution-Phase Synthesis Using Flash Chromatography

Shahnaz Ghassemi, Ph.D.

Abstract

Post-reaction work-up is a major bottleneck in the synthetic process. Generally, the work-up steps of an organic reaction take considerably longer than the actual synthesis. The major impediment with solution-phase synthesis is the multiple aqueous work-up steps often necessary to remove excess reagent and by-products when isolating desired compounds. It is often common for some reactions to require four or five aqueous extractions followed by drying and filtration. Although these extractions are easy to perform, they require additional chemist interaction and delay the goal of obtaining pure compound for further study. In addition, the formation of emulsions during these extraction/wash steps causes lower yields and increases purification time. However, solution-phase synthetic techniques offer many advantages over solid-phase approaches, including unlimited scale, easy manipulation, and reduction in validation time.

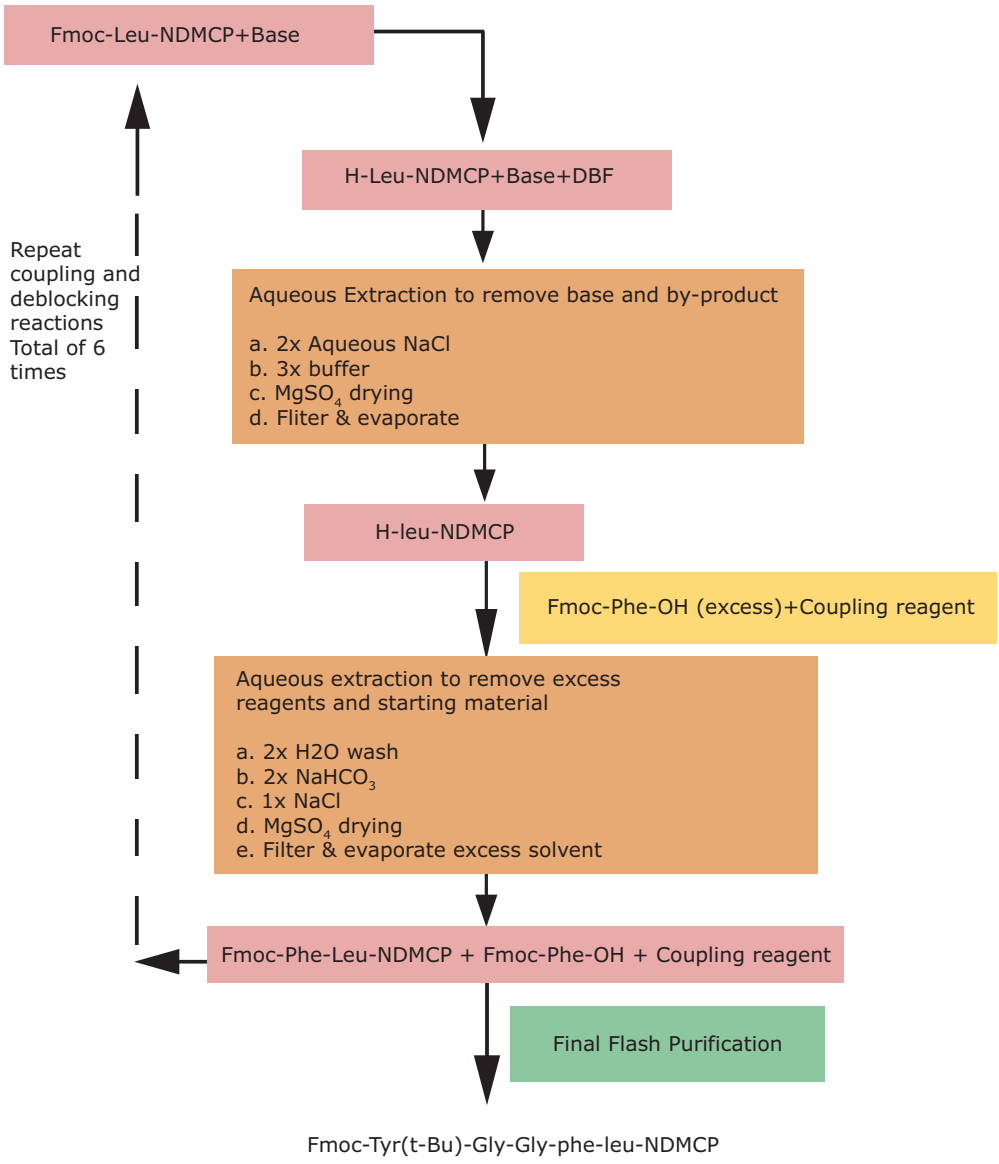
By planning the solution-phase synthesis to include a Flash chromatography purification step, the need for a post-reaction workup is eliminated. To illustrate the advantages of incorporating high-performance flash chromatography (HPFC) into a solution-phase synthesis reaction procedure, a polypeptide (Fmoc-Tyr(t-Bu)-Gly-Gly-Phe-Leu-NDMCP) was synthesized by an eight-step solution-phase technique using a Biotage HPFC system in-line for fast product isolation.

Fast Solution-Phase Synthesis of Fmoc-Tyr(t-Bu)-Gly-Gly-Phe-Leu-NDMCP

The desired polypeptide product was synthesized using the traditional solution-phase synthesis technique that started with Fmoc-Leu-NDMCP. The eight steps included four amino acid coupling reactions and four Fmoc-deblocking reactions. This work compares two sample work-up methods: 1) the traditional aqueous work-up and 2) the in-line HPFC technique for isolation of intermediates and final products.

Method 1: Aqueous Work-Up Technique

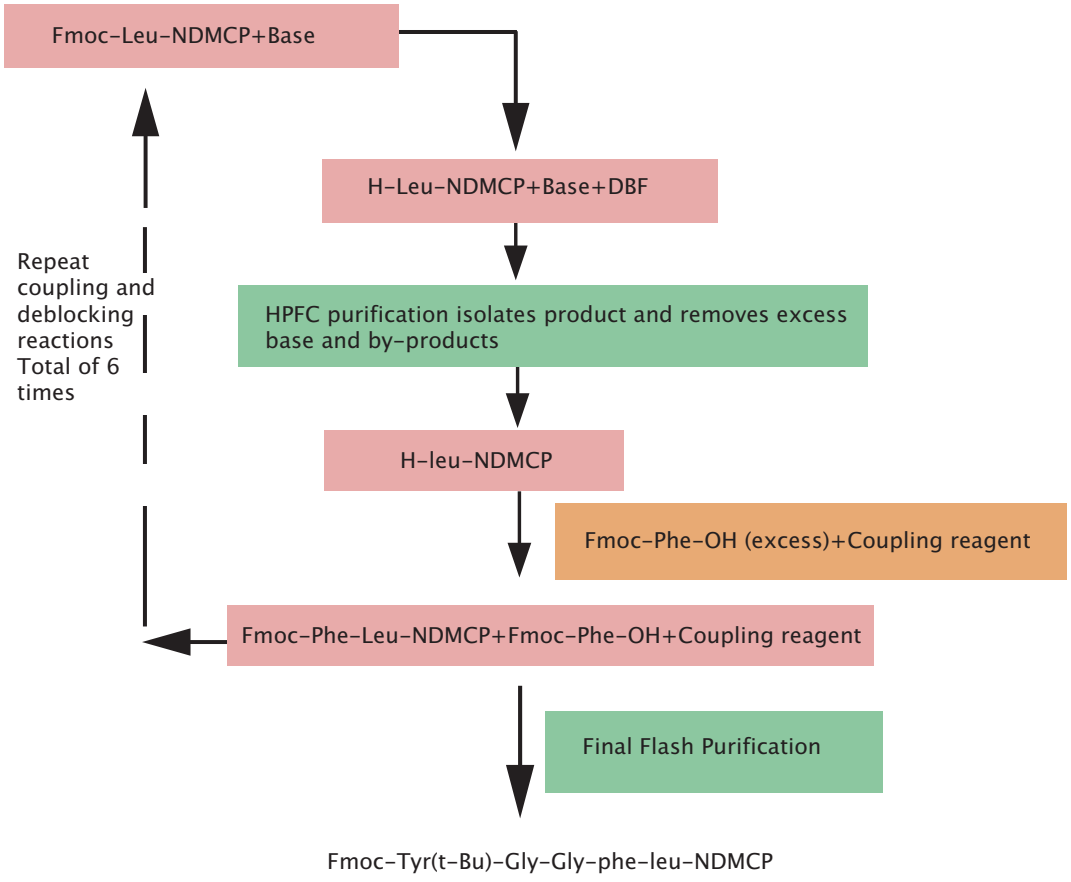
After reacting the Fmoc base peptide (Fmoc-Leu-NDMCP) with base and DBF (dibenzofulvene), the aqueous work-up procedure requires two washes with NaCl, three washes with buffer followed by drying with magnesium sulfate and then, finally, filtering the product and evaporating the excess solvent. After the coupling reagent is added and the reaction occurs, additional aqueous extractions are required, again followed by magnesium sulfate drying steps. Multiple aqueous washes with dilute acid or dilute base are utilized to remove excess reagents, by-products or excess reagents after each synthetic step multiple aqueous washes followed by the required drying, filtration, and evaporation (Flow Chart 1).



Flow Chart 1. Aqueous workup for removing excess reagents and by-product

Method 2: In-Line HPFC Technique

The new integrated technique incorporating Flash chromatography after each Fmoc-deblocking step eliminates the aqueous wash protocol. The crude reaction mixture is directly added to a Biotage FLASH 25+ Samplet™ cartridge without any aqueous workup. Samplet cartridges allow for quick, direct loading of soluble and insoluble samples onto the FLASH cartridge. The Samplet cartridge was inserted into the FLASH 25+ cartridge and the compounds were purified using dichloromethanel/methanol (DCM/MeOH) gradients. This integrated procedure reduces sample handling and decreases the overall cycle time while providing higher yield with purer product, (Flow Chart 2). The collected fractions were tested by TLC and ninhydrin test. Mass spectra (running ESI+ mode) were used to confirm identity of each isolated product after flash chromatography.

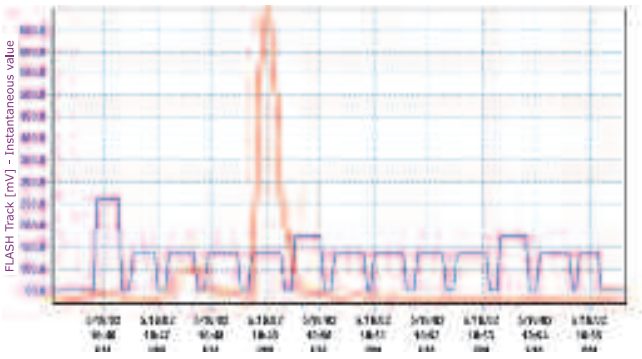


Flow Chart 2. The new integrated technique incorporating Flash chromatography after each Fmoc-deblocking step eliminates the aqueous-wash protocol.

Results

This multi-step solution synthesis yielded 765 mg (83.3%) of highly pure (greater than 90%) Fmoc-Tyr(t-Bu)-Gly-Gly-Phe-Leu-NDMCP in less than eight hours. Synthesis of the same compound by traditional solution-phase techniques using aqueous extractions was complicated because of the formation of emulsion during the aqueous wash required at each step, and the final yield was less than 40%. This synthesis required two to three days to complete this multi-step synthesis.

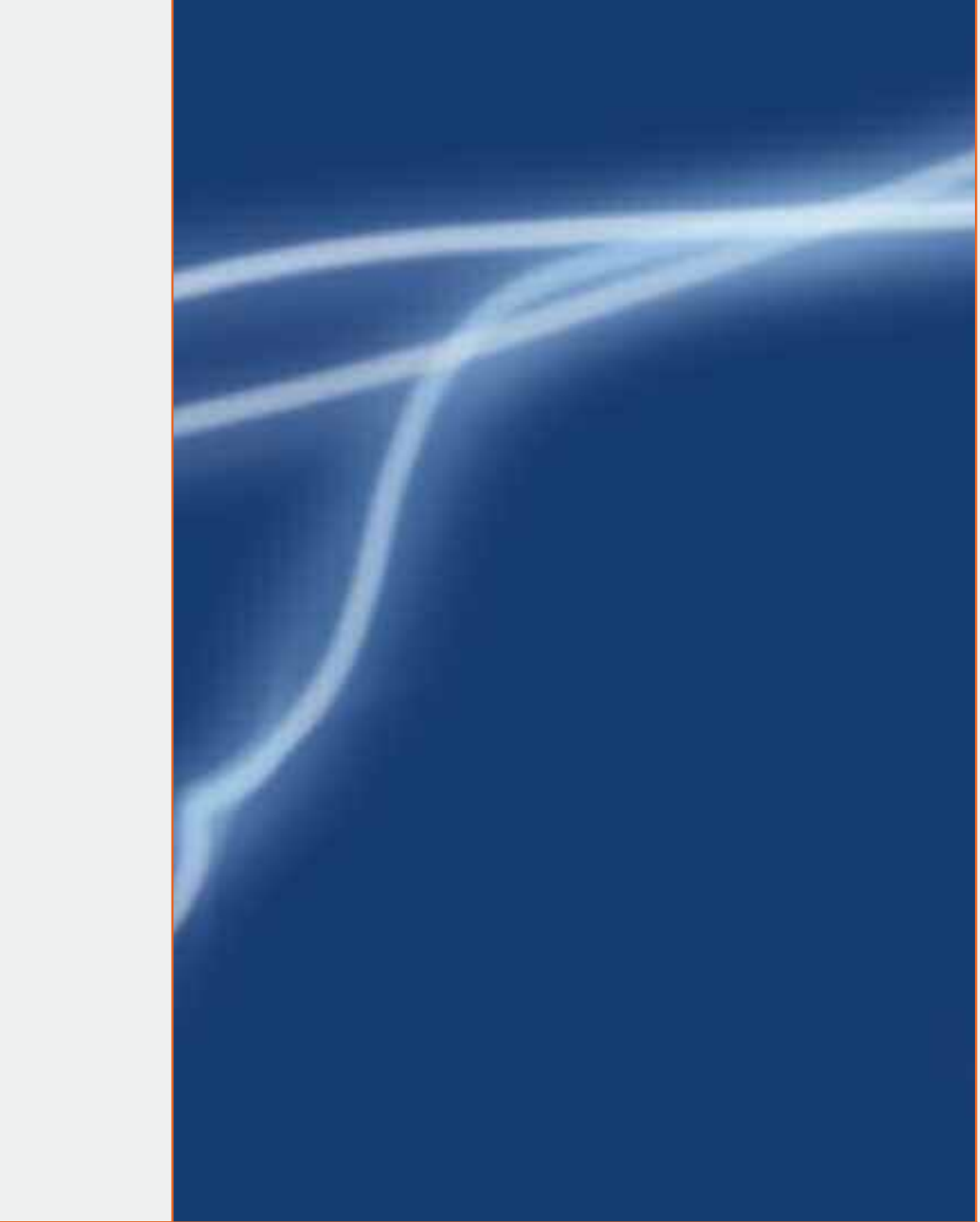
Figure 2. Gradient FLASH separation quickly isolates desired product from the reaction mixture after each Fmoc de-blocking step. The Horizon system was programmed with the following conditions:



Cartridge:	Biotage FLASH 25+M (25 x 150 mm)
Load:	450 mg
Detection:	254 nm
Solvent:	A: DCM
Solvent B:	MeOH
Gradient:	0-10% B in 500 mL
Flow rate:	32 mL/min.

Conclusion

Substituting aqueous workup with FLASH™ chromatography increases the yield and purity of the final product. Because no aqueous washes are required, there is much less sample handling and no product loss due to emulsions, drying with MgSO4, and filtration. Also, using FLASH chromatography ensures up to 95% purity of isolated intermediate product at each synthetic step, with very little product lost. The ability to combine Flash purification and synthesis into a single process increased the yield of the overall reaction by 100% and provided a faster process for a multiple-step synthesis that was easily completed in a single day.



Synthesis Solutions and Optimization

Microwave Synthesis Solutions

Initiator™ Microwave Synthesis System

The Initiator microwave synthesizer enables medicinal chemists to quickly synthesize compounds using microwave heating. Through superior heating features, the Initiator is able to quickly achieve temperatures and pressures beyond traditional reflux heating. The base system is easily upgradable to an 8- or 60-position sample bed that supports the production of focused libraries, multi-user environments, and scale-out. The Initiator 8 and 60 provide flexible operation that enables the use of both large and small vials in combination at any time and in any order without manual intervention.

Biotage Microwave Vials

Biotage microwave vials support microwave synthesis from mg to grams, without the need for re-optimization. Four vial sizes allow safe, convenient, and reproducible syntheses from 0.2 mL to 20 mL. Methods that are optimized for a lower volume are typically transferable across the entire volume range.

Biotage PathFinder

Biotage PathFinder is the world's largest database of established methods for microwave synthesis. Chemists worldwide have web-based access to more than 5,200 diverse and new microwave methods. Using simple keyword and/or substructure search, it is fast and easy to find microwave conditions for your reactions of interest along with experimental details and information needed to perform the reactions.

Biotage Solid Supported Reagents and Scavengers

Biotage's solid supported reagents and scavengers can be used in both conventional and microwave synthesis for simplifying the post-synthesis workup and purification processes. The solid supports can withstand the high temperatures of microwave heating, which accelerates conventionally slow reactions. Excess reagents and byproducts can quickly be removed by filtration rather than liquid-liquid extraction, chromatography, or crystallization. A variety of scavenger resins and bound reagents are available to facilitate a wide range of solution-phase reactions and work-ups.

Optimizing Microwave Synthesis

Understanding Microwaves

Microwave is a collective name for electromagnetic irradiation with frequencies in the range of 0.3-300 GHz. To avoid interferences between the different applications, it has been agreed that appliances for heating purposes will operate at 2.45 GHz corresponding to a wavelength of 12.2 cm.

Energy in the form of microwaves can be transferred to substances that are present in the beam line of the microwave radiation. Absorption of the energy occurs when dipolar molecules rotate to align themselves with the fluctuating electric field component of the irradiation or when ions move back and forth by the same phenomenon (Figure 1).

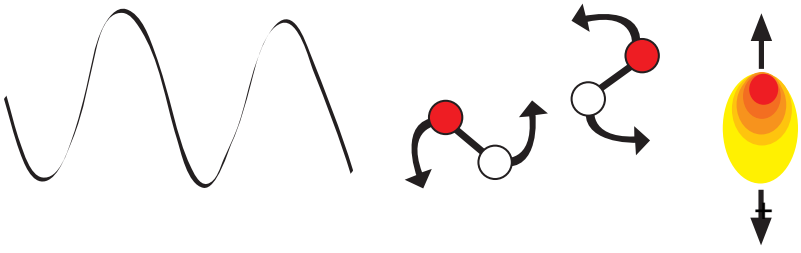


Figure 1. Dipolar molecules and ions, which try to move with an oscillating electric field.

It should be pointed out that the energy-quantum of the microwave irradiation is totally inadequate for interacting directly with atom-atom bonds or for exciting specific molecules. When molecules rotate or move back and forth in a matrix, they generate heat by friction. The amount of heat generated by a given reaction mixture is a complex function of its dielectric property, volume, geometry, concentration, viscosity, and temperature.[1] Thus, two different samples irradiated at the same power level for the same period of time will most likely end up with rather different final temperatures.

Essentially, the ability of a substance to be heated in a microwave field is dependent upon two factors: (1) the efficiency with which the substance adsorbs the microwave energy, normally described by its dielectric properties, ε' and (2) the efficiency with which the adsorbed energy can be converted to heat, described by the loss factor, ε''.

A convenient way to evaluate the ability of two closely related substances to convert microwave energy into heat is to compare their respective "loss tangent" values, where the loss tangent is defined as the tangent of the ratio of the loss factor and the dielectric properties, Eqn. 1. For a deeper insight into the mechanism of microwave dielectric heating, the review by Mingos et al.[2] is recommended.

$$\tan \delta = \varepsilon''/\varepsilon' \qquad \textbf{Eqn. 1}$$

Synthesis Optimization

However, Biotage microwave synthesizers eliminate the problems of selecting the appropriate matrix because these machines are capable of reliably heating a wide variety of substances and have both variable power output and temperature control.

Multimode vs. Single Mode

Despite several subcategories there are two fundamentally different types of construction of microwave-heating devices, namely multimode and single mode. The main difference between the two is in the buildup of the energy field within the systems. In both cases, microwaves are generated by a magnetron and led into the reaction chamber, the cavity, through a wave-guide. When the microwaves in a multimode apparatus enter the cavity, they are reflected by the walls generating a three-dimensional stationary pattern of standing waves within the cavity, called modes. Multimode microwaves are optimized to give high efficiency for 200-1000g loads and consequently they operate less reliably for smaller loads. However, for chemistries required on larger scales, the multimode device is appropriate since single-mode devices would be inefficient; therefore, this is what is used for our large-scale microwave, Advancer™.

Ideally, to obtain a well-defined heating pattern for small loads, a microwave apparatus utilizing a single-mode cavity is preferred. This type of cavity allows only one mode to be present. Much higher field strengths can be obtained, giving rise to more rapid heating. A properly designed cavity also prevents the formation of hot and cold spots within the sample, resulting in a uniform heating pattern. This is very important when microwave technology is used in organic chemistry, since the heating pattern for small samples can be well controlled. This allows for higher reproducibility and predictability of results as well as optimization of yields, which are usually more difficult when using a domestic microwave oven. All research-scale microwaves from Biotage are equipped with single-mode resonators.

Why Does Microwave Irradiation Speed Up Chemical Reactions?

Chemical reactions, performed using microwave synthesis techniques, are rapid mainly because microwaves are able to quickly achieve higher temperatures and pressures in the reaction vials. All Biotage microwave synthesizers can achieve temperatures of up to 250 °C and pressures of up to 20 bar allowing reactions to be carried out much faster than traditional reflux heating.

In early literature, there were many claims of a specific microwave effect responsible for the observed rate accelerations.[3,4,5] Later experiments show some of these early reports to be artifacts[6], while others are debatable or difficult to explain.[7] An attempt to rationalize a possible specific microwave effect has been published by Perreux *et al.*[8] Most of the reports on specific effects, however, can be rapidly dismissed due to poor temperature control. These

inaccuracies in temperature measurements often occur when performing the reactions in domestic ovens, with microtiter plates or on solid supports, where there are inherent difficulties in measuring the temperature accurately.[2,5] Even with today's specialized equipment, it is very difficult to capture the true temperature of a reaction performed on a dry, solid support or in a continuous-flow system.

When trying to understand these questions, the introduction of the so-called "cooling while heating technique"[9] is very misleading. This technology proposes the reaction mixture is heated as the outside of the vessel is simultaneously cooled, hypothetically increasing the energy input. However, since the temperature is normally read on the surface of the vial, the accuracy of the temperature measurement is lost along with reproducibility, controllability, and predictability.

The temperature difference of measured and actual temperature is strongly dependent on the microwave-absorbing properties of the sample, the temperature of the cooling gas, the velocity of the cooling gas, the thickness of the vial-wall etc., and can easily be as much as 50 °C (Figure 2).

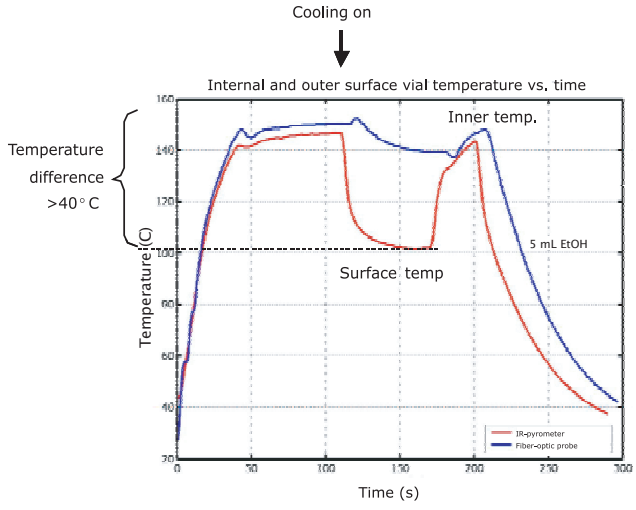


Figure 2. Difference of measured and actual temperature in 5 mL of ethanol. The actual temperature is measured via a fiber-optic probe inserted directly into the solvent.

Under some circumstances, the rapid rate of microwave heating can produce heat profiles that are not easily accessible using traditional heating techniques. In such cases, experiments performed using microwave synthesis may well result in a different outcome to conventionally heated reactions, even if the final reaction temperature is the same.[10]

Another phenomenon that might account for some of the claims of specific effects, for reactions run under atmospheric pressure, is the superheating effect.[2,11] Under microwave irradiation at atmospheric pressure, the boiling point of solvents can be raised up to 26 °C above their conventional values. The enhanced boiling point can be maintained in pure solvents for as long as the microwave radiation is applied. Substrates or ions present in the solvent aid in the formation of a boiling nuclei, and the rate at which the temperature of the mixture returns back to the normal boiling point is solvent dependent. It is now accepted that the major part

of rate enhancements observed with microwave synthesis is strictly due to thermal effects, even though the unique temperature profiles accessible by microwave radiation may result in novel outcomes. While the existence of a specific microwave effect cannot be completely ruled out, the effect appears to be a rarity of marginal synthetic importance.

Where to Start with Microwave Synthesis?

Microwave synthesis is normally conducted under conditions that vary considerably from what is conventionally used in today's chemistry laboratories. Biotage microwave systems support a wide variety of different reaction conditions, accommodating different solvents, volumes, concentrations, and phases; and are characterized by reproducible results. Because microwave synthesis occasionally uses uncommon methods, the novel user might feel unsure of what conditions to use; therefore Biotage has developed a database, Biotage PathFinder, which rapidly gives even novice users in the field a flying start toward the productivity increases inherent in microwave synthesis.

Biotage PathFinder is a Web-based service featuring a unique microwave synthesis database including more than 5,200 carefully selected microwave reactions. It gives chemists direct access to years of experience in microwave synthesis, conducted on Biotage microwave systems and delivered in a detailed, easy-to-use, and accessible format. More information can be found in the Biotage PathFinder section on page 130 of this catalog or online at www.biotagepathfinder.com.

With more experience in microwave chemistry, it is possible to translate conventional methods into microwave methods. As previously mentioned, reactions proceed faster using microwave synthesis simply because they are conducted at higher temperatures. As a basic rule of thumb, using the Arrhenius equation, a 10-degree increase in reaction temperature doubles the reaction speed. For example, if your reaction took four hours at 60 °C, it will take approximately two hours at 70 °C. However keep in mind, this new reaction temperature must be evaluated according to substrate and reagent stabilities as in all chemistry. The reaction temperature and time can be easily converted using the prediction chart provided in Table 1.

Prediction Chart

Microwave Synthesis Time Prediction Chart

Temp °C	Time - change in field color represents change in unit (houers/minutes/seconds)									
20	1	2	4	6	8	12	24	48	96	172
30	30	1	2	3	4	6	12	24	48	86
40	15	30	1	1.5	2	3	6	12	24	43
50	8	15	30	45	1	2	3	6	12	22
60	4	8	15	23	30	45	1.5	3	6	11
70	2	4	8	11	15	23	45	1.5	3	5
80	56	2	4	6	8	11	23	45	1.5	3
90	28	56	2	3	4	6	11	23	45	1.3
100	14	28	56	1.4	2	3	**6**	11	23	40
110	7	14	28	42	56	1.4	3	6	11	20
120	4	7	14	21	28	42	1.4	3	6	10
130	2	4	7	11	14	21	42	1.4	3	5
140	53	2	4	5	7	11	21	42	1.4	3
150	26	53	2	3	4	5	11	21	42	1
160	13	26	53	1	2	3	**5**	11	21	38
170	7	13	26	40	53	1	3	5	11	19
180	3	7	13	20	26	40	1	3	5	9
190	1.6	3	7	10	13	20	40	1	3	5
200	49	1.6	3	5	7	10	20	40	1	2
210	25	49	2	2	3	5	10	20	40	1
220	12	25	49	1	1.6	2	5	10	20	35
230	6	12	25	37	49	1	2	5	10	18
240	3	6	12	19	25	37	1	2	5	9
250	2	3	6	9	12	19	37	1	2	4

Table 1. Time Prediction chart
Change in field color represents change in unit (hour/minutes/seconds) relevant to your starting unit. For example, if your reaction took 6 hours at 100 °C (in this instance, white=hours), it will take approximately 5 minutes at 160 °C (blue=minutes), see red numbers in the table above.

With courtesy of David Rudge, AstraZeneca, Macclesfield, UK

Synthesis Optimization

Practical Tips and Tricks When Performing Microwave Synthesis

Solvent

- Different solvents interact very differently with microwaves because of their diverse polar and ionic properties.

- Acetonitrile, DMF, and alcohols are often used for microwave-assisted organic synthesis.

- You might not need to change from the solvent that is specified for the reaction under traditional chemistry conditions. First, try using the solvent that you would normally use.

- Polar solvents (e.g. DMF, NMP, DMSO, methanol, ethanol, and acetic acid) couple well with microwaves due to their polarity (i.e. the temperature will rise substantially with these solvents).

- Nonpolar solvents (e.g. toluene, dioxane, THF) can be heated only if other components in the reaction mixture respond to microwave energy (i.e. if the reaction mixture contains either polar reactants or ions). When using less polar solvents, more concentrated reaction mixtures are preferred. Under such circumstances, very high temperatures can be achieved.

- Ionic liquids are reported as new, environmentally friendly, recyclable alternatives to dipolar aprotic solvents for organic synthesis. The dielectric properties of ionic liquids make them highly suitable for use as solvents or additives in microwave-assisted organic synthesis. Ionic liquids absorb microwave irradiation extremely efficiently and they have a low vapor pressure, enhancing the heating process. Despite ionic liquids being salts, they dissolve easily in a wide range of organic solvents, and can be used to increase the microwave absorption of low-absorbing reaction mixtures.

- Solvents can behave differently at elevated temperatures and most solvents become less polar with increased temperature. Water is the most interesting case. At elevated temperatures, the bond angle in water widens and its dielectric properties approach those of organic solvents. Water at 250 °C actually has dielectric properties similar to acetonitrile at room temperature. Thus, water can be used as a pseudo-organic solvent at elevated temperatures where organic molecules will dissolve, not only because of the temperature, but also because of the change in dielectric properties. This makes some reactions that normally would not run in water perfectly feasible.

- Solvents with low boiling points (e.g. methanol, dichloromethane, and acetone), give lower achievable temperatures due to the pressure buildup in the vessel. If a higher absolute temperature is desirable to achieve a fast reaction, it is advisable to change to a closely related solvent with a higher boiling point (e.g. dichloroethane instead of dichloromethane).

Microwave Solvent Temperature and Pressure Chart

Solvent (Volume=2.5 mL)	Boiling Point (1 atm) (°C)	Attained Temp (°C)	Attained Pressure (bar)
1-Methyl-2-pyrrolidinone (NMP)	202	250	1
1,2-Dichloroethane	83	180	5
1,2-Dimethoxyethane (DME)*	85	130	3
1,4-Dioxane*	100	56	0
Acetone	56	150	7
Acetonitrile	81	180	13
Dichloromethane	40	110	5
Dimethylsulfoxide (DMSO)	189	250	1
Ethanol	78	155	13
Methanol	65	145	17
N,N-Dimethylformamide (DMF)	153	250	4
o-Dichlorobenzene	180	250	2
Tetrahydrofuran (THF)*	65	110	3
Water*	100	165	10
Xylenes*	137	50	0

Table 2. Microwave Solvent Temperature and Pressure Chart
To show the responses of various solvents to microwave irradiation, we measured the temperature and pressure of pure solvents after 100 seconds of microwave irradiation in the Biotage Emrys™ Optimizer. "Fixed Hold Time" was set to "Off," "Absorption Level" was set to "Normal," and the temperature was set to 250 °C.

* Some solvents can reach higher temperatures if they contain microwave-absorbing material and are heated for a longer time. For the very poorly microwave-absorbing solvents, much higher temperatures have been observed in various reactions, for example: xylene (150 °C), 1,4-dioxane (200 °C), water (220 °C), 1,2-dimethoxyethane (200 °C), and tetrahydrofuran (180 °C).

Volume

Do not exceed or fall below the vial's specified volume. Too low a volume will give an incorrect temperature measurement; too high a volume does not leave sufficient head space for pressure build-up. Since microwave heating is strongly dependent upon geometry and volume, Biotage provides four different vial sizes to ensure similar performance and scalability throughout the entire volume range (Figure 3).

Figure 3. Biotage Microwave Vials.
For more information on Biotage's Microwave Vials, go to page 119.

Synthesis Optimization

Concentration

The concentration depends on the type of chemistry that is performed. A unimolecular reaction is independent of concentration and can be performed in very diluted solutions. Bi- or tri-molecular reactions, on the other hand, are highly dependent on the concentration; a higher concentration gives a faster reaction. The maximum obtainable concentration is dependent on the properties of the substrates and reagents as well as the properties of the solvent(s).

Phase

In a Biotage microwave synthesizer, all different phases can be used, i.e., solution phase, solid phase, solid-supported reagents, solvent-free and scavenger resins. Please consider the difficulties in correctly measuring the temperature when solvent-free techniques are used.

Stirring

Always add a magnetic stirring bar to the process vial. Stirring improves mass transport, avoids tearing of solid materials and is beneficial for rapid heat distribution.

Inert Atmosphere

In general, inert atmosphere is not initially employed in microwave chemistry and is often not needed even if the reaction is carried out in this way conventionally. If needed, flush the vial with an inert gas before capping.

Time

As expected, the reaction time will be a function of the reaction temperature and the thermal stability of substrates, reagents, and products. A typical reaction normally requires two to 15 minutes of irradiation. When trying out a new reaction for the first time, three to five minutes of reaction time is normally used, provided the required temperature is compatible with all of the ingredients. See also the prediction chart on page 43.

Temperature

Biotage Initiator works in a temperature range from 40 °C up to 250 °C. Optimally,the reaction temperature should be as high as substrates and products allow before they start decomposing or as high as the reaction solvent allows, whichever is lowest.

Pressure

The reactions can safely be performed at pressures of up to 20 bar. If the pressure in a vial becomes higher, the heating is automatically stopped and cooling begins. For an indication of the expected pressure of a reaction, please use the solvent table or the vapor pressure calculator at www.biotagepathfinder.com.

Optimize your reaction

Optimize Your Reaction

With the speed and simplicity offered by microwave synthesis in general and Biotage microwave synthesizers in particular, optimization has never been easier.

Optimizing a microwave synthesis is very similar to optimizing a conventional synthesis. If your first reaction was not a success, changing the target temperature and reaction time can cause significant improvement. All remaining parameters (e.g. concentration, solvent, reagent, etc.) should be varied when applicable.

If the reaction is not proceeding at all or not going to completion:

- Increase the temperature. As long as the reactants/reagents can withstand the higher temperature, the only limit is the pressure build-up in the vial and the security limit of 250 °C.
- Extend the reaction time.
- Increase the concentration(s) of reagent(s).
- Change the solvent. Some solvents (e.g. water) will behave differently at high temperatures as they become less polar. This makes some reactions that normally would not work in polar solvents perfectly feasible.
- Change the reagent(s). Due to the high temperatures that can be reached, sometimes a less reactive, but more temperature-stable, reagent can be used.

If you see decomposition of reactants/reagents/products:

- Lower the temperature.
- Shorten the reaction time. It may be that the desired product is actually formed, but then decomposes rapidly at elevated temperatures. In some cases it is therefore possible to "trap" the product by using a shorter reaction time.
- Decrease the concentration(s) of reagent(s).
- Change to a more temperature-stable reagent.

How Microwave Synthesis Impacts Chemistry Research and Development

Microwave synthesis can have a significant impact on chemistry research and development if its strengths, namely speed and simplicity, are capitalized upon.

Speed

The main benefit of microwave synthesis is shorter reaction times through an increase in reaction temperature. Herein we describe how this affects chemistry development.

Synthesis Optimization

Chemistry, like all sciences, consists of iterations of hypotheses and experiments with results guiding the progress and development of projects. The shorter reaction times that microwave synthesis provides make it ideal for rapid reaction scouting and optimization, allowing chemists to proceed very rapidly through the hypothesis-experiment-result iterations, resulting in more decision points per time unit (Figure 4).

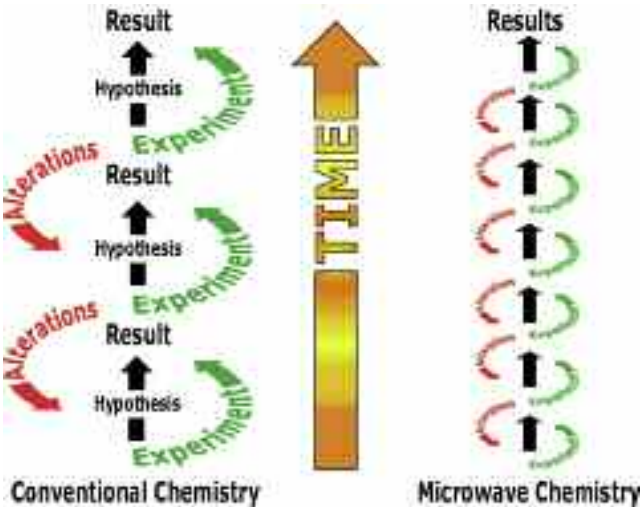


Figure 4. Microwave-assisted organic chemistry can be used to speed up the chemistry development by allowing more experiments to be conducted per time unit.

The only prerequisite for this approach to be productive is that reactions need to be successful enough times to make it worthwhile (i.e., the molecules have to withstand the extreme thermal conditions for the short time that the reaction proceeds). At a time when the trend in organic synthesis is moving toward using ambient conditions, it may seem incredulous to heat reactions above 200 °C nevertheless; most reagents, catalysts, and substrates have been shown to survive extreme temperatures for short periods of time.

In order to fully benefit from this technique, chemists have to be ready to risk trying reactions at high temperatures and be prepared to fail or succeed. While failure could cost a few minutes, success would gain many hours or even days. To gain the most from microwave synthesis, it needs to be regularly used as the preferred technique for synthesis.

Simplicity

Simplicity is one of the assets of modern microwave equipment. Reactions are performed in glass vials sealed with crimp caps; the vials are subsequently heated in the microwave cavity at a constant temperature for a set period of time. The reaction can be analyzed by sampling through the septum. With the availability of proper analytical facilities, the time from the genesis of an idea to the result can be a matter of minutes, enabling the chemist to rapidly test the feasibility of novel synthetic routes.

Figure 5. The simple preparations needed to perform microwave synthesis on a Biotage system.

Productivity

Successful chemistry development relies on two basic foundations: (1) the level of synthetic complexity and (2) the likelihood of a positive outcome.

Thus, a synthetic procedure with a greater likelihood of success with the least possible effort usually becomes established and widely used. As mentioned previously, the synthetic procedure with microwave synthesis is generally of very low complexity. Until recently, there has been an uncertainty about the likelihood of success using microwave synthesis. However, during the past couple of years, there has been a real break-through in this area as indicated by the vast number of reviews published,[12] showing the utility of this technique. The extreme simplicity, the proven likelihood of good results, and the wide reaction range that can be easily performed has made microwave synthesis one of the most valuable tools for the chemist during the past few years.

This simple dogma can have enormous effects on the chemistry development as shown by Chris Sarko and his colleagues[13] at the second Coherent Synthesis conference in San Diego, April 2002. The same group showed that the technology-enhanced chemistry development by over 1000% in individual optimization cycles and that an overall productivity enhancement of 200 - 400% was achieved in their library syntheses.

Solid-bound Reagents and Scavengers Simplify Microwave Synthesis Workup

The utilization of solid-bound reagents, instead of the free-form reagent in microwave synthesis, simplifies the workup since the spent reagent can simply be filtered off at the end of the reaction. Reagents that are otherwise incompatible in their free form can be utilized within the same pot, thus allowing multistep processes to be performed without the need for work-up between steps, which not only saves time but also enables "green" chemistry. For example, oxidation and reduction reactions can be performed in one pot through sequential addition of the appropriate solid-bound reagents without the need for filtration or work-up between steps. The polymer backbone is quite stable to the high temperatures of microwave heating as well as to mechanical agitation used in these short reactions.

Solid-bound scavengers can selectively react with excess reagents and reaction byproducts to quench reactions, allowing removal of bound chemicals by filtration. Using solid-bound scavengers, chemists can save time and achieve compound purities exceeding 85% for many reactions. Solid-bound scavengers can also be used as an alternative to extraction and chromatography, or to greatly speed up initial cleanup of large reagent excesses prior to chromatography. Biotage makes scavengers for a variety of electrophiles, nucleophiles and metals. Similar to the solid-supported reagents, incompatible functionalities can be utilized together as a "scavenger cocktail" to remove multiple impurities, as shown in Figure 1.

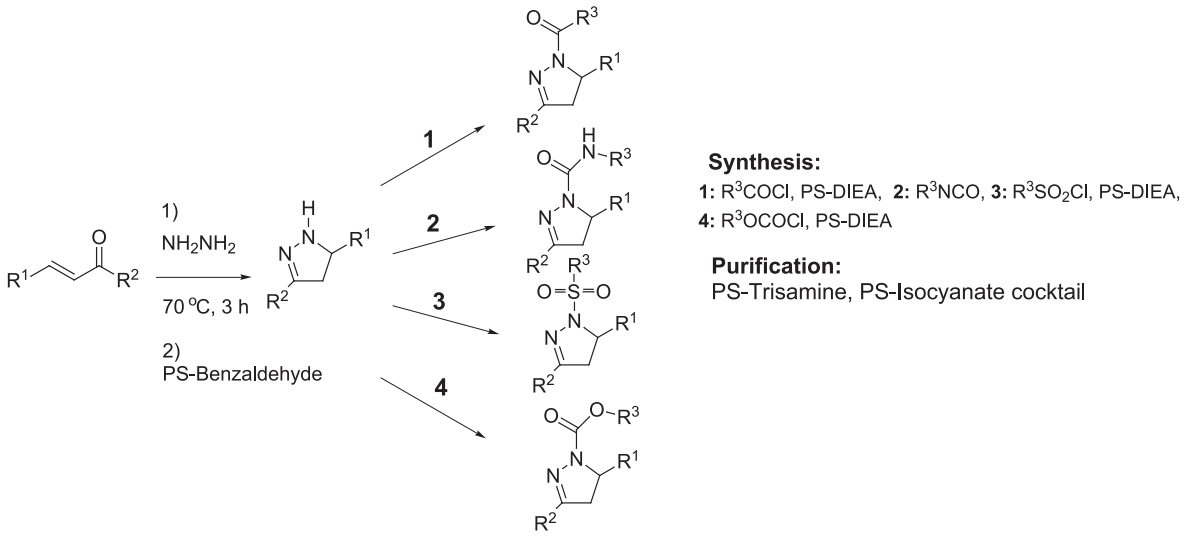


Figure 1. Purification of N-substituted pyrazolines using multiple scavenger resins. Multiple scavenger resins may be used simultaneously to speed purification. In this example, N-substituted pyrazolines were synthesized from chalcone templates.[13] A cocktail of PS-Isocyanate and PS-Trisamine was used in the second step to remove unreacted pyrazoline and electrophile, respectively. By using a mixture of two scavenger resins, removal of both starting materials is assured, for cases where full conversion of the limiting pyrazoline core does not occur.

Reagents and Scavengers

The use of scavenger/reagent resins in a catch-and-release protocol allows the product to be immobilized while the impurities and solvents are washed away. The product is then released from the solid support using a low-boiling solvent and a competing nucleophile. This technique is especially useful when the reaction yields a complex mixture and when the reaction solvent is high boiling (e.g. DMF, NMP, etc.).

Using microwave heating speeds up sluggish reactions and also enables the use of solvents that are normally "nonswelling" in relation to low cross-linked PS-resins.

It is also advantageous to use polymer scavengers in conjunction with polymer reagents to remove excess soluble reagents or byproducts from a reaction mixture after completion. Because bound reagents and bound scavenger functionalities do not react with each other, scavengers may be added directly to a reaction while a polymer reagent is present for final purification.

Mesh to Micron Conversion Table

Mesh	Micron
20	850
25	710
35	500
50	300
60	250
70	212
100	150
140	106
200	75
325	45
400	38

Table 1. A table which converts the mesh sizes for resin beads to their average diameter in microns.

Reagent Selection

Resin Selection for Solution-Phase Synthesis

Solvent Compatibility

Lightly cross-linked polystyrene resins typically require the use of solvents that will swell the resin to allow reagents from the bulk solution to gain access to the resin-bound functional groups. If the reaction solvent does not swell the resin, it may be necessary to add a co-solvent that is compatible with the resin. In this catalog, the names of lightly cross-linked polystyrene resins have a "PS-" prefix.

The resin-bound functional groups of the more highly cross-linked macroporous resins come in contact with reagents by diffusion through the pore network and do not require the use of a solvent that will swell the resin. Macroporous resins are effective in any solvent that is not reactive with the resin functionality and do not swell or undergo significant volume changes in the presence of solvents that swell PS resins, such as DCM and THF. In this catalog, the names of macroporous resins have an "MP-" prefix.

Mixtures of a swelling and non-swelling solvent, such as 1:1 THF/MeOH, can often be used to effect reactions that require the presence of the non-swelling solvent. The swelling properties of lightly cross-linked polystyrene can be affected by the functional group when present at high levels (high capacity or loading). Biotage generally maintains the capacity of polymer reagents below 2 mmol/g to avoid these effects and minimize reactivity differences between reagent groups on the polymer. Table 1 identifies effective and ineffective solvents for polystyrene bead swelling.

Solvent Type	Swelling Solvents	Non-swelling Solvents
Hydrocarbon	Toluene, xylene	Hexane
Chlorinated	DCM, dichloroethane, chlorobenzene	
Ether	Tetrahydrofuran (THF), dioxane, diglyme	Ethyl ether
Ketone	Cyclohexanone	Acetone
Polar aprotic	DMF, dimethylsulfoxide (DMSO), N-methylpyrolidone (NMP)	ACN
Protic	Ethoxyethanol	MeOH, EtOH, isopropanol, water

Table 1. Solvent compatibility of polystyrene resins. Lightly cross-linked polystyrene ("PS-") resins need to be used in solvents that swell the resin beads.

Reagent Selection Guide

Which Kind of Reagent? What Application?	Recommended Polymer Reagent
Bases	
Basic Quenching, Neutralize Ammonium Salts	MP-Carbonate
Strong Tertiary Amine Base (e.g. mesylate formation)	PS-DIEA
Tertiary Amine Base (e.g. format of amides, sulfonamides, carbamates)	PS-NMM
Strong Base (e.g. alkylation of phenols amines, acivated methylene compounds; esterification of carboxylic acids)	PS-TBD
Acids	
Acid Quenching	MP-TsOH
Amine Purification	MP-TsOH
Coupling Agents	
Amide or Ester	PS-Carbodiimide PS-HOBt (HL) ACTU
Activated Ester	PS-HOBt (HL) ACTU
Protecting Group Transfers	PS-HOBt (HL)
Reductants	
Carbonyl Reduction	MP-BH_4
Reductive Amination	MP-$CNBH_3$ MP-BH_4 (with $Ti(OiPr)_4$) MP-$BH(OAc)_3$
Electrophilic Activation	
Halogenation (chlorination, bromination, iodination)	PS-Triphenylphosphine
Phenylether Formation (e.g. Mitsunobu reaction)	PS-Triphenylphosphine
Thioester Active Intermediate	PS-Thiophenol
Alcohol Activation	PS-TsCl
Acid and Sulfonyl Chloride Activation	PS-DMAP
Nucleophilic Activation	
Carbon-Carbon Bond (e.g. Wittig reaction)	PS-Triphenylphosphine
Sulfonyl Hydrazone Formation (e.g. Hurd-Mori thiadiazole synthesis)	PS-$TsNHNH_2$
Catalysts	
Acids	MP-TsOH
Acyl Transfer	PS-DMAP
Tetrakis (triphenylphosphine) palladium (O)	PS-PPh_3-Pd
Oxidant	
TEMPO	MP-TsO-TEMPO

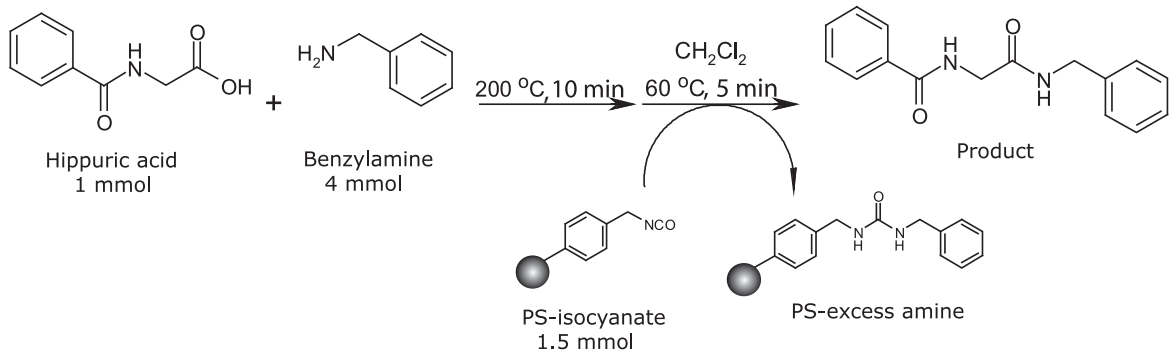
Microwave Stability Study

Microwave Resin Stability

Both PS- and MP- scavengers and reagents were tested for microwave stability in three commonly used solvents (e.g. DCM, THF, and DMF) at the highest temperatures achievable in each solvent for 5-15 mins. The resins were then analyzed for capacity, breaking/agglomeration, and the presence of volatile or nonvolatile leachable decomposition products.

Summary of Results

- PS- and MP- behaved similarly; PS-supports swelled and occupied more volume
- The resins were stable to microwave heating and did not break or agglomerate
- No volatile or nonvolatile leachable decomposition products were found over the range of solvents studied (e.g. DCM, THF, and DMF)
- The capacities of the PS- and MP-isocyanate and MP-triacetoxyborohydride resins was reduced significantly. This, however, does not mean that they cannot be used with microwave heating because
  - (a) the reaction would most probably be performed at a lower temp/time (Example 1)
  - (b) the reaction rates may be faster than the decomposition rates



Example 1.

REFERENCES

References

1. Galema, S. A. Microwave Chemistry. *Chem. Soc. Rev.* **1997**, 26, 233-238.

2. Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. Dielectric parameters relevant to microwave dielectric heating. *Chem. Soc. Rev.* **1998**, 27, 213.

3. Gedye, R. et al. The use of microwave ovens for rapid organic synthesis. *Tetrahedron Lett.* **1986**, 27, 279-282.

4. Giguere, R. J. et al. Application of commercial microwave ovens to organic synthesis. *Tetrahedron Lett.* **1986**, 27, 4945-4948.

5. Langa, F. et al. Microwave irradiation: more than just a method for accelerating reactions. *Contemp. Org. Synth.* **1997**, 4, 373-386.

6. Gedye, R. N., Wei, J. B. Rate enhancement of organic reactions by microwaves at atmospheric pressure. *Can. J. Chem.* **1998**, 76, 525-532.

7. Pagnotta, M.; Pooley, C. L. F.; Gurland, B.; Choi, M. Microwave activation of the mutarotation of alpha-D-glucose - an example of an intrinsic microwave effect. *J. Phys. Org. Chem.* **1993**, 6, 407-411.

8. Perreux L., Loupy A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium and mechanistic considerations. *Tetrahedron*, **2001**, 57, 9199-9223.

9. Hayes, B. L., *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing: Matthews, NC **2002**.

10. Stuerga, D.; Gonon, K.; Lallemant, M. Microwave heating as a new way to induce selectivity between competitive reactions. application to isomeric ratio control in sulfonation of naphthalene. *Tetrahedron* **1993**, 49, 6229-6234.

11. Baghurst, D. R.; Mingos, D. M. P. Superheating effects associated with microwave dielectric heating. *J. Chem. Soc. Chem Commun.* **1992**, 674-677.

12. a) Dzierba, C. D.; Combs, A. P. Microwave-Assisted Chemistry as a Tool for Drug Discovery. *Annual Reports in Medicinal Chemistry* **2002**, 37, 247-256.

    b) Santagada, V.; Perissutti, E; Caliendo, G. The Application of Microwave Irradiation as New Convenient Synthetic Procedure in Drug Discovery. *Curr. Med. Chem.* **2002**, 9, 1251-1284.

    c) Wathey, B.; Tierney, J.; Lidström, P. Westman, J. The Impact of Microwave-Assisted Organic Chemistry on Drug Discovery. *Drug Discovery Today*, **2002**, 7, 373-380.

    d) Wilson, N. S.; Roth, G. P. Recent Trends in Microwave-Assisted Synthesis. *Curr. Opin. Drug Disc. & Dev.* **2002**, 5(4), 620-629.

    e) Larhed, M; Hallberg, A. Microwave-Assisted High Speed Chemistry: A New Technique in Drug Disvovery. Drug Discovery Today **2001**, 6, 406-416.

    f) Kappe, C. O. High Speed Combinatorial Synthesis utilizing Microwave Irradiation. *Curr. Opin. Chem. Bio.* **2002**, 6(3), 314-320.

    g) Larhed, M.; Moberg, C.; Hallberg, A. Microwave-Accelerated Homogenous Catalysis in Organic Chemistry. *Acc. Chem. Res.* **2002**, 35(9), 717-727.

    h) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave-Assisted Organic Synthesis-A Review. *Tetrahedron*, **2001**, 57, 9225-9283.

    i) Lidström, P., Westman, J., Lewis, A. Enhancement of Combinatorial Chemistry by Microwave-Assisted Organic Synthesis. *Comb Chem. High Throughput Screen*. **2002**, 5, 441-458.

    j) Lidström, P.; Tierney, J. P. (ed) *Microwave Assisted Organic Synthesis*. Blackwell Publishing, Oxford, UK **2005**.

13. Sarko, C. Timesavings associated with microwave-assisted synthesis: a quantitative approach, in Lidström, P.; Tierney, J. P., (Ed) *Microwave Assisted Organic Synthesis*. Blackwell Publishing Oxford, UK **2005**.


Biotage

Solid-bound Reagents

Save Time and Achieve Higher Purities

Solid-bound Reagents

Resins allow chemists to quickly remove excess reagents and by-products of organic synthesis reactions using filtration rather than liquid-liquid extraction, chromatography, or crystallization. In addition, polymer-bound reagents provide some unique benefits, such as selectivity and immobilization of toxic intermediates. Biotage has developed a variety of scavenger resins and bound reagents to facilitate a wide range of solution-phase reactions and workups.

Resin-bound Reagents

Resin-bound reagents perform in a manner similar to their unbound equivalents, making it easy to optimize synthetic transformations to take advantage of reagent immobilization. Resin-bound reagents are particularly useful for multiple-step reactions, saving time, and reducing solvent requirements. A subset of resin-bound reagents, known as catch-and-release resins, "catch" molecules as activated polymer intermediates, then (after a wash-step and second transformation) release the purified product into solution. Resin-bound reagents from Biotage include acids, bases, coupling agents, and other types.

Polymer-bound reagents are functional polymers designed to perform synthetic transformations by mimicking the activity of their solution counterparts. Polymer-bound reagents simplify product purification, because spent and excess reagents can be easily removed by filtration (Figure 1). The utility of polymer-bound reagents and scavengers is not limited to one-step transformations and can be extended to multiple-step syntheses of complex molecules, including natural products.[1]

It is often advantageous to use polymer scavengers in conjunction with polymer reagents to remove excess soluble reagents or by-products from a reaction mixture after completion. Because bound reagent and bound scavenger functionalities do not react with each other, scavengers may be added directly to a reaction while a polymer reagent is still present for final purification.

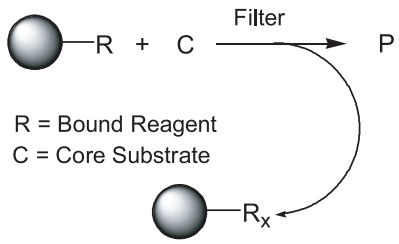


Figure 1. Polymer-bound reagents simplify product purification, because spent and excess reagents can be removed by filtration.

References

1. Bauer, U. *et. al. Tetrahedron Lett.* **2000**, 41, 2713.

Solid-bound Reagents

Polymer-Supported Coupling Agents

- PS-Carbodiimide
- PS-HOBt(HL)
- PS-DMAP

PS-Carbodiimide simplifies the difficult task of purification after amide and ester synthesis as the cyclohexylurea by-product remains bound to the resin. PS-HOBt(HL) is a polymer-supported precursor for resin-bound active esters that, once synthesized, may be used for parallel synthesis of amides by mixing them with appropriate amines and isolating the final products by filtration and evaporation. PS-DMAP catalyzes amide and ester formation and is useful for pre-forming acylated or sulfonated pyridinium salts. We also offer ACTU, a uronium salt coupling agent specific for coupling carboxylic acids to PS-HOBt(HL) in 100% DMF.

Polymer-Supported Reducing Agents

- MP-Borohydride
- MP-Triacetoxyborohydride
- MP-Cyanoborohydride
- PS-DES

MP-Borohydride is effective in a wide range of reductions reported for sodium borohydride, including carbonyl and imine reduction, and reductive amination with titanium isopropoxide, allowing the product to be isolated by simple filtration. MP-Triacetoxyborohydride is a versatile reducing agent for the reductive amination of carbonyl compounds. It offers scope and reactivity similar to sodium triacetoxyborohydride in reductive amination reactions and is active under neutral conditions. MP-Cyanoborohydride is effective for a wide range of reductive aminations and offers the advantage that the toxic cyanide by-products remain resin bound and are removed by filtration. PS-DES is a resin-bound equivalent of triethylsilane and has a number of applications as a mild reductant.

Polymer-Supported Catalyst

- PS-PPh_3-Pd

PS-PPh_3-Pd catalyzes Suzuki and Heck coupling reactions, taking the place of the homogeneous catalyst. The palladium and triphenyl phosphine remain resin-bound, simplifying product isolation and purification.

Polymer-Supported Oxidizing Agent

- MP-TsO-TEMPO

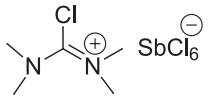
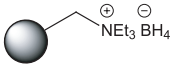
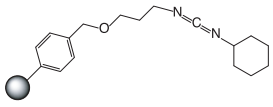
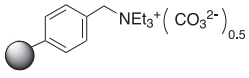
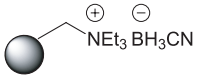
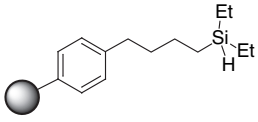
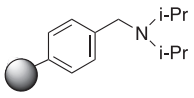
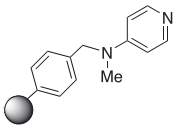
MP-TsO-TEMPO cleanly oxidizes activated primary and secondary alcohols to the corresponding aldehydes and ketones under mild reaction conditions. Use of the reagent avoids the generation of unwanted side products.

Abbreviations

ACN	—	acetonitrile	Fmoc	—	9-fluorenylmethoxycarbonyl
Boc	—	t-Butoxycarbonyl	HOAc	—	acetic acid
Cbz	—	Carbobenzyloxy	HOAt	—	N-hydroxy-9-azabenzotriazole
DBAD	—	di-tert-butylazodicarboxylate	HOBt	—	N-hydroxybenzotriaole
DCE	—	1,2 dichloroethane	MeOH	—	methanol
DCM	—	dichloromethane	PEG	—	polyethylene glycol
DEAD	—	diethylazodicarboxylate	Py	—	pyridine
DIC	—	diisopropylcarbodiimide	PyBroP	—	Bromo-tris-pyrrolidine phosphonium hexafluorophosphate
DIEA	—	diisopropylethylamine			
DMA	—	dimethylacetamide	TBAF	—	tetrabutylammonium fluoride
DMAP	—	dimethylaminopyridine	TEA	—	triethylamine
DMF	—	dimethylformamide	TFA	—	trifluoroacetic acid
EtOH	—	ethanol	THF	—	tetrahydrofuran

Solid-bound Reagents

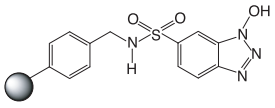
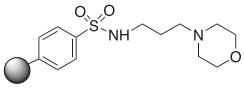
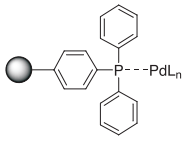
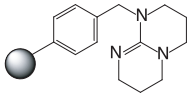
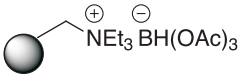
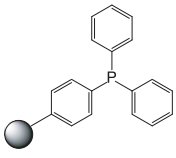
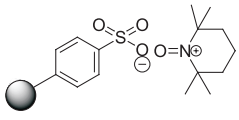
Table of Solution-Phase Solid-bound Reagents

Product	Class	Structure	Function	Part Numbers	Page
ACTU	Resin-bound Coupling Agent		Preparation of PS-HOBt(HL) active esters; coupling of acids and amines	3 g - 800516 10 g - 800465 25 g - 800466 100 g - 800467 1000 g - 800468	62
MP-Borohydride	Resin-bound Reducing Agent		Reduction of carbonyl compounds, azides and oximes, reductive amination, reduction of conjugated enones to unsaturated alcohols	3 g - 800512 10 g - 800401 25 g - 800402 100 g - 800403 1000 g - 800404	66
PS-Carbodiimide	Resin-bound Coupling Agent		Coupling agent for amide and ester synthesis, other activated ester formation	3 g - 800508 10 g - 800369 25 g - 800370 100 g - 800371 1000 g - 800372	68
MP-Carbonate	Resin-bound Base		General base, neutralizes ammonium salts, scavenges acids, acidic phenols	3 g - 800493 10 g - 800267 25 g - 800268 100 g - 800269 1000 g - 800314	71
MP-Cyanoborohydride	Resin-bound Reducing Agent		Reductive amination; reductive methylation of primary and secondary amines, reduction of imines; reduction of conjugated enones to unsaturated alcohols	3 g - 800511 10 g - 800405 25 g - 800406 100 g - 800407 1000 g - 800408	73
PS-DES	Resin-bound Reducing Agent		Reducing agent, precursor for silyl triflate, cyanide and azide	3 g - 800507 10 g - 800142 25 g - 800143 100 g - 800144	77
PS-DIEA	Resin-bound Base		Tertiary amine base	3 g - 800494 10 g - 800279 25 g - 800280 100 g - 800281 1000 g - 800312	78
PS-DMAP	Resin-bound Base		Catalyst for acylation reactions, catch-and-release applications	3 g - 800492 10 g - 800288 25 g - 800289 100 g - 800290 1000 g - 800313	80

Solution-phase resins sorted alphabetically. See individual resin entries for additional application information.

Solid-bound Reagents

Table of Solution-Phase Solid-bound Reagents

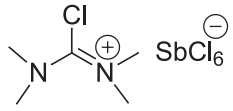
Product	Class	Structure	Function	Part Numbers	Page
PS-HOBt(HL)	Resin-bound Active Ester Reagent		Active ester reagent, coupling of acids and amines, protecting group (Fmoc, Cbz, Boc) transfer	3 g - 800509 10 g - 800417 25 g - 800418 100 g - 800419 1000 g - 800420	82
PS-NMM	Resin-bound Base		Tertiary amine base	3 g - 800496 10 g - 800282 25 g - 800283 100 g - 800284 1000 g - 800318	88
PS-PPh_3-Pd	Resin-bound Catalyst		Catalyst for Suzuki and Heck coupling reactions, a polymer-supported equivalent of tetrakis (triphenylphosphine)-palladium(0)	1 g - 800473 10 g - 800474 25 g - 800475 100 g - 800476	90
PS-TBD	Resin-bound Base		Alkylation of phenols and amines, esterification of carboxylic acids using alkyl halides, alkylation of activated methylene compounds, dehalogenation of organic halides, high throughput synthesis of aryl triflates and aryl nonaflates, Williamson ether synthesis	3 g - 800513 10 g - 800421 25 g - 800422 100 g - 800423 1000 g - 800424	93
MP-Triacetoxyborohydride	Reducing Agent		Reductive amination with primary and secondary amines	3 g - 800517 10 g - 800413 25 g - 800414 100 g - 800415 1000 g - 800416	98
PS-Triphenylphosphine	Resin-bound Phosphine		Chlorination of acids and alcohols, Wittig and Mitsunobu reactions, scavenging of alkyl halides	3 g - 800510 10 g - 800378 25 g - 800379 100 g - 800380 1000 g - 800381	103
MP-TsO-TEMPO	Oxidant		Oxidation of activated primary and secondary alcohols to the respective aldehydes and ketones	3 g - 800518 10 g - 800482 25 g - 800483 100 g - 800484 1000 g - 800485	108

Solution-phase resins sorted alphabetically. See individual resin entries for additional application information.

ACTU

ACTU

Coupling Reagent

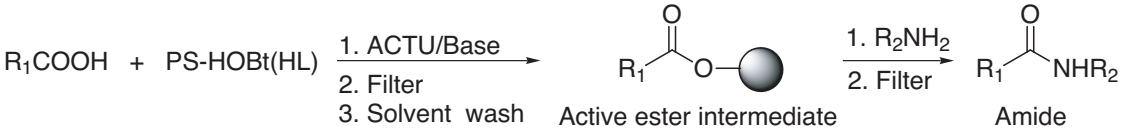


Chemical Name: Chloro-1,1,3,3-tetramethyluronium hexachloroantimonate
Applications: Preparation of PS-HOBt(HL) active esters; coupling of acids and amines
Typical conditions to load acid onto PS-HOBt(HL): 1.2 equiv of carboxylic acid, 1 equiv ACTU, 5 equiv of 2,6-lutidine or 2 equiv of DIEA in DMF at room temperature for 30–60 min
Compatible Solvents: DMF, DMA
Storage: Cool, dry location

Polymer-supported HOBt active esters react with primary and secondary amines to produce amides of high quality.[1,2] The standard method for making PS-HOBt(HL) active esters using 1,3-diisopropylcarbodiimide (DIC) with catalytic N,N-dimethylaminopyridine (DMAP), typically requires a DCM/DMF solvent mixture.[1,3] 2-Chloro-1,1,3,3-tetramethyluronium hexachloroantimonate (ACTU) is a new reagent which allows polymer-supported active esters of PS-HOBt(HL) to be prepared in pure DMF. ACTU addresses the problem that many carboxylic acids of interest are not soluble in DCM.

An alternative method for amide synthesis, which is effective in DMF, employs PS-Carbodiimide with HOBt as an additive.[4-6] The use of ACTU with PS-HOBt(HL) complements this method and has the additional advantage that the product amide is usually formed in a low-boiling solvent thus avoiding having to isolate the product from DMF. Moreover, unlike the PS-Carbodiimide method, the ACTU/PS-HOBt(HL) protocol does not require post-reaction scavenging.

ACTU and PS-HOBt(HL) are used to synthesize amides, according to Scheme 1. The polymer-supported active ester intermediate may be prepared in bulk and distributed to multiple reaction vessels, or used to prepare amides in a one-pot process. Since active ester and amide formation are two distinct steps, the PS-HOBt(HL) ester can be purified by solvent washing to remove excess coupling reagent, by-products, and DMF prior to the acylation step. Amine acylation can be performed in more volatile solvents, such as THF or DCM. This is an advantage of the bound active ester approach compared with using soluble coupling agents, e.g. HBTU, or the PS-Carbodiimide/HOBt method. With these alternative methods the product has to be isolated from high-boiling DMF.



Scheme 1. ACTU and PS-HOBt(HL) are used to synthesize amides

Active Ester Formation

Optimum conditions for preparing PS-HOBt(HL) active esters using ACTU are given in Table 1. Two sets of coupling conditions worked well with a wide range of carboxylic acids. Examples of active ester yields for various acids are shown in Table 2. Method A (page 64) worked well for most of aromatic and aliphatic carboxylic acids and was found to be very efficient in terms of carboxylic acid usage. In some cases, a greater excess of carboxylic acid was required in order to achieve high yields of active esters (Method B, page 65). Application of a double coupling afforded similar results to Method B (page 65). We found phenylacetic acid and quinaldic acid to form PS-HOBt(HL) esters more reliably and in higher yield than when using the DIC/DMAP method. The difficulty in preparing polymer-supported active esters from phenylacetic acid or acids containing basic groups has been reported.[8]

Variables	Method A	Method B
Equiv Carboxylic acid	1 –1.2	3
Equiv ACTU	1	2
Equiv Base	2,6-lutidine = 5 or DIEA = 3	2,6-lutidine = 4
Time	30 – 60 min	45 min
Temperature	Room Temperature	Room Temperature
Solvent	DMF	DMF

Table 1. Optimum conditions for preparing PS-HOBt(HL) active esters using ACTU

Acylation Step

Amide formation was effected by allowing the PS-HOBt(HL) ester to react with ca. 0.7 equivalent of amine in THF or DCM. Many N-nucleophiles were found to be effective, including primary, secondary, and aromatic amines, as well as amine hydrochlorides. Acylation of nucleophilic amines such as benzylamine did not require addition of a tertiary amine base. However, in reactions with less nucleophilic amines, amide formation was facilitated by adding 0.7 equivalent of triethylamine (TEA) or N,N-diisopropylethylamine (DIEA). Likewise, 1.4 equivalent of tertiary amine was added to reactions with amine hydrochlorides. The use of DMF and/or heat also enhanced acylation of non-nucleophilic amines.[9]

We have found it to be important to wash the bound active ester resin thoroughly with DMF to remove amine hydrochloride salts. In cases where amine acylation was effected in the presence of TEA or DIEA in DCM, incomplete washing of PS-HOBt(HL) ester with DMF prior to acylation afforded samples with amine hydrochloride as an impurity in the product.[10] This was not observed for amine acylation with TEA or DIEA in THF, due to the lower solubility of the amine hydrochloride in THF.[11]

A small array of amides was prepared to explore the scope of this methodology (Table 3, page 64). High purity products were obtained in all cases. Yields were generally high and in the cases where modest yields were obtained with aliphatic amines, this was attributed to incomplete active ester formation. Acylation of aniline was generally in the 70–80% range, which can be attributed to its lower nucleophilicity. Acylation may also be performed with the PS-HOBt(HL) ester as the limiting reagent, in which case excess amine may be scavenged from the product with PS-Isocyanate, MP-Isocyanate, or MP-TsOH.

Carboxylic acids		% Active Ester Formation		
		ACTU (Method A[a])	ACTU (Method B)	DIC/DMAP[b]
1	Benzoic acid	95	N/A	96
2	2,2-Diphenylpropionic acid	95	N/A	89
3	Bromocinnamic acid	97	N/A	N/A
4	Cyclopentylpropionic acid	88	N/A	80
5	Boc-Phe-OH	42	65	45
6	Boc-Ala-OH	N/A	67 (72)[c]	N/A
7	Phenylacetic acid	36	70 (70)[c]	29
8	4-Iodophenoxyacetic acid	8	20	35
9	4-oxo-4H-1-benzopyranoic acid	20	41	22
10	5-Bromonicotinic acid	46	66 (69)[c]	40
11	Quinaldic acid	62	87	47

Table 2. [a]1.2 equivalent of carboxylic acid; [b]4:1 DCM:DMF solvent mixture; [c]double coupling using 2 equiv carboxylic acid, 1.5 equivalent ACTU and 4 equivalent of 2,6 lutidine

ACTU

The ACTU/PS-HOBt(HL) method was compared with PS-Carbodiimide/HOBt for the preparation of benzamides of several acids. Both methods afforded similar results for benzoic acid. ACTU/PS-HOBt(HL) gave a higher yield with phenylacetic acid (93% vs. 70%), whereas PS-Carbodiimide/HOBt gave higher yields with Boc-Ala (90% vs. 61%). The better performance of PS-Carbodiimide/HOBt with Boc-Ala is consistent with previously reported results with amino acids (e.g. Fmoc-Phe and Boc-Phe).[4]

Acid	Method	% Yield			
		Benzylamine	Aniline	1-Phenylpiperazine	Val-OMe HCl
Benzoic	A	95 (99[b])	79	90	-
Cyclopentylpropionic	A	92	76	100	77
Phenylacetic	B	93 (70[b])	73	94	-
Quinaldic	B	100	82	100	-
Z-Phg	B	82	-	85	83
Boc-Ala	B	61 (90[b])	52	67	51

Table 3. Synthesis of amides using ACTU and PS-HOBt(HL)

[a]Benzylamine acylation was carried out in the absence of tertiary amines such as DIEA or TEA.
[b]Product yield using PS-Carbodiimide/HOBt: 2 equiv PS-Carbodiimide, 1.5 equiv acid, 1.7 equiv HOBt and 1 equiv amine in DMF

Racemization

Racemization during amide formation using ACTU/PS-HOBt(HL) was investigated for the coupling of N-benzyloxycarbonyl-L-phenylglycine (Z-Phg) with valine methyl ester. Couplings were performed at 0 °C and 20 °C in DMF and DMF:DCM (1:9) (Table 4). For comparison, couplings were also performed under identical conditions using HATU. Racemization is indicated by the presence of the DL-diastereomer as determined by ^{1}H NMR. Chirality was preserved with ACTU/PS-HOBt(HL) at 0 and 20 °C, and afforded racemization levels significantly lower than HATU at 20 °C. Product yields were similar for ACTU/PS-HOBt(HL) and HATU (60–80%) with higher yields observed at 20 °C.

The racemization generated with ACTU/PS-HOBt(HL) coupling was compared with that of other polymer-supported coupling reagents for the coupling of Z-Phg and Val-OMe HCl (Table 5). Racemization was less using ACTU/PS-HOBt(HL) than when DIC/DMAP was used in conjunction with PS-HOBt(HL).

Solvent	Temperature (°C)	ACTU/PS-HOBt(HL) % DL Diastereomer	HATU % DL Diastereomer
DMF	0	0	8
DMF	20	0	29
DMF:DCM (1:9)	0	0	0
DMF:DCM (1:9)	20	<5	12

Table 4. Racemization study-coupling of Z-Phg-OH and Val-OMe HCl with ACTU/PS-HOBt (HL)

Representative Procedures

Benzyl cyclopentylpropionamide (Method A)

To 200 mg of PS-HOBt resin (1 mmol/g, 0.2 mmol) in a reaction vessel was added a solution of cyclopentylpropionic acid (34 mg, 0.24 mmol) and 2,6-lutidine (107 mg, 1 mmol) in 1 mL of DMF and the reaction mixture was agitated for 2 min. A solution of ACTU (94 mg, 0.2 mmol) in 1 mL DMF was then added and the reaction mixture was agitated for 40 min. The resin was drained and washed with DMF (3 x 3 mL, 5–7 min per wash) and DCM (3 x 3 mL). A solution of benzylamine (15 mg, 0.14 mmol) in 2 mL of DCM was added

to the resin and the reaction mixture was agitated for 16 h. The resin was filtered and washed with DCM (3 x 3 mL). The combined filtrate and washings were concentrated to give the product benzyl cyclopentylpropionamide in 92% yield (NMR purity >95%).

Coupling Agent	% DL Diastereomer	% Yield
ACTU/PS-HOBt(HL)	0	67
DIC/DMAP/PS-HOBt(HL)	30	59
DIC/DMAP	33	65
PS-Carbodiimide	0	70

Table 5. Comparison of racemization for polymer-supported coupling agents[a]
[a] Z-Phg-OH+Val-OMe HCl, 0°C, DMF:DCM (1:9)

1-(Phenylacetyl)-4-phenylpiperazine (Method B)

To 200 mg of PS-HOBt resin (1 mmol/g, 0.2 mmol) in a reaction vessel was added a solution of phenylacetic acid (82 mg, 0.6 mmol) and 2,6-lutidine (86 mg, 0.8 mmol) in 1 mL of DMF and the reaction mixture was agitated for 2 min. A solution of ACTU (188 mg, 0.4 mmol) in 1 mL DMF was then added and the reaction mixture was agitated for 40 min. The solution was drained and the resin was washed with DMF (3 x 3 mL, 5–7 min per wash) and DCM (3 x 3 mL). A solution of 1-phenylpiperazine (23 mg, 0.14 mmol) and triethylamine (14 mg, 0.14 mmol) in 2 mL of DCM was added to the resin and the reaction mixture was agitated for 16 h. The resin was filtered and washed with DCM (3 x 3 mL). The combined filtrate and washings were concentrated to give the product 1-(Phenylacetyl)-4-phenylpiperazine in 94% yield (NMR purity >95%).

Racemization Studies

To 200 mg of PS-HOBt resin (1 mmol/g, 0.2 mmol) in a reaction vessel was added a solution of N-benzyloxycarbonyl-L-phenylglycine (85 mg, 0.3 mmol) and 2,6-lutidine (86 mg, 0.8 mmol) in 1 mL of DMF and the reaction mixture was agitated for 2 min. A solution of ACTU (94 mg, 0.2 mmol) in 1 mL DMF was then added and the reaction mixture was agitated for 40 min at room temperature. The solution was drained and the resin was washed with DMF (3 x 3 mL, 5–7 min per wash) and DCM (3 x 3 mL). A solution of valine methyl ester (23 mg, 0.14 mmol) and DIEA (36 mg, 0.28 mmol) in 2 mL of DCM was added to the resin and the reaction mixture was agitated for 16 h. The resin was filtered and washed with DCM (3 x 3 mL). The combined filtrate and washings were concentrated to give the product Z-Phg-Val-OMe in 67% yield (NMR purity 100%).

Ordering Information

Part Number	Quantity
800516	3 g
800465	10 g
800466	25 g
800467	100 g
800468	1000 g

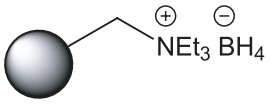
References

1. PS-HOBt(HL) technical information, page 82.
2. Pop, I. E; Deprez, B. P.; Tartar, A. L. *J. Org. Chem.* **1997**, 62, 2594.
3. Hudson, D. *J. Org. Chem.* **1988**, 53, 617.
4. Lannuzel, M.; Lamothe, M.; Perez, M. *Tetrahedron Lett.* **2001**, 42, 6703.
5. PS-Carbodiimide technical information, page 68.
6. General procedure for amide synthesis with PS-Carbodiimide and HOBt in DMF: PS-Carbodiimide (2 equivalents), acid (1.5 equivalent) and HOBt (1.7 equivalent) were combined in 2 mL of DMF and agitated for 10 minutes. The amine (1 equivalent) was added and the reaction mixture agitated for 16 h. MP-Carbonate (2.5 equivalent relative to HOBt) was added to the mixture and the reaction agitated for 2 h. The solution was filtered and the solvent evaporated to obtain the amide product.
7. The method using PS-HOBt(HL) esters for distribution to multiple reaction wells or vessels is described in the PS-HOBt(HL) technical information, page 82.
8. Salvino, J. W.; Kumar, N. V.; Orton, E.; Airey, J.; Kiesow, T.; Crawford, K.; Mathew, R.; Krolikowski, P.; Drew, M.; Engers, D.; Krolikowski, D.; Herpin, T.; Gardyan, M.; McGeehan, G.; Labaudiniere, R. *J. Comb. Chem.* **2000**, 2, 691.
9. The amine hydrochloride impurity observed was always derived from the tertiary amine added in the acylation step.
10. An alternative wash protocol was utilized prior to amine acylation in THF. The bound active ester was washed three times with THF/MeOH (2:1, 10 min per wash) and three times with THF.
11. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, 115, 4397.

MP-Borohydride

MP-Borohydride

Reducing Agent



Resin Type: Macroporous polystyrene
Capacity: 2.5-3.5 mmol/g (based on titration)
Bead Size: 350-1250 microns. 18-52 mesh (95% within)
Chemical Name: Macroporous triethylammonium methylpolystyrene borohydride
Application: Reduction of carbonyl compounds, azides and oximes; reductive reduction of conjugated enones to unsaturated alcohols
Typical Conditions for Aldehyde and Ketone Reduction: 1.0 mmol of carbonyl compound in ethanol or methanol and 0.5 mmol of MP-Borohydride stirred at room temperature for 2 – 12 h, depending on the nature of the carbonyl compound. Product isolated by filtration to remove the resin.
Typical Conditions for Reductive Amination: 1.2 mmol of carbonyl compound, 1.0 mmol of primary or secondary amine in ethanol and 0.1 mL of acetic acid stirred for 4 h at room temperature, followed by 1.5 mmol of MP-Borohydride with gentle agitation overnight at room temperature. Product isolated by filtration to remove the resin.
Compatible Solvents: THF (2.9 mL/g), DCM (3.4 mL/g), MeOH (3.4 mL/g), DMF (2.9 mL/g).
Storage: We recommend storage in a closed container at 5 °C. MP-Borohydride is stable at room temperature for at least one month.

MP-Borohydride is a macroporous, resin-bound borohydride that is a resin-bound equivalent of tetraalkylammonium borohydride. The bound borohydride is a versatile reducing agent[1,2,3] used for the reduction of carbonyl compounds and imines, and the reductive amination of aldehydes and ketones. The resin, in conjunction with some transition metal salts, can also be used for a number of other important reductive applications,[4,5,6] such as reduction of oximes, azides, and alkyl halides. The reduced products are isolated by simple filtration from the resin.

In addition to crystallization and flash chromatography, reductive amination products can be purified by catch-and-release of the amines with MP-TsOH.[7] In the case of reductive amination using an excess of primary amine, PS-Benzaldehyde can be used to scavenge the excess starting primary amine from the product secondary amine. MP-Borohydride can also be used together with titanium(IV) isopropoxide for the reductive amination of aldehydes and ketones. For details, see page 161 for PS-DEAM technical information. Unlike other commercially available resin-bound borohydride reagents, MP-Borohydride is relatively odorless.

Capacity and Stability
The borohydride content of the resin was determined by measuring hydrogen evolution after addition of 1 M HCl. The resin has been found to be stable at 5 °C for at least four months.

Representative Procedure

Reduction of Aldehydes (Table 1, Entry 1)
A mixture of benzaldehyde (0.1 g, 1.0 mmol) and MP-Borohydride (2.6 mmol/g, 0.2 g, 0.5 mmol) in MeOH (5 mL) was stirred at room temperature for 3 h. The resin was filtered and the resin washed with DCM (2 x 3 mL). The combined solution was concentrated to afford benzyl alcohol in 89% yield and 98% GC purity.

Reduction of Ketones (Table 1, Entry 4)
A mixture of cyclohexanone (0.1 g, 1.0 mmol) and MP-Borohydride (2.6 mmol/g, 0.3 g, 0.78 mmol) in absolute MeOH (5 mL) was stirred at room temperature for 8 h. The resin was filtered and washed with DCM (2 x 3 mL). The combined solution was concentrated to afford cyclohexanol in 85% yield and 96% GC purity.

MP-Borohydride

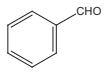
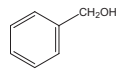
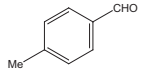
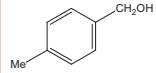
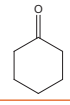
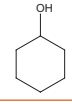
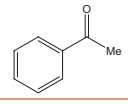
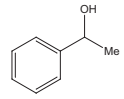
Entry	Carbonyl Compound	Reduced Product	Time (h)	% Yield (isolated)	% Purity (GC)
1			3	89	98
2			3	85	100
3	$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4CH_2OH$	3	80	98
4			8	85	96
5			14	–	6

Table 1. Reduction of carbonyl compounds with MP-Borohydride

Ordering Information

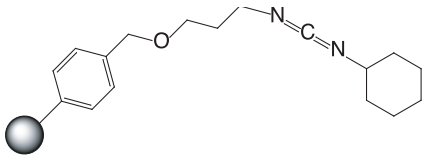
Part Number	Quantity
800512	3 g
800401	10 g
800402	25 g
800403	100 g
800404	1000 g

References

1. Gibson, H. W.; Bailey, F. C. *J. Chem. Soc. Chem. Commun.* **1977**, 815.
2. Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1253.
3. Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, J. P. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1251.
4. Yoon, N. M.; Park, K. B.; Gyoung, Y. S. *Tetrahedron Lett.* **1983**, 24, 5367.
5. Kabalka, G. W.; Wadgaonkar, P. P.; Chatla, N. *Synth. Commun.* **1990**, 20, 293.
6. Yoon, N. M.; Choi, J.; Ahn, J. H. *J. Org. Chem.* **1994**, 59, 3490.
7. Part Numbers: 800478, 3 g; 800479, 25 g; 800480, 100 g; 800481, 1000 g

PS-Carbodiimide

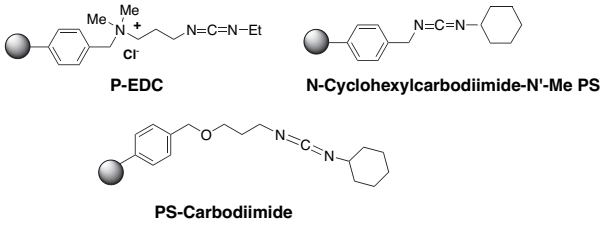
PS-Carbodiimide



Resin-bound Coupling Agent

Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical loading 1.3 mmol/g, minimum loading 1.1 mmol/g (based on generation of Ac_2O from AcOH, measured by ^1H NMR)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: N-Cyclohexylcarbodiimide-N'-propyloxymethyl
Application: Coupling agent for amide and ester synthesis, formation of pentafluorophenyl (PFP) and other activated esters.
Typical Acid/Amine Coupling Conditions: 2 equivalents of resin, 1.5 equivalent of acid, 1.0 equivalent of amine in DCM overnight at room temperature
Compatible Solvents: DCM (7.0 mL/g), DCE (7.4 mL/g), THF (6.9 mL/g), toluene (4.5 mL/g), and other solvents that swell polystyrene
Storage: Cool, dry location

PS-Carbodiimide is a neutral, tethered carbodiimide that can be used for the synthesis of amides and esters. The carbodiimide loading capacity is determined by ^1H NMR (generation of Ac_2O from AcOH in $CDCl_3$).[1] Amide formation may be conducted either without HOBt (Methods A and B), or with HOBt (Method C) (Tables 1 and 2). Excess HOBt can be scavenged after the reaction using MP-Carbonate or PS-Trisamine resin.[2] PS-Carbodiimide has been found to give superior results in comparison with N-Cyclohexylcarbodiimide-NI-Me PS resin[3] and the quaternary carbodiimide resin P-EDC (Scheme 1, Table 1). In general, PS-Carbodiimide was found to synthesize amides in high yield and purity without evidence of residual amine or carboxylic acid. Unreacted carboxylic acid, normally used in excess relative to the amine, remains bound to the resin during workup. PS-Carbodiimide may also be used for the synthesis of pentafluorophenyl (PFP) activated esters (Table 3) and N-hydroxysuccinimidyl esters.[5] PS-Carbodiimide has been found to lose less than 5% of its activity when stored at 4 °C for 2 years.



Scheme 1. Structures of carbodiimide resins

Representative Procedure

Amide Synthesis

Method A:

PS-Carbodiimide resin (2.0 equivalents) was added to a dry reaction vessel. The acid (1.5 equivalent) in DCM (with 10% DMF added, if required) was added to the dry resin and the mixture stirred at room temperature. After 5 min, amine (1.0 equivalent) in DCM was added and the reaction stirred at room temperature for 12 h to afford the amide product. Typical reaction solvent volumes are 10 mL/g resin (Scheme 2).

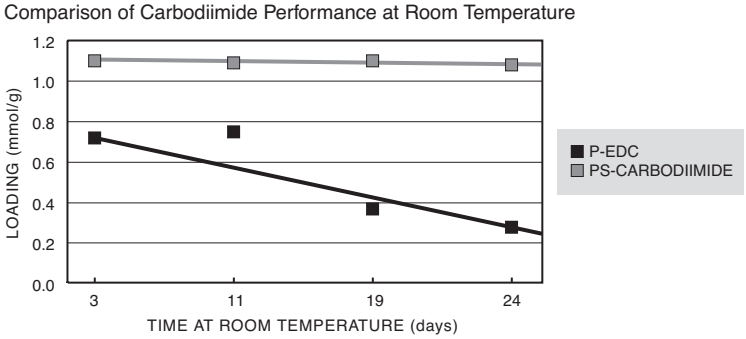


Figure 1. Stability of PS-Carbodiimide and PS-EDC at room temperature

Method B:

Amine (1.0 equivalent) and acid (1.5 equivalent) in DCM (with 10% DMF added if necessary) was added to a dry reaction vessel and the mixture stirred for 10 min prior to addition of PS-Carbodiimide resin (2 equivalents) with a reaction solvent volume of 10 mL/g resin. The reaction was then stirred overnight.

Method C:

PS-Carbodiimide (2.0 equivalents), acid (1.5 equivalent), and HOBt (1.7 equivalent) were dissolved in DCM, added to a dry reaction vessel and stirred for 5–10 min prior to addition of amine (1.0 equivalent). The reaction was stirred at room temperature overnight. After the reaction, the HOBt was scavenged using MP-Carbonate or PS-Trisamine resin (5 equivalents) for 2 h at room temperature prior to filtration.

Entry	Resin	Acid	Amine	HPLC Purity[a]	GC Amine[b] Residue %	% Yield (isolated)
1	PS-Carbodiimide	3,3-Diphenylpropionic	1,2,3,4-Tetrahydroisoquinoline	90	0	86
2	N-Cyclohexyl-N'Me	3,3-Diphenylpropionic	1,2,3,4-Tetrahydroisoquinoline	90	11	85
3	P-EDC	3,3-Diphenylpropionic	1,2,3,4-Tetrahydroisoquinoline	88	7–20	73
4	PS-Carbodiimide	3,3-Diphenylpropionic	3,3-Diphenylpropylamine	100	0	86
5	N-Cyclohexyl-N'Me	3,3-Diphenylpropionic	3,3-Diphenylpropylamine	100	10–25	77
6	P-EDC	3,3-Diphenylpropionic	3,3-Diphenylpropylamine	84	30	72
7	PS-Carbodiimide	3-Iodobenzoic acid	Benzylamine	100	0	90
8	N-Cyclohexyl-N'Me	3-Iodobenzoic acid	Benzylamine	93	10–20	72
9	P-EDC	3-Iodobenzoic acid	Benzylamine	94	10–20	60
10	PS-Carbodiimide	3-Iodobenzoic acid	1,2,3,4 Tetrahydroisoquinoline	98	0	88
11	N-Cyclohexyl-N'Me	3-Iodobenzoic acid	1,2,3,4-Tetrahydroisoquinoline	18	96	75
12	P-EDC	3-Iodobenzoic acid	1,2,3,4-Tetrahydroisoquinoline	10	97	73
13	PS-Carbodiimide	Boc-Phe-OH	3,5-Dimethylaniline	100	0	89
14	N-Cyclohexyl-N'Me	Boc-Phe-OH	3,5-Dimethylaniline	98	0	83
15	P-EDC	Boc-Phe-OH	3,5-Dimethylaniline	96	0	76

Table 1. Amide formation results (Method A) for three different carbodiimide resins
[a] HPLC analysis: Microsorb C18 3 µ (100 Å) column. CH_3CN:H_2O with 0.1% TFA, 10-100%, 10 min.
[b] GC analysis: HP-5 phenylmethylsilicone column 120-300 °C, 20 °C/min, 10 min.

Entry	Method	Acid	Amine	HPLC Purity[a]	GC Amine[b] Residue %	% Yield (isolated)
1	B	3,3-Diphenylpropionic	1,2,3,4-Tetrahydroisoquinoline	95	5	81
2	C	3,3-Diphenylpropionic	1,2,3,4-Tetrahydroisoquinoline	85	0	88
3	B	3,3-Diphenylpropionic	Benzylamine	80	0	95
4	C	3,3-Diphenylpropionic	Benzylamine	85	0	92
5	B	3-Iodobenzoic acid	1,2,3,4-Tetrahydroisoquinoline	96	5	96
6	C	3-Iodobenzoic acid	1,2,3,4-Tetrahydroisoquinoline	85	0	96
7	B	3-Iodobenzoic acid	Benzylamine	94	16	94
8	C	3-Iodobenzoic acid	Benzylamine	98	0	94

Table 2. Amide formation using PS-Carbodiimide (Methods B and C)
[a] HPLC analysis: Microsorb C18 3 µ (100 Å) column. CH_3CN:H_2O with 0.1% TFA, 10-100%, 10 min.
[b] GC analysis: HP-5 phenylmethylsilicone column 120-300 °C, 20 °C/min, 10 min.

PS-Carbodiimide

Entry	Acid	HPLC Purity[a]	% Yield (isolated)
1	Fmoc-L-Alanine	83	89
2	3-Iodobenzoic	98	98
3	2-Phenylpropionic	84	96
4	3,3-Diphenylpropionic	93	96

Table 3. PFP ester formation using PS-Carbodiimide
[a] HPLC analysis: Microsorb C18 3 µ (100 Å) column. CH_3CN:H_2O with 0.1% TFA, 10-100%, 10 min.

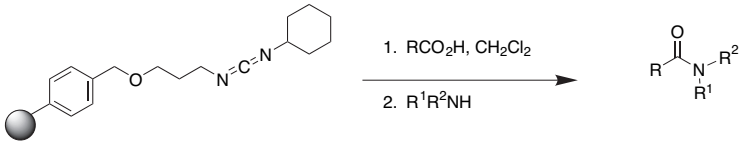
General Procedure for Reaction Work-up

The reaction mixture is filtered and the amide product is collected in the filtrate. The resin is washed two times with the reaction solvent (DCM or DCM/DMF as needed for solubility). A sample from the combined fractions is generally analyzed by GC before concentration to evaluate product purity and presence (if any) of unreacted amine. Concentration affords the amide product in high yield.

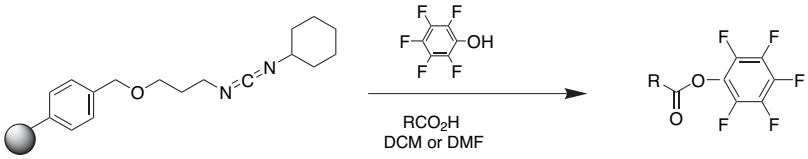
Representative Procedure

Pentafluorophenyl Ester Formation

PS-Carbodiimide resin (1.6 equivalent) was added to a dry reaction vessel. The acid (1.3 equivalent) in DMF or DCM was added to the dry resin and the mixture stirred at room temperature for 5 min, followed by addition of PFP (1.0 equivalent). After 18 h at room temperature, the activated ester product was filtered away from the resin and washed twice with DCM or DMF. HPLC analysis of activated esters show purities ranging from 89–98% (Scheme 3).



Scheme 2. Synthesis of amides using PS-Carbodiimide resin



Scheme 3. Synthesis of activated PFP esters using PS-Carbodiimide resin

Ordering Information

Part Number	Quantity
800508	3 g
800369	10 g
800370	25 g
800371	100 g
800372	1000 g

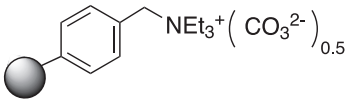
References

1. Parlow, J. J.; Mischke, D. A.; Woodard, S. S. J. *Org. Chem.* **1997**, 62, 5908.
2. Flynn, D. L.; Devraj, R. V.; Naing, W.; Parlow, J. J.; Weidner, J. J.; Yang, S. *Med. Chem. Res.* **1998**, 8, 219.
3. Weinshenker, N. M.; Shen, C. M. *Tetrahedron Lett.* **1972**, 13, 3281.
4. Desai, M. C.; Stramiello, S. L. M. *Tetrahedron Lett.* **1993**, 34, 7685.
5. Adamczyk, M.; Fishpaugh, J. R.; Mattingly, P. G. *Tetrahedron Lett.* **1995**, 36, 8345.

MP-CARBONATE

MP-Carbonate

Resin-bound Base



Resin Type: Macroporous poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 2.8 mmol/g, minimum capacity 2.5 mmol/g (based on nitrogen elemental analysis)
Bead Size: 350–1250 microns, 18–52 mesh (95% within)
Chemical Name: Macroporous triethylammonium methylpolystyrene carbonate (0.5% inorganic antistatic agent)
Application: General base, ammonium salt neutralization, scavenging acids and acidic phenols. The neutralization of insoluble amine hydrochlorides requires the use of 0.05–0.1 equivalent of diisopropylethylamine (DIEA) as a soluble transfer base
Typical Scavenging Conditions: 3 equivalents relative to substrate, 0.5–2 h, 20 °C
Compatible Solvents: DCM (3.0 mL/g), DCE (3.0 mL/g), THF (2.8 mL/g), DMF (2.9 mL/g)

MP-Carbonate resin is a macroporous polystyrene anion exchange resin that is a resin-bound equivalent of tetraalkylammonium carbonate. MP-Carbonate may be used as a general base to quench reactions, neutralize amine hydrochlorides, or to scavenge a variety of acidic molecules such as carboxylic acids or acidic phenols. Removal of excess carboxylic acids or acidic phenols (e.g. phenol or nitrophenol), from solution generally requires 3–4 equivalents of MP-Carbonate. Removal of excess hindered phenol requires larger amounts of resin, typically up to 5-fold excess of MP-Carbonate. Complete removal takes from 30 min to 2 h. Upon completion of the scavenging, the resin is rinsed 3x with a suitable solvent, (e.g. DCM, THF, or EtOH). Representative acid and phenol scavenging examples are presented in Table 1.

Substrates	MP-Carbonate (equivalents)	Time (h)	Scavenged %
Benzoic acid	3	1	100
Hexanoic acid	4	1	100
Bromobenzoic acid	3	1	100
Phenol	4	1	100
Nitrophenol	2	1	100
2-Allylphenol	6	1	93
2,6-Dimethylphenol	7	1	80

Table 1. Comparative scavenging times in DCM

MP-Carbonate is also very useful for neutralizing trialkylammonium salts (e.g. hydrochlorides and trifluoroacetates), to generate the free base. Applications include neutralizing reactants, products and ammonium salts of volatile amines (e.g. DIEA or TEA), produced in a chemical transformation. The latter case allows for neutralization and amine removal in the concentration step, circumventing an aqueous workup. In cases where the ammonium salt is insoluble, a catalytic amount of DIEA (0.05–0.1 equivalent) can be added as a soluble transfer base.

MP-Carbonate

Representative Procedure

Neutralization of Amine Hydrochloride Salt

Ephedrine hydrochloride salt (1 equivalent) was converted to the free amine with MP-Carbonate (4 equivalents) in DCM or methanol for one hour. Since ephedrine hydrochloride is not soluble in DCM, a catalytic amount of DIEA (0.05 equivalent) was added as a transfer base and was removed during sample concentration. The resin was removed by filtration and washed twice with DCM. The filtrate was concentrated to give ephedrine in 100% yield (MeOH) and 82% yield (DCM) (NMR purity: 100%).

Ordering Information

Part Number	Quantity
800493	3 g
800267	10 g
800268	25 g
800269	100 g
800314	1000 g

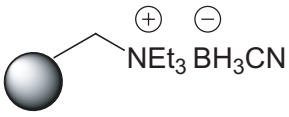
References

1. Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.* **1997**, 38, 7959.

MP-Cyanoborohydride

MP-Cyanoborohydride

Reducing Agent



Resin Type: Macroporous poly(styrene-co-divinylbenzene)
Loading: Typical loading 2.3 mmol/g, minimum loading 2.0 mmol/g (based on acid/base titration)
Bead Size: 350–1250 microns, 18–52 mesh (95% within)
Chemical Name: Macroporous triethylammonium methylpolystyrene cyanoborohydride (0.5% inorganic antistatic agent)
Application: Reductive amination; reductive methylation of primary and secondary amines, reduction of imines; reduction of conjugated enones to unsaturated alcohols
Typical Conditions for Reductive Amination: 1.2 mmol of carbonyl compound, 1.0 mmol of primary or secondary amine in THF, 1.0 mL of HOAc, and 2.5 mmol of MP-Cyanoborohydride stirred overnight at room temperature. Product isolated by filtration to remove the resin
Compatible Solvents: THF (2.9 mL/g), DCM (3.0 mL/g), DMF (2.9 mL/g), MeOH (2.9 mL/g)

MP-Cyanoborohydride is a macroporous polymer-supported cyanoborohydride,[1] which is a resin-bound equivalent of tetraalkylammonium cyanoborohydride. The bound cyanoborohydride can be utilized as a versatile reducing agent[2,3] for the reductive amination of carbonyl compounds and reduction of imines. Resin-bound cyanoborohydride can also be utilized for a number of other important reductive applications.[1] Examples include reduction of a,b-unsaturated carbonyl compounds to the corresponding unsaturated alcohols, conversion of pyridinium ions to tetrahydropyridine derivatives, and dehalogenation reactions. The reaction work-up protocol is greatly simplified by using the resin-bound reagent. Specifically, compared with the small molecule sodium cyanoborohydride, it is reported[1] that toxic cyanide is not released on reaction workup and therefore does not contaminate the product or pose a danger towards the user.

The general protocol for the use of MP-Cyanoborohydride for reductive amination is summarized in Table 1. Reactions are performed with 2.5 equivalents of MP-Cyanoborohydride relative to the limiting reagent. The carbonyl compound is used as the limiting reagent in the synthesis of secondary amines to suppress overalkylation. For tertiary amine synthesis, the carbonyl compound is used in excess to allow the use of catch-and-release purification with MP-TsOH cartridges[4] or SCX cartridges.[5] The reactions are carried out with at least 5 equivalents of HOAc to facilitate formation of imine or iminium ions, which undergo reduction with MP-Cyanoborohydride. Tetrahydrofuran (THF) is preferred to dichloroethane as solvent due to its greater stability in the presence of reactive amines.

After reduction is complete, the crude reaction mixture is comprised of the product amine as an acetate salt and excess amine or carbonyl compound depending on the stoichiometry employed. At this point, there are several options for final purification (Figure 1). These options are described in more detail in the following sections.

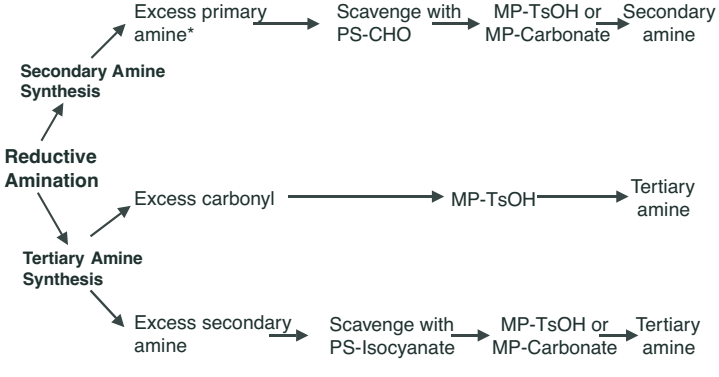


Figure 1. Stoichiometry, scavenging, and purification options

MP-CYANOBOROHYDRIDE

Amine	Carbonyl	Amine : Carbonyl Stoichiometry	% HOAc in Solvent	Scavenger Resin	Final Purification
1°	Aldehyde	1.2 : 1	25	PS-Benzaldehyde or MP-TsOH	MP-Carbonate
1°	Ketone	1.2 : 1	25	PS-Benzaldehyde	MP-TsOH or MP-Carbonate
2°	Aldehyde	0.8 : 1	5	None	MP-TsOH
2°	Ketone	0.8 : 1	5	None	MP-TsOH

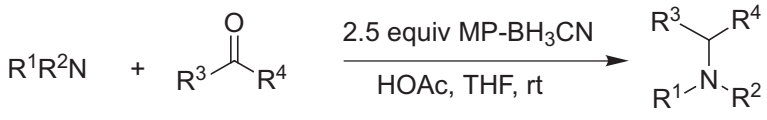


Table 1. Stoichiometry, scavenging, and purification options

Secondary Amine Synthesis

Minimization of overalkylation is a key consideration for reductive alkylation of primary aliphatic amines. The amine was used in 20% excess in order to favor selectivity towards monoalkylation. Reductive amination reactions proceeded overnight at room temperature in a 25% HOAc/THF solvent mixture. The product mixture was treated with PS-Benzaldehyde to selectively scavenge excess primary amine. In these reactions, 25% HOAc/THF was used to assure complete scavenging of amines. Since only 5 equivalents of HOAc are required for the reductive amination step, the additional HOAc to bring the concentration to 25 vol % can be introduced with the scavenging resin. After filtration and evaporation, the residue is dissolved in DCM and neutralized with MP-Carbonate or by catch-and-release purification with MP-TsOH or SCX cartridges (e.g., ISOLUTE SCX-2)[5] to afford the product amine as a free base in good-to-excellent yield and purity.

This protocol was demonstrated in the reductive alkylation of a set of primary amines (Table 2, entries 1-3). High purity and yield were obtained in the reductive alkylation of cyclopentanone. Reaction of N-(3-aminopropyl)morpholine with cyclohexanecarboxaldehyde afforded approximately 30% overalkylated product. In the case of 3-aminopyridine, it was advantageous to carry out the reductive amination in 25% HOAc to facilitate imine formation of this less reactive heterocyclic amine. A cocktail of PS-Benzaldehyde and PS-$TsNHNH_2$ was used to scavenge both primary amine and carbonyl compound to afford the desired amine in high yield and purity. MP-Carbonate was used to neutralize the secondary amine in all three examples.

Tertiary Amine Synthesis

Reductive amination using secondary amines with aldehydes and ketones was carried out with amine as the limiting reagent and 5 equivalents of HOAc. The product amines were purified from nonbasic impurities by catch-and-release using MP-TsOH cartridges. Upon completion of the reaction, the spent resin was filtered from the solution and the filtrate was passed through an MP-TsOH cartridge followed by washing with DCM to remove non-basic impurities. The product tertiary amine was eluted from MP-TsOH with a solution of 2 M ammonia in MeOH and isolated as a free base by concentration to dryness.

Application of the general procedure was demonstrated in the reductive alkylation of piperidine with p-tolualdehyde to afford the desired tertiary amine in high yield and purity (Table 2, entry 4). Alicyclic secondary amines, (e.g., N-benzylmethylamine), are effective as substrates as demonstrated by the reductive amination

of cyclohexanecarboxaldehyde (Table 2, entry 5). Although the procedure is generally effective for ketones, less reactive ketones require more forcing conditions. Reductive amination of acetophenone with piperidine was successful with 5 equivalents of HOAc in EtOH at 65 °C (Table 2, entry 6).[6]

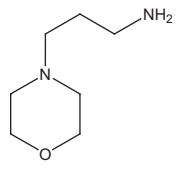
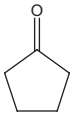
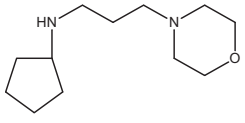
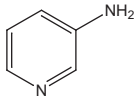
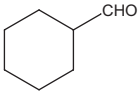
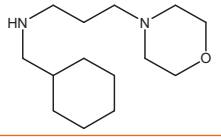
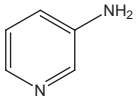
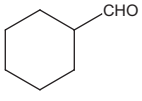
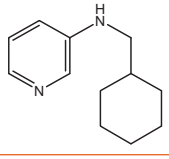
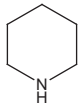
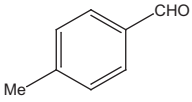
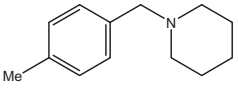
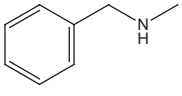
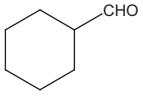
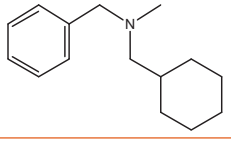
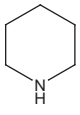
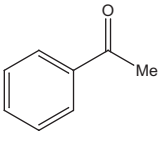
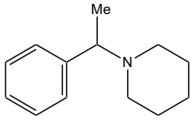
Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				97	99
2				88	71[a]
3				85	100
4				81	97
5				87	97
6[b]				74	98

Table 2. Reductive alkylation of amines
[a]Dialkylated product present as the major impurity.
[b]The conditions required for acetophenone are 5 equivalents HOAc, EtOH, 65 °C.

If the carbonyl compound contains a basic moiety, catch-and-release purification will not selectively bind the product, and it is recommended to use excess secondary amine in the reductive amination and purify with PS-Isocyanate. It is important to limit the HOAc to 5 equivalents, since higher levels can lead to acetamide formation in the scavenging step. Isolation of the free amine is achieved by neutralization with MP-Carbonate or catch-and-release purification after scavenging.

Boron Impurities

Amine products were tested for the presence of boron by elemental analysis. When catch-and-release purification was used, the level of boron present in the samples was less than 10 ppm. MP-Carbonate neutralization afforded products with a boron level of 200 ppm. Both of these values are well below the boron levels measured for the

MP-CYANOBOROHYDRIDE

crude product, which was generally in the 0.2-0.4 wt. % range. It is therefore important to apply catch-and-release purification or the neutralization procedure to remove boron impurities. The crude samples were tested for free cyanide with cyanide test strips and showed levels less than 15 ppm.

Representative Procedure

Reductive Alkylation of Primary Amines (Table 2, Entry 1)

To a 0.5 M THF solution of N-(3-aminopropyl)morpholine (1.2 mL, 0.60 mmol) was added 1.0 mL of a 0.5 M THF solution of cyclopentanone (0.50 mmol), 1.0 mL HOAc, and 1.0 mL THF. MP-Cyanoborohydride resin (0.5 g, 2.5 mmol/g, 1.25 mmol, 2.5 equivalents) was added and the reaction agitated at room temperature for 16 h. To the reaction mixture was added PS-Benzaldehyde (0.5 mmol) and the scavenging reaction mixture was stirred at room temperature for 16 h. The solution was filtered and the filtrate was concentrated to dryness. The crude product was dissolved in 2 mL of THF, and 0.89 g of MP-Carbonate (2.8 mmol/g, 2.5 mmol) was added. After 1.5 h the mixture was filtered and the filtrate was concentrated in vacuo to yield the desired secondary amine as a free base. The product secondary amine was characterized by gas chromatography and ^{1}H NMR.

Representative Procedure

Reductive Alkylation of Secondary Amines (Table 2, Entry 4)

To a 0.5 M THF solution of piperidine (1.0 mL, 0.5 mmol) was added 1.2 mL of a 0.5 M THF solution of p-tolualdehyde (0.6 mmol), 0.14 mL HOAc (5 equivalent), and 0.75 mL THF. MP-Cyanoborohydride resin (0.5 g, 2.5 mmol/g, 1.25 mmol, 2.5 equivalents) was added and the reaction agitated at room temperature for 16 h. The reaction was filtered and the filtrate was passed through a preconditioned (DCM) MP-TsOH column (1 g). The flow rate was adjusted to 1 mL/min, which was maintained for all subsequent elution steps.[4] The cartridge was washed with DCM (20 mL) and the washing was discarded. The product tertiary amine was released using 2 M NH_3–MeOH (5 mL) followed by DCM (15 mL). The combined eluent was concentrated in vacuo to yield the desired tertiary amine as a free base. The product tertiary amine was characterized by gas chromatography and ^{1}H NMR.

Ordering Information

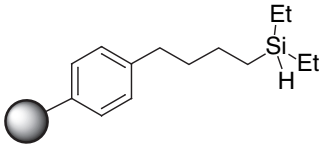
Part Number	Quantity
800511	3 g
800405	10 g
800406	25 g
800407	100 g
800408	1000 g

References

1. Hutchins, R. O.; Natale, N. R.; Taffer, I. M. *J. Chem. Soc. Chem. Commun.* **1978**, 1088.
2. Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A-G.; Hall, B. J. *J. Chem. Soc. Perkin Trans.* 1, **1998**, 2239.
3. Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc. Perkin Trans.* 1, **1998**, 3127.
4. Catch and release purification is described in the MP-TsOH technical section. The MP-TsOH column was conveniently prepared by adding 0.7 g of resin to a 6 mL isolute filtration column (Part Number 120-1113-C) fitted with a universal PTFE stopcock (Part Number 121-0009). Alternatively, MP-TsOH cartridges (Part Number 800477-0050-C) can be used.
5. ISOLUTE SCX-2 (Part Number 532-0050-C). For examples of SCX in purification of amines: Lawrence, R. M.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553. Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett* **1997**, 38, 3357.
6. An alternative method for reductive amination of sterically hindered ketones utilizes MP-Borohydride in the presence of titanium(IV) isopropoxide. The titanium is removed by PS-DEAM in a subsequent scavenging step. Details are provided in the PS-DEAM technical section.

PS-DES

Reducing Agent



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 1.5 mmol/g, minimum loading 1.3 mmol/g (determined by reduction of trityl bromide and quantification of the triphenylmethane produced)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Poly(styrene-co-divinylbenzene) butyldiethylsilane
Application: Reducing agent, precursor for silyl triflate, cyanide and azide
Typical Conditions for Silyl Triflate Formation: Resin treated with 2.5% trimethylsilyl chloride in DCM 30 min as a drying step, rinsed with DCM followed by 2% triflic acid in DCM (6 equivalents)
Compatible Solvents: DCM (8.4 mL/g), THF (8.2 mL/g), DMF (3.1 mL/g)

PS-DES is a resin-bound equivalent of triethylsilane and has a number of applications as a mild reductant.[1] PS-DES is readily converted to silyl chloride,[2] silyl triflate,[3,4] silyl cyanide,[5] and silyl azide.[5] The triflate of PS-DES has been used to form polymer-supported versions of Danishefsky's diene for Diels-Alder reactions[3] and silyl ketene acetals as intermediates in ester enolate Claisen rearrangements.[4] The polymer-supported silyl triflate is an effective activator for glycosidations with glycosyl acetates.[6]

Ordering Information

Part Number	Quantity
800507	3 g
800142	10 g
800143	25 g
800144	100 g

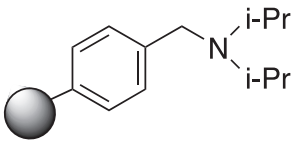
References

1. Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents, Burke, S. D. and Danheiser R. L., Ed.; Wiley, New York: **1999**; p. 479.
2. Hu, Y.; Porco, Jr. J. A.; Labadie, J.W. Gooding, O. W. J. *Org. Chem.* **1998**, 63, 4518.
3. E. M. Smith. *Tetrahedron Lett.* **1999**, 40, 3285.
4. Hu, Y.; Porco, Jr. J. A. *Tetrahedron Lett.* **1998**, 39, 2711.
5. Missio, A.; Marchioro; C. Rossi, T.; Panunzio, M.; Selva, S.; Seneci, P. *Biotech. and Bioeng. (Comb. Chem.)* **2000**, 71, No. 1, 38.
6. Kirschning, A.; Jesberger, M.; Schönburger, A. *Org. Lett.* **2001**, 3, 3623.

PS-DIEA

PS-DIEA

Resin-bound Base

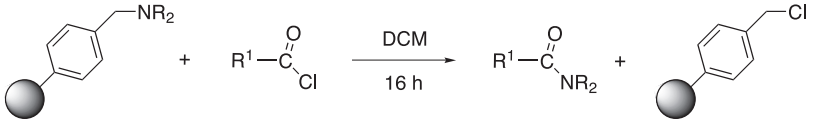


Resin Type: 2% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 3.7 mmol/g, minimum loading 3.4 mmol/g (based on nitrogen analysis)
Bead Size: 150–1000 microns, 22–165 mesh (95% within)
Chemical Name: N,N-(Diisopropyl)aminomethylpolystyrene (0.5% inorganic antistatic agent)
Application: Tertiary amine base
Typical Application Conditions: 2–3 equivalents relative to limiting reagent
Compatible Solvents: DCM (3.0 mL/g), THF (4.2 mL/g), DMF (2.5 mL/g)

PS-DIEA is a high-loaded tertiary amine base that is a resin-bound equivalent of DIEA. PS-DIEA is useful in applications requiring a tertiary amine base, and where the resin-bound ammonium salt by-products can be readily separated by filtration.[1] Synthesis of amides, sulfonamides, and carbamates can be effected using filtration as the only purification step when PS-DIEA is used in conjunction with PS-Trisamine or PS-Isocyanate as scavenger resins.

PS-DIEA is linked to the polystyrene backbone through a benzylic position by analogy with other resin-bound amine bases (e.g. morpholinomethyl polystyrene). A limitation of the benzylic amine linkage is its susceptibility to cleavage by electrophiles, to form small molecule impurities (e.g. amides or carbamates).[2,3] Chloroformates are more reactive than benzoyl chloride in cleaving benzylic amines. We have found that the increased steric hindrance associated with the diisopropyl substitution affords a significantly more stable benzylic tertiary amine base even in the presence of reactive electrophiles like chloroformates.

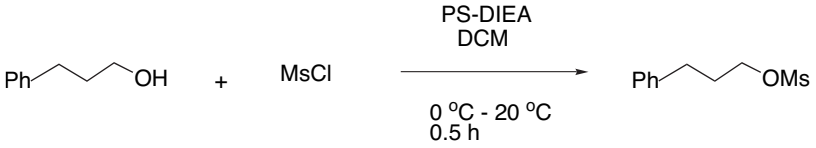
The stability of polymer-bound tertiary amines towards electrophiles was studied as a function of amine structure. A solution of benzoyl chloride or methyl chloroformate in DCM was allowed to react with dimethylamino, N-morpholino and diisopropylamino functional methyl polystyrenes for 16 h at room temperature and the filtrate was concentrated and examined for cleavage products (Scheme 1). The results showed good correlation between steric hindrance and amine stability (Table 1). Dimethyl-aminomethyl polystyrene was the least stable and showed some formation of dimethyl benzamide with benzoyl chloride. Morpholinomethyl polystyrene was stable to benzoyl chloride but underwent cleavage with methyl chloroformate to afford methyl morpholino carbamate in 90% yield. In contrast, PS-DIEA was very stable under these conditions and afforded only a 2.5% yield of carbamate. The higher stability of PS-DIEA towards active electrophiles should allow its use in reaction with either excess electrophile or amine with little or no cleavage of the benzylic amine. In those cases where some cleavage is observed, the more stable non-benzylic amine resin PS-NMM can be employed (see PS-NMM product description on page 88).



-NR_2 = -NMe_2, -morpholine, -N(*i*-Pr)$_2$ R^1 = Ph-, MeO-

Scheme 1. Stability of tertiary amine resins to acid chlorides and chloroformates

PS-DIEA was applied in the preparation of the mesylate of 3-phenylpropanol according to a literature procedure (Scheme 2).[4] The use of 3 equivalents of PS-DIEA afforded complete conversion to the desired mesylate in 95% isolated yield. Reaction workup required filtration and rinsing of the resin, followed by removal of the solvent and excess methanesulfonyl chloride in vacuo. This was much simpler than the aqueous extraction required when TEA was used as the base. Alternatively, the excess methanesulfonyl chloride could have been removed by adding PS-Trisamine.



Scheme 2. Synthesis of 3-Phenylpropanol Mesylate

Amine Resin (R)	Electrophile (R1)	Clevage Product (%)
Me	Ph	9
Morpholine	Ph	0
Morpholine	MeO	90
I-Pr	MeO	2.5

Table 1. Stability of tertiary amine resins to acid chlorides and chloroformates

Representative Procedure

Mesylate Formation

A 10 mL round bottom flask was charged with 800 mg of PS-DIEA resin (3.8 mmol/g, 3.0 mmol), 2.5 mL of DCM, and 1 mmol of a primary alcohol and cooled in an ice bath. Then, 0.12 mL (1.5 mmol) of methanesulfonyl chloride was added, dropwise, to the stirred solution. The reaction mixture was removed from the ice bath and allowed to warm to room temperature for 0.5 h. The resin was removed by filtration and rinsed 3x with DCM. The combined filtrate was concentrated and the residual methanesulfonyl chloride was removed in vacuo in the presence of potassium hydroxide desiccant to afford the desired mesylate. This procedure was used to prepare the mesylate of 3-phenylpropanol in 95% yield.

Ordering Information

Part Number	Quantity
800494	3 g
800279	10 g
800280	25 g
800281	100 g
800312	1000 g

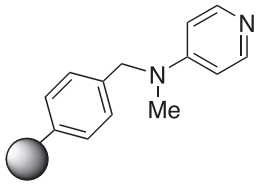
References

1. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, 119, 4882.
2. Conti, P.; Demont, D.; Cals, J.; Ottenheijm, H. C. J.; Leysen, *D. Tetrahedron Lett.* **1997**, 38, 2915.
3. Yang, B. V.; O'Roarke, D.; Li, J. *Synlett* **1993**, 195.
4. Gooding, O. W.; Bansal, R. P. *Synth. Commun.* **1995**, 25, 1155.

PS-DMAP

PS-DMAP

Resin-bound Base



Resin Type: 4% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 1.5 mmol/g, minimum loading 1.4 mmol/g (based on nitrogen analysis). Approximately 0.35 mmol/g capacity for acyl/sulfonyl chloride in catch-and-release applications.[1]
Bead Size: 200–800 microns, 30–80 mesh (95% within)
Chemical Name: N-(Methylpolystyrene)-4-(methylamino) pyridine
Application: Catalyst for acylation reactions, catch-and-release applications
Typical Catalysis Conditions: 10 mol% (0.1 equivalent) relative to alcohol, overnight, 110 °C
Compatible Solvents: Toluene (1.8 mL/g), DCM (3.8 mL/g), DMF (2.6 mL/g), THF (1.9 mL/g)

PS-DMAP is a resin-bound equivalent of DMAP, which may be used as a catalyst for acylation and related reactions. Typical catalysis conditions require 10–20 mol% relative to the nucleophile. Catalytic PS-DMAP accelerates the acylation of sluggish nucleophiles (e.g. tertiary alcohols).

The application for PS-DMAP as a catalyst for the esterification of tertiary alcohols was investigated using 1- methylcyclohexanol.[2,3] A 0.5 M solution of 1-methylcyclohexanol (1 equivalent) in toluene was acylated with acetic anhydride (1.64 equivalent) in the presence of TEA (1.5 equivalent) and PS-DMAP (0.1 equivalent). The reaction mixture was heated at the reflux temperature overnight. 1-Methylcyclohexane acetate was isolated by filtration, followed by an aqueous work-up. Alternatively, MP-Carbonate was added at the completion of the reaction to remove TEA and was followed by concentration. The results of this reaction are given in Table 1. The PS-DMAP reaction gave 95% pure product in comparison with the 98% purity with DMAP.

Catalyst	Product Purity (% GC)
None	79.1
PS-DMAP	94.9
DMAP	97.7

Table 1. Synthesis of 1-methylcyclohexyl acetate

PS-DMAP may also be used for catch-and-release of acid chlorides and sulfonyl chlorides to synthesize a variety of acyl and sulfonyl derivatives, including esters, amides, and sulfonamides.[4,5] Catch-and-release involves the reaction of the electrophilic reagent with PS-DMAP, forming an N-substituted pyridinium salt which is then reacted with various nucleophiles such as alcohols, amines, and thiols without the addition of a tertiary amine base.[6] In Scheme 1, an acid chloride is caught and subsequently released by reaction with an amine. Key to this approach is the ability to purify the resin-bound salt with solvent washes. By using the nucleophile as the limiting reagent, the product is isolated in high purity by filtration, with the excess electrophile remaining bound to the resin. PS-DMAP has a functional loading of approximately 0.35 mmol/g for catch-and-release applications.

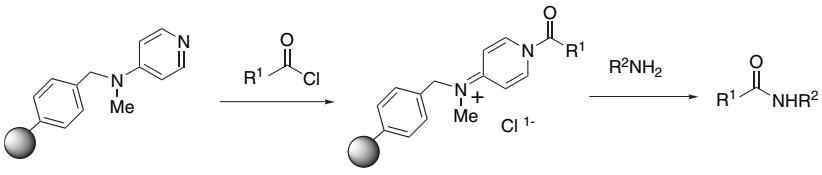
In catch-and-release applications, PS-DMAP is typically allowed to react with 2 equivalents of acyl or sulfonyl halide in DCM for 1 h at room temperature. The resin is then washed with DCM followed by the addition of 0.7 equivalent of amine. After 16 h the product is isolated by filtration and concentration. Table 2 gives the results for a range of amides and sulfonamides prepared by this procedure. Particularly noteworthy is the high product purity afforded by this methodology, with single-peak gas chromatograms observed in most cases. In cases where low levels of amine starting material remain, scavenging may be accomplished with PS-Isocyanate.

Representative Procedure

Alcohol Acylation

One equivalent of alcohol was reacted with acetic anhydride (1.64 equivalent), TEA (1.5 equivalent), and 0.1 equivalent PS-DMAP in toluene (17.5 mL/g of resin) and heated at reflux temperature overnight. After cooling, MP-Carbonate (6 equivalents) was added and the mixture was agitated for 4 h. The resin was removed by filtration and washed two to three times with DCM. The combined filtrate was concentrated to afford the desired

product. This procedure was used to prepare 1-methylcyclohexane acetate in 95% yield. For less reactive anhydrides or acid chlorides, a mixture of PS-Trisamine (1.5 equivalent) and MP-Carbonate (4 equivalents) can be used to work-up the reaction.



Scheme 1. Amide formation by catch-and-release using PS-DMAP

R-COCl/R-SO_2Cl	Amine	Product Purity (% GC)	% Yield
Benzoyl Chloride	Cyclohexylamine	100	83
Benzoyl Chloride	2,2-Diphenylethylamine	100	82
Benzoyl Chloride	Piperonylamine	100	81
Tosyl Chloride	Cyclohexylamine	100	82
Tosyl Chloride	Benzylamine	100	88
Tosyl Chloride	Piperonylamine	100	89
p-Anisoyl Chloride	Benzylamine	100	77
p-Anisoyl Chloride	Piperonylamine	100	80
2-Naphthalene sulfonyl	Cyclohexylamine	86	68
2-Naphthalene sulfonyl	Benzylamine	100	66

Table 2. Amide and sulfonamide formation by catch-and-release using PS-DMAP

Catch-and-Release Amide/Sulfonamide Formation

1 equivalent of PS-DMAP (approximately 0.35 mmol/g capacity) was quaternized with an acid or sulfonyl chloride (2 equivalents) in DCM (5 mL/g of resin) and mixed at room temperature for 1 h. The resin was washed five times with DCM to remove excess acid and/or sulfonyl chloride 0.7 equivalent of an amine in DCM (5 mL/g of resin) was added and the reaction was mixed at room temperature for 16 h. The resin was filtered, washed three times with DCM, and the filtrate concentrated to afford the amide or sulfonamide product. This procedure was used to prepare cyclohexyl benzamide and cyclohexyl toluenesulfonamide in 82-83% yield, respectively.

Ordering Information

Part Number	Quantity
800288	10 g
800289	25 g
800290	100 g
800313	1000 g

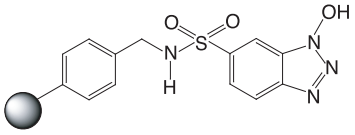
References

1. Based upon experimental findings for catch-and-release applications, an average of 25% of the total DMAP sites are available for reaction on PS-DMAP resin.
2. Keay, J. G.; Scriven , E. F. *V. Chem. Ind.* **1994**, 53, 339.
3. Guendouz, F.; Jacquier, R.; Verducci, J. *Tetrahedron* **1988**, 44, 7095.
4. Tomoi, M.; Akada, Y.; Kakiuchi, H. *Makromol. Chem., Rapid Commun.* **1982**, 3, 537.
5. Shai, Y.; Jacobson, K. A.; Patchornik, A. *J. Am. Chem. Soc.* **1985**, 107, 4249.
6. Patchornik, A. *Chemtech* **1987**, 58.

PS-HOBt(HL)

PS-HOBt(HL)

Resin-bound Active Ester Reagent

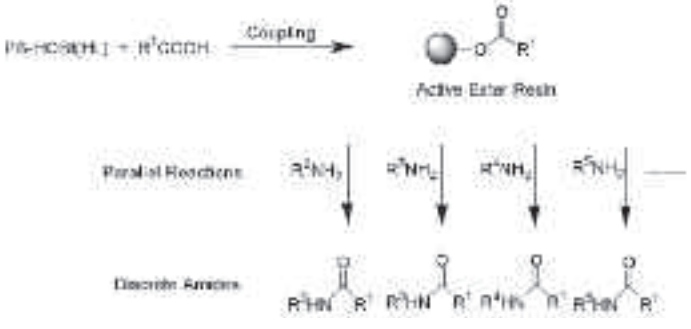


Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 1.0 mmol/g, minimum loading 0.9 mmol/g (based on benzoylation of benzylamine)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: 1-Hydroxybenzotriazole-6-sulfonamidomethyl polystyrene
Application: Active ester reagent; coupling of acids and amines; protecting group (Fmoc, CBz, Boc) transfer
Typical Acid Loading Conditions: 1.5 equivalent of carboxylic acid, 4.5 equivalent of DIC, 0.6 equivalent of DMAP in a 4:1 DCM/DMF solvent mixture at room temperature for 2 h
Typical Protecting Group Loading Conditions: 3 equivalent of FmocCl or CbzCl and 5 equivalents of Py in DCM at room temperature for 1 hour
Compatible Solvents: DMF (7.5 mL/g), THF (4.8 mL/g), DCM (3.0 mL/g), and other solvents that swell gel-type polystyrene

PS-HOBt(HL) is a sulfonamide-linked, resin-bound equivalent of 1-hydroxybenzotriazole (HOBt).[1] PS-HOBt(HL) is used to generate bound HOBt active esters, which can either be made and used in situ, or isolated and stored as stable intermediates. Treatment of bound HOBt ester with an amine leads to amide formation in generally high purity without the need for further purification.

To date, the recommended procedure for loading PS-HOBt has required PyBroP as the coupling agent. We have developed an improved loading procedure based on the use of diisopropylcarbodiimide and DMAP. The new procedure has proven to be much more reliable, efficient, and cost effective. It requires fewer equivalents of carboxylic acid and does not require a double coupling as is the case when PyBroP is used.

Resin-bound active esters offer some unique advantages for parallel amide synthesis. The resin-bound active esters of PS-HOBt(HL) can be prepared using the coupling protocol and purified by solvent washes. Amide formation is accomplished by simply adding the appropriate amine to the active ester resin. By using the amine as the limiting reagent, acylation of the amine generates the amide as the sole compound in solution. Only filtration and concentration are required to isolate the product. A series of resin-bound HOBt active esters can be prepared in bulk from PS-HOBt(HL) and split into individual reactors for reaction with amine (Scheme 1). Depending on the stability of the bound active ester, long-term storage is possible and the resin can be used as required to make amides. The stability of the bound active ester is dependent on the structure of the corresponding acid.

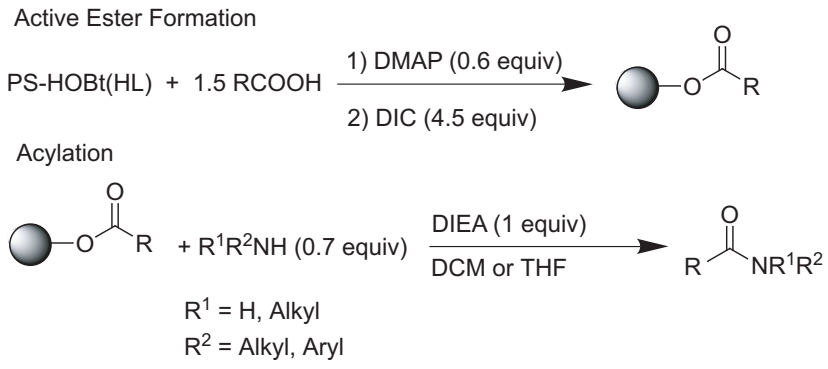


Scheme 1. Parallel synthesis of amides with PS-HOBt(HL) active esters

Formation of active esters of PS-HOBt(HL) was investigated using statistical design of experiments (DoE).[2] This work demonstrated optimal conditions for active ester formation and used 1.5 equivalent of carboxylic acid, 4.5 equivalents of DIC, 0.6 equivalent of DMAP, and a 4:1 DCM/DMF solvent mixture at room temperature for 2–3 h (Scheme 2). The order of addition proved to be an important variable. DMAP and the carboxylic acid were mixedwith PS-HOBt(HL), followed by addition of DIC. The purpose of including DMF as a co-solvent is to improve the solubility of the carboxylic acid component. It is preferable to keep the DMF composition in the reaction mixture to a minimum (<20%) since it compromises the level of active ester formation. If more DMF is required to dissolve the carboxylic acid, the ACTU coupling reagent[3] is recommended.[4]

PS-HOBt (HL)

The formation of PS-HOBt(HL) active esters from five carboxylic acids using the DIC/DMAP protocol afforded resin-bound active esters with loading levels in the range of 65–96% of theory (Table 1). The best results were obtained with aromatic and aliphatic carboxylic acids. In addition to DIC/DMAP, 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) was found to be an alternative coupling agent for PS-HOBt(HL) active ester formation.[5]



Scheme 2. Amide synthesis with PS-HOBt (HL)

Amide formation is effected by mixing the PS-HOBt(HL) ester resin with 0.5–0.7 equivalent of amine, and 1 equivalent of DIEA in DCM, THF, or DCE. The reaction takes place at room temperature with both aliphatic and aromatic amines, although less nucleophilic aromatic amines may require 65 °C. Likewise, other non-nucleophilic amines (e.g. aminothiazoles), can react at elevated temperatures to afford amides, depending on the amine structure. Products are isolated by filtration and concentration. The acylation reaction has been successfully carried out with benzyl amine in wet DCM, demonstrating that this step is fairly robust to moisture. The use of DIEA is optional for aliphatic amines; however, its use often results in higher yields. DIEA is required for less nucleophilic amines, such as anilines, and is readily removed under reduced pressure. Acylation can also be performed with PS-HOBt(HL) active ester as the limiting reagent, in which case excess amine is scavenged from the product with PS-Isocyanate.

Active esters from a set of carboxylic acids that included aromatic, aliphatic, cinnamic, and amino acids were formed from PS-HOBt(HL) using the DIC/DMAP protocol. These were used to acylate benzylamine and 1-phenylpiperazine at room temperature, and aniline at 63 °C (Table 2). The amines were used as the limiting reagent at 0.7 equivalent relative to the loading of the starting PS-HOBt(HL) resin (1.0 mmol/g). Isolation by filtration with solvent removal under reduced pressure afforded the amide products. The aromatic, aliphatic, and cinnamic acids afforded high purity products in good-to-excellent yields. In some cases, excess 1-phenylpiperazine was present in the product and was removed by scavenging with PS-Isocyanate. Amides from Boc-Ala, Boc-Phe and 4-bromophenylacetic acid generally afforded modest yields of amide.

An alternative coupling reagent for preparation of PS-HOBt(HL) active esters is 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP).[5] Comparison of coupling conditions using 1.5 and 4 equivalents of BEP showed 1.5 equivalent to give better results. A limited set of carboxylic acids was converted to PS-HOBt(HL) active esters using BEP and then used to acylate benzyl amine (Table 3). The results demonstrate that BEP is a viable alternative to the DIC/DMAP procedure and may be preferred for some substrates as indicated by the improved yield of amide obtained from 4-bromophenylacetic acid and Boc-Phe-OH.

	Loading (mmol/g)			
Acid	**PS-HOBt(HL)**	**Active Ester Theoretical**	**Active Ester Measured**	**Loading %**
Benzoic acid	1.0	0.91	0.87	96
Cyclopentyl propionic	1.0	0.89	0.85	96
Cinnamic acid	1.0	0.88	0.65	73
Quinaldic acid	1.0	0.87	0.56	65
Boc-Phe	1.0	0.80	0.56	70

Table 1. PS-HOBt(HL) active ester formation using DIC/DMAP

PS-HOBt (HL)

The stability of isolated PS-HOBt(HL) active esters derived from the carboxylic acids in Table 2 has been monitored by measuring amide yield and purity obtained after acyl transfer to benzyl amine over time. At 4 °C over a one-month test period, benzoic, quinaldic, and cinnamic bound esters showed excellent stability, while 3-phenylpropionic and Boc-phe esters were observed to undergo approximately 30% decrease in loading. The decrease in loading for 3-phenylpropionic and Boc-Phe esters was more rapid at room temperature, demonstrating that low temperature storage is beneficial. Active esters of benzoic and quinaldic acids were stable at room temperature, and in the case of benzoic acid, a sample was successfully stored for over three months with no degradation. In the case of acids that underwent some degradation on storage, the resin samples were washed with THF prior to reaction with amine, and afforded high purity products upon cleavage. The results demonstrate that most active esters can be prepared in bulk and stored cold for future use; however, the shelf-life can vary from days to months depending on carboxylic acid structure.

Representative Procedures

Making PS-HOBt(HL) Active Esters Using DIC/DMAP

The solvents and reagents for preparing PS-HOBt(HL) active esters should be dry and care should be taken to avoid contamination by atmospheric moisture. To 150 mg of PS-HOBt(HL) resin (1.0 mmol/g, 0.15 mmol) was added 2 mL of a 0.045 M solution of DMAP in DCM (0.090 mmol) and 0.6 mL of a 0.38 M carboxylic acid solution in DMF (0.23 mmol). The mixture was shaken/agitated briefly. This was followed by the addition of 0.4 mL of 1.65 M DIC in DCM (0.66 mmol) and the solution was mixed for 3 h at room temperature. The resin was filtered, washed with DMF (3 x 3 mL), DCM (3 x 3 mL), DMF (3 x 3 mL), and THF (3 x 3 mL) and dried to afford purified resin-bound HOBt active ester. **Note:** *The co-solvent composition should be ~20% DMF. If more DMF is required to dissolve the acid, the ACTU coupling reagent is recommended.*

	Benzylamine RT		**1-Phenylpiperazine RT**		**Aniline 63 °C**	
Acid	% Yield	% Purity	% Yield	% Purity	% Yield	% Purity
Benzoic	93	92	87	96	86	94
2-Naphthoic	92	89	82	93[a]	92	87
4-Biphenylcarboxylic	90	92	80	96	82	90
Cinnamic	73	98	65	97	55	95
3-Phenylpropionic	75	99	76	99[a]	90	95
Cyclohexanecarboxylic	92	96	92	99	83	99
Cyclopentylpropionic	80	98	77	99	90	95
Boc-Ala-OH	56	93	64	99[a]	61	97
Boc-Phe-OH	54	98	64	99[a]	54	97
4-Bromophenylacetic	39	88	88	83[a]	40	95

Table 2. Synthesis of amides using PS-HOBt(HL)
[a]Sample incubated with PS-Isocyanate; approximately 1 equivalent relative to the PS-HOBt(HL)

PS-HOBt (HL)

Acid	% Yield	% Purity
2-Naphthoic	98	95
3-Phenylpropionic	60	97
Boc-Ala	34	90
Boc-Phe	74	97
4-Bromophenylacetic	72	88

Table 3. Synthesis of amides from benzylamine using BEP for formation of PS-HOBt(HL) active esters

Loading Carboxylic Acids at the 4 g Scale

To 3.75 g of PS-HOBt(HL) (1.0 mmol/g, 3.75 mmol) was added 50 mL of a 0.045 M solution of DMAP in DCM (2.25 mmol) and 15.0 mL of a 0.38 M of carboxylic acid solution in DMF (5.63 mmol). The mixture was stirred for 15 minutes, followed by addition of 10.0 mL of 1.65 M DIC in DCM (16.5 mmol). The mixture was then stirred for 3 h at room temperature. The resin was filtered, washed with the same solvents as the small scale reactions (60 mL of solvent) and dried to afford purified resin-bound HOBt active ester.

Loading Carboxylic Acids with BEP

2-Bromo-1-ethylpyridinium tetrafluoroborate (BEP) was prepared according to the literature procedure.[5] To 150 mg of PS-HOBt(HL) resin (1.0 mmol/g, 0.15 mmol) was added 1.5 mL of a 0.16 M solution of BEP in DCM (0.024 mmol) and 0.6 mL of a 0.38 M carboxylic acid solution in DMF (0.23 mmol). The mixture was shaken/agitated briefly. This was followed by the addition of 1.0 mL of 0.53 M solution of DIEA in DCM (0.53 mmol) and the mixture was stirred for 3 h at room temperature. The resin was filtered, washed with DMF (3 x 3 mL), DCM (3 x 3 mL), DMF (3 x 3 mL), and THF (3 x 3 mL) and dried to afford purified resin-bound HOBt active ester.

Amide Synthesis

To PS-HOBt(HL) active ester resin (0.15 mmol) was added a mixture of amine (0.07 mmol) and DIEA (0.1 mmol) in DCM or THF (2 mL) and the mixture was stirred at 25 °C for 3 h. The resin was filtered, and rinsed with DCM or THF (3 x 3 mL). The combined filtrate was concentrated to afford the desired amide. If the PS-HOBt(HL) active ester resin has been stored for an extended period, it is recommended that it be washed two to three times with DCM or THF prior to use.

Loading Protecting Groups

PS-HOBt(HL) can be used as an effective activating reagent for transfer of protecting groups (e.g., Fmoc and Cbz, to amines).[1]

PS-HOBt (HL)

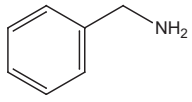
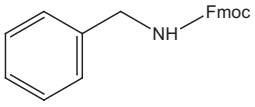
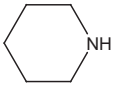
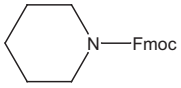
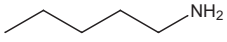
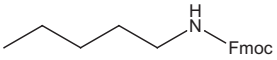
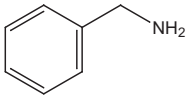
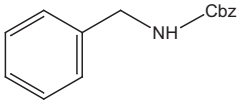
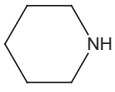
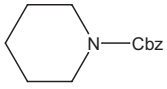
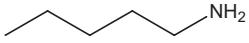
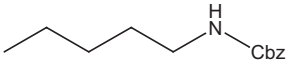
Entry	Protecting Group P-Cl	Amine R^1R^2NH	Protected Amine PNR^1R^2	% Yield	HPLC % Purity
1	Fmoc-Cl			78	99
2	Fmoc-Cl			75	10
3	Fmoc-Cl			76	100
4	Cbz-Cl			87	97
5	Cbz-Cl			42	95
6	Cbz-Cl			70	95

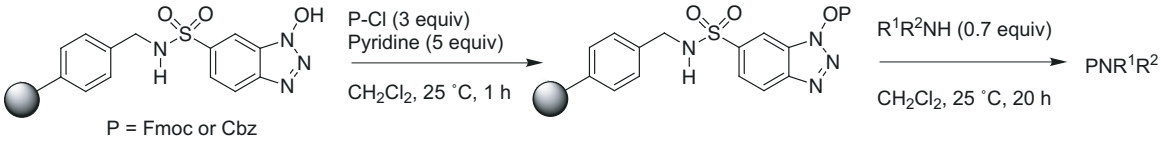
Table 4. Protection of amines using PS-HOBt resin

PS-HOBt (HL)

Protection of Amines as Fmoc Derivatives (Table 4, Entry 1)

225 mg of PS-HOBt resin (0.9 mmol/g, 0.2 mmol) and a solution of FmocCl (127 mg, 0.49 mmol) in 1.1 mL DCM were added to a reaction vessel. A solution of pyridine (65 mg, 0.82 mmol) in 1.2 mL DCM was then added. The mixture was stirred for 1 h at 25 °C.

The reaction mixture was drained and the resin washed with DCM (3 x), DMF (3 x), DCM (3 x), and diethyl ether (3 x). A solution of benzylamine (14 mg, 0.13 mmol) in 3.2 mL DCM was added, and the mixture was stirred for 20 h at 25 °C. Finally, the resin was filtered and washed three times with DCM. The filtrate was then concentrated to give Fmoc-benzylamine in 78% yield (HPLC purity 99%). ^{1}H NMR ($CDCl_3$, 300 MHz): ∂ 7.75 (d, 2 H, Ar-H), 7.60 (d, 2H, Ar-H), 7.45-7.20 (m,9 H, Ar-H), 5.10 (s, 1 H, N-H), 4.48 (d, 2 H, CH2), 4.40 (d, 2 H, CH2), 4.25 (t, 1 H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): d 156.40, 143.92, 141.34, 138.38, 127.65, 127.52, 127.03,125.00, 119.96, 66.69, 47.32, 45.12 ppm.



Ordering Information

Part Number	Quantity
800509	3 g
800417	10 g
800418	25 g
800419	100 g
800420	1000 g

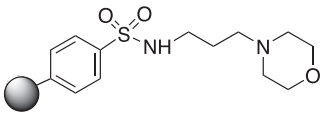
References

1. Pop, I. E..; Deprez, B. P.; Tartar, A.L. *J. Org. Chem.* **1997**, 62, 2594.
2. Gooding, O. W.; Vo, L.; Bhattacharyya, S.; Labadie, J. W. *J. Comb. Chem.*, submitted.
3. Part Numbers: 800516, 3 g; 800465, 10 g; 800466, 25 g; 800467, 100 g; 800468, 1000 g.
4. Li, P.; Xu J.-C. *Tetrahedron* **2000**, 56, 8119.
5. Dendrinos, K. G.; Kalivretenos, A. G., *J. Chem. Soc., Perkin Trans.* 1 **1998**, 1463.

PS-NMM

PS-NMM

Resin-Bound Base



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 1.9 mmol/g, minimum loading 1.7 mmol/g (based on nitrogen analysis)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: 3-(Morpholino)propyl polystyrene sulfonamide
Application: Tertiary amine base
Typical Reaction Conditions: 2–3 equivalents of PS-NMM resin relative to electrophile
Compatible Solvents: DCM (7.8 mL/g), THF (5.8 mL/g), DMF (8.7 mL/g), MeOH (2.2 mL/g)
Storage: Cool, dry location

PS-NMM is a resin-bound equivalent of N-methyl morpholine (NMM) and is useful as a bound tertiary amine base for a variety of chemical transformations. Synthesis of amides, sulfonamides, and carbamates can be effected using filtration as the only purification step when PS-NMM is used in conjunction with PS-Trisamine or PS-Isocyanate as scavenger resins.

PS-NMM is linked to the polystyrene backbone through a propylene sulfonamide moiety, as opposed to other resin-bound morpholine bases (e.g., morpholinomethyl polystyrene), which are linked at the benzylic position. We have found that the non-benzylic tertiary amine base PS-NMM is significantly more stable than benzylic tertiary amine base variants in the presence of reactive electrophiles like chloroformates. No cleavage of PS-NMM was observed in the presence of methyl chloroformate (DCM, 16 h), whereas treatment of morpholino-methyl polystyrene under similar conditions led to 90% cleavage.

Representative uses of PS-NMM resin in the formation of amides, sulfonamides, and carbamates are provided in Table 1. The data show that the use of PS-NMM as the base in the synthesis of methyl carbamates from alkyl or aromatic amines affords the desired carbamate as the sole product. In contrast, use of morpholinomethyl polystyrene as the tertiary amine resulted in the formation of methyl morpholine carbamate as a side product due to secondary cleavage of the N-benzyl-linked secondary amine.[2,3] The level of methyl morpholine carbamate formed was 16% when aniline was the reactant, even though aniline was used in excess to the chloroformate. The level of cleavage of benzyl-linked tertiary amines will be more significant in cases where the chloroformate is used in excess.

Electrophile	Amine	Resin	Yield (%)	% Purity (GC)
4-Cl benzoyl chloride	Benzylamine	PS-NMM	94	100
Tosyl chloride	Benzylamine	PS-NMM	93	89
Methyl chloroformate	Benzylamine	PS-NMM	99	100
Methyl chloroformate	Benzylamine	P-Morpholine[a]	77	96[b]
Methyl chloroformate	Aniline	PS-NMM	67	100
Methyl chloroformate	Aniline	P-Morpholine[a]	67	84[c]

Table 1. Formation of amides, sulfonamides, and carbamates using PS-NMM resin
[a]Morpholinomethyl polystyrene
[b]Contains 4 area % Methyl morpholine carbamate
[c]Contains 16 area % Methyl morpholine carbamate

Ordering Information

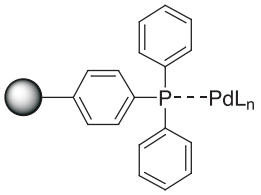
Part Number	Quantity
800496	3 g
800282	10 g
800283	25 g
800284	100 g
800318	1000 g

References

1. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, 119, 4882.
2. Conti, P.; Demont, D.; Cals, J.; Ottenheijm, H. C. J.; Leysen, D. *Tetrahedron Lett.* **1997**, 38, 2915.
3. Yang, B. V.; O'Roarke, D.; Li *J. Synlett.* **1993**, 195.

PS-PPh_3-Pd

PS-PPh_3-Pd
Polymer-bound Triphenylphosphine-Pd(0)



Resin Type: Poly(styrene-co-divinylbenzene)
Loading: Typical loading 0.1 mmol/g, minimum loading 0.08 mmol/g (ICP analysis)
Bead Size: 75–150 micron
Chemical Name: Polystyrene Triphenylphosphine Palladium(0)
Application: Catalyst for Suzuki and Heck reactions
Typical Reaction Conditions: 0.5 mol% catalyst, 16 h, 75 °C
Compatible Solvents: DMF (3.5 mL/g), THF (4.1 mL/g), DCM (4.9 mL/g)
Storage: Cool, dry location

PS-PPh_3-Pd resin is a polystyrene-bound equivalent of the small molecule catalyst tetrakis(triphenylphosphine) palladium(0) [$Pd(Ph_3P)_4$]. The primary application for the resin is as a catalyst for Suzuki-Miyaura coupling reactions between arylboronic acids and aryl halides. PS-PPh_3-Pd may also have applications in other types of palladium-catalyzed processes in which $Pd(Ph_3P)_4$ is used. The resin was developed to perform in a manner similar to that of the well-established catalyst, while facilitating reagent handling and simplifying workup, product isolation, and removal of palladium.

The small molecule catalyst, $Pd(Ph_3P)_4$, is a standard first choice for a number of carbon-carbon bond forming reactions, including Suzuki-type cross coupling reactions.[1] The Suzuki reaction is one of the most widely practiced coupling protocols for the preparation of symmetrical and unsymmetrical biaryl compounds.[2] $Pd(Ph_3P)_4$ is preferred to other palladium catalysts for this application because of its mild reaction conditions and broad scope of reactivity. However, despite the widespread use of palladium-mediated catalytic reactions, removal of residual palladium during workup and product isolation remains a major problem. Reducing the palladium content to the parts per million (ppm) level, as is required for active pharmaceutical ingredients, is particularly challenging.[3]

PS-PPh_3-Pd offers scope and reactivity similar to that of $Pd(Ph_3P)_4$ with the additional convenience of a polymer-supported reagent for handling and purification. Unlike the small molecule reagent, PS-PPh_3-Pd has been found to be stable to air and can be stored at room temperature for extended periods of time without degradation. The resin may be weighed out on the bench using regular weighing tools and requires no special handling techniques. Typical reaction conditions for Suzuki cross-coupling reactions of aryl bromides and iodides with arylboronic acids utilize 0.5 mol% of PS-PPh_3-Pd catalyst. The reactions are performed in a mixture of dimethoxyethane (DME) and EtOH (1:1) in the presence of aqueous K_2CO_3 at 75 °C for 16 h. After the reaction is complete, the reaction mixture is diluted with DCM and water, followed by separation and filtration of the organic layer through a silica gel SPE cartridge.[4] The product is then concentrated. Using this protocol the products are typically obtained in excellent yield and purity, and contain <100 ppm residual palladium. When lower levels of palladium are required, a palladium scavenging resin, MP-TMT,[5] may be employed prior to the final concentration step. Control experiments utilizing the small molecule catalyst $Pd(Ph_3P)_4$ afforded products containing palladium levels as high as 1700 ppm. When using N-heterocyclic bromides as coupling partners, the same procedure is followed except that the organic layer is loaded onto an MP-TsOH cartridge.[6] The solution is allowed to flow through the cartridge, followed by washing with methanol to remove non-basic impurities. The product is then released from the cartridge by the addition of ammonia in methanol, followed by washing with methanol. Concentration of the combined methanol solutions affords the product.

To evaluate the scope and reactivity of PS-PPh_3-Pd resin, a series of Suzuki coupling reactions was performed. Substrates included various aryl bromides and arylboronic acids, as shown in Table 1. Coupling reactions were carried out using 0.5 mol% of the bound catalyst. For comparison purposes, most of the reactions were also conducted with 0.5 mol% of the small molecule catalyst, $Pd(Ph_3P)_4$, as a control. In all cases, the standard

PS-PPh3-Pd

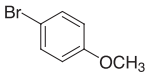
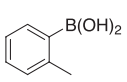
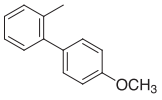
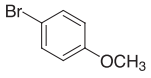
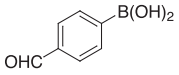
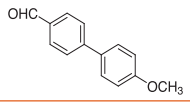
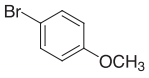
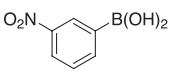
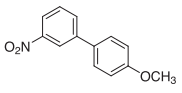
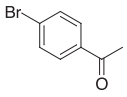
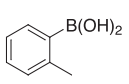
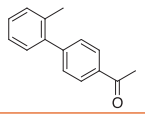
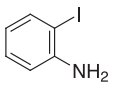
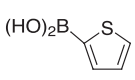
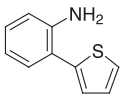
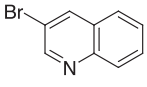
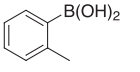
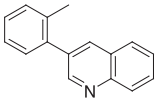
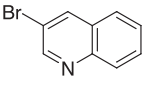
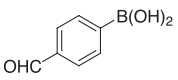
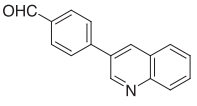
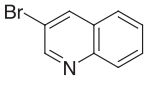
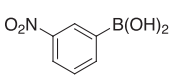
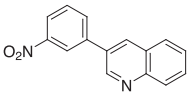
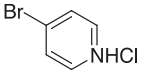
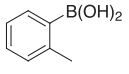
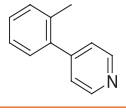
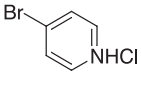
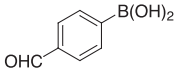
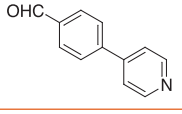
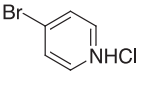
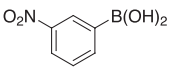
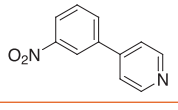
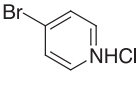
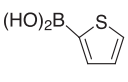
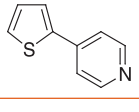
Entry	Aryl Halide	Boronic Acid	Product	PS-PPh3-Pd Conversion (Purity) % Pd(Ph3P)4	Conversion (Purity) %
1				97 (97)	100 (94)
2				98 (87)	97 (87)
3				98 (85)	99 (90)
4				100 (95)	ND
5				51 (36)	100 (93)
6				98 (98)	76 (79)
7				89 (85)	93 (73)
8				93 (69)	99 (76)
9				99 (97)	99 (89)
10				99 (94)	99 (96)
11				99 (90)	99 (92)
12				99 (99)	99(95)

Table 1. Suzuki coupling of aryl boronic acids with aryl halides

PS-PPh_3-Pd

protocol was followed and the products analyzed by GC to determine the % conversion of starting material. The chemical purity was determined by GC and/or ^{1}H-NMR.

A range of aryl bromides, including the heterocyclic bromides, underwent high conversion to product with the series of boronic acids studied. In most cases the results for the resin-bound catalyst were comparable to the small molecule catalyst. An exception to this trend was observed for the case of 2-iodoaniline and 2-thienylboronic acid (Table 1, Entry 5) where Pd(Ph_3P)$_4$ provided products in higher yield and purity than PS-PPh_3-Pd. While both catalysts gave excellent results, use of the bound catalyst provided easier weighing and dispensing and afforded products with substantially lower levels of residual palladium.

Capacity, Stability, and Handling

The palladium loading of the resin catalyst was determined by elemental analysis. Unlike the small molecule catalyst, the resin has been found to be stable to storage and use in air. The resin may be weighed out on bench using regular weighing methods. Given its uniform density, the resin may also be dispensed by automated filling devices or manual dispensing systems such as the ArgoScoop resin dispenser (Part Number 900131). Static electric charge may make handling difficult in dry conditions. Avoiding plastic weighing tools minimizes this effect.

Palladium Impurities in the Products

The crude products obtained by using both the bound catalyst, PS-PPh_3-Pd, and the small molecule catalyst, Pd(Ph_3P)$_4$, were tested for the presence of residual palladium. On average, the palladium levels in the products from PS-PPh_3-Pd catalyzed reactions were found to be in the 50–100 ppm range. Products from Pd(Ph_3P)$_4$ catalyzed reactions gave palladium levels in the 1000–1700 ppm range.

Representative Procedures

Suzuki Reaction of Aryl Halides with Arylboronic Acid (Table 1, Entry 1)

4-bromoanisole (0.187 g, 1 mmol) in DME (1 mL) was added to PS-PPh_3-Pd(0) (0.05 g, 0.005 mmol, 0.10 mmol/g), followed by 2-methylbenzeneboronic acid (0.162 g, 1.2 mmol) in EtOH (1 mL), and K_2CO_3 (0.207 g, 1.5 mmol) in water (0.5 mL). The reaction mixture was agitated for 16 h at 75 °C, cooled to room temperature and diluted with DCM (1 mL) and water (2 mL). The organic layer was then passed through a silica SPE cartridge (500 mg, Part Number 440-0050-C), pre-conditioned with DCM (4 mL). The effluent was collected, the cartridge was washed with DCM (3 x 3 mL), and the combined effluent plus washings were concentrated to afford 4-(o-tolyl)anisole in 95% yield (0.19 g, GC purity 97%). The residual palladium content in the product was determined to be 90 ppm. The amount of palladium found in the control experiment using the small molecule catalyst Pd(Ph_3P)$_4$ was 1700 ppm.

Ordering Information

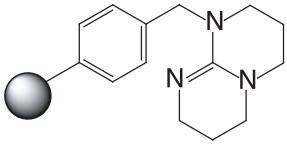
Part Number	Quantity
800473	3g
800474	10 g
800475	25 g
800476	100 g

References

1. See, for example, (a) Handbook of Reagents for Organic Synthesis Reagents, Auxiliaries and Catalysts for C-C Bond Formation, Coates, R. M.; Denmark, S. E. Eds., Wiley, New York, **1999**, pp 596-604 and references cited therein; (b) Stanforth, S. P. *Tetrahedron*, **1998**, 54, 263.
2. (a) Miyaura, N.; Yanagi, T.; Suzuki, *A. Synth. Commun.* **1981**, 11, 513; (b) Suzuki, A. *Pure Appl. Chem.* **1994**, 66, 213; (c) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, 95, 2457.
3. (a) Chen, C; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, 68, 2633; (b) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. & Dev.* **1997**, 1, 311.
4. Part Number 440-0100-C.
5. Part Numbers: 800469, 10 g; 800470, 25 g; 800471, 100 g; 800472, 1000 g.
6. Part Number 800477-0050-C.

PS-TBD

Resin-bound Base



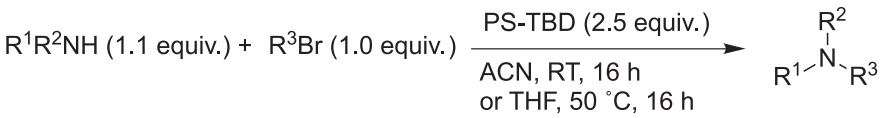
Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 1.3 mmol/g, minimum loading 1.1 mmol/g (based on acid/base titration)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: 1,5,7-triazabicyclo[4.4.0]dec-5-ene polystyrene
Application: Alkylation of phenols and amines; esterification of carboxylic acids using alkyl halides; alkylation of activated methylene compounds; dehalogenation of organic halides; high throughput synthesis of aryl triflates and aryl nonaflates; Williamson ether synthesis
Typical Application Conditions: 2–3 equivalents relative to limiting reagent
Compatible Solvents: DCM (7.6 mL/g), DMF (3.5 mL/g), THF (6.6 mL/g), MeOH (6.6 mL/g), ACN (2.5 mL/g)

PS-TBD is a polymer-supported base, which consists of a bicyclic guanidine moiety (1,5,7-triazabicyclo [4.4.0]dec-5-ene) anchored on polystyrene. PS-TBD is a stronger polymer-supported base than the PS-DIEA and PS-NMM resins, which are bound tertiary amines that are used in organic synthesis and reagent scavenging. Published applications of PS-TBD include alkylation of phenols[1] and amines;[2] esterification of carboxylic acids using alkyl halides; alkylation of activated methylene compounds; de-halogenation of organic halides;[3] high throughput synthesis of aryl triflates and aryl nonaflates,[4] and the regioselective synthesis of lysophospholipids.[5]

In alkylation reactions, the resin may be used in a catch-and-release protocol, whereby an acidic species is caught on the PS-TBD resin as a resin-bound nucleophile (e.g. phenol forming a bound phenolate). On reaction with an electrophile, the product is released into solution. By using the electrophile as the limiting reagent, full conversion to product can be achieved, while the excess nucleophile remains bound to the resin. Filtration and solvent evaporation affords the desired product in high purity.

Synthesis of Tertiary Amines by Reaction of Secondary Amines with Activated Alkyl Bromides

A series of tertiary amines was synthesized by reaction of secondary amines with activated alkyl bromides in the presence of PS-TBD (Scheme 1). The amine was used in slight excess (1.1 equivalent) of the alkyl bromide and best results were obtained with 2.5 equivalents of PS-TBD. The choice of solvent and temperature of the reaction was found to be important, with optimal conditions provided by THF at 50 °C or ACN at room temperature. Complete conversion of the alkyl bromide occurred in 16 h to afford a mixture of the desired tertiary amine and residual secondary amine (ca. 0.1 equivalent).



Scheme 1. Synthesis of tertiary amines by reaction of secondary amines with activated alkyl bromides

PS-TBD

The excess secondary amine was selectively scavenged from the mixture by the addition of MP-Isocyanate (a macroporous scavenger for amines) and subsequent stirring at room temperature. MP-Isocyanate was used in preference to PS-Isocyanate because of its higher reactivity in ACN. Filtration and concentration afforded the desired tertiary amines as homogeneous products in good-to-excellent yields (Table 1). While the conditions for the synthesis of the amines may be generalized for certain substructures, the effect of the substrates needs to be considered. For example, the reaction of dibutylamine with both ethyl α-bromoacetate and 4′-bromobenzyl bromide afforded higher yields in ACN at room temperature than in THF at elevated temperatures (71% vs. 30% and 70% vs. 60%, respectively). The low yield and high purity in THF may be due to loss of the volatile amine at elevated temperatures in conjunction with reaction of the resultant excess alkyl bromide with the resin to form a bound quaternary salt. In contrast, the reaction of indole-3-carboxaldehyde with 4′-bromobenzyl bromide afforded higher yields in THF at 50 °C than in ACN (90% vs. 33%).

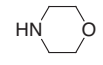
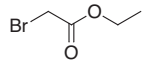
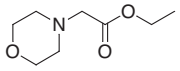
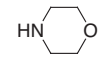
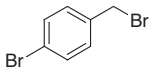
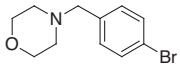
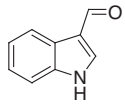
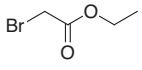
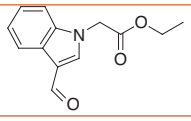
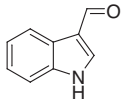
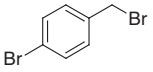
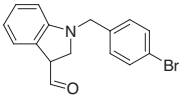
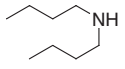
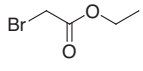
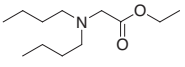
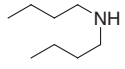
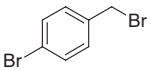
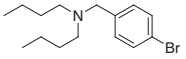
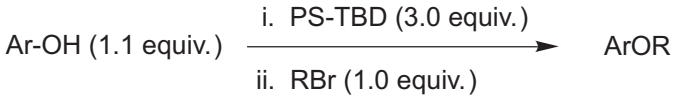
			ACN RT, 16 h		**THF 50 °C, 16 h**	
Amine	**Electrophile**	**Product**	**% Yield**	**% Purity**	**% Yield**	**% Purity**
			84	100	64	100
			83	100	87	100
			68	100	79	100
			33	100	90	100
			71	100	30	100
			70	100	60	100

Table 1. Results of amine alkylation using PS-TBD resin

Williamson Ether Synthesis

The use of PS-TBD in Williamson ether synthesis was investigated as an example of a catch-and-release protocol using this resin. A series of phenols was incubated with PS-TBD and then treated with a series of alkyl bromides as the limiting reagent (Scheme 2). The reaction was initially examined using 1.5 and 3 equivalents of PS-TBD. The phenols were incubated with PS-TBD for an hour to generate bound phenolates. The alkyl bromides were then added. Three equivalents of PS-TBD resin afforded complete conversion of bromides to aryl ethers, which after filtration and concentration were of high purity. The same reactions carried out with 1.5 equivalent of PS-TBD resulted in phenol contamination in the majority of cases. Since 3 equivalents of PS-TBD was more effective at sequestering the phenol from the final reaction mixture as bound phenolate, it was chosen for a more complete series of aryl ethers using both THF and ACN as solvents (Table 2, page 96).



Scheme 2. The use of PS-TBD resin in the Williamson ether synthesis

In contrast to PS-TBD mediated tertiary amine synthesis, the use of ACN in the Williamson ether synthesis was demonstrated to be effective only at elevated temperature. Heating these reactions in ACN to 55 °C for 16 h was optimal and generated the ethers in excellent purities and in high yields, in comparison with the corresponding reactions carried out in THF. Reactions in THF were effective at room temperature; however, the product yield and purity were variable. In cases where low purity products were obtained, mixtures of unidentified by-products were observed.

To demonstrate the formation of bound phenolate using PS-TBD, a 0.3 M solution of 4-methoxyphenol in ACN was mixed with 1 equivalent of the resin. The solution was sampled and the concentration of 4-methoxyphenol was measured relative to an internal standard. After 2 h, the resin had sequestered 84% of the 4-methoxyphenol from solution. The resin-bound phenolate was then drained and washed with ACN. Analysis showed that no. 4-methoxy-phenol was lost from the PS-TBD in this process. This indicates that the phenolate PS-TBD salt is stable to ACN washing. In a similar set of experiments, the uptake of phenol by PS-TBD in THF was about half of that observed in ACN.

Representative Procedures

Alkylation of Secondary Amines Using PS-TBD Resin

PS-TBD resin (0.28 mmol, 2.5 equivalents, 200 mg, 1.4 mmol/g) was incubated with a solution of amine (0.12 mmol, 1.1 equivalent, 0.49 mL, 0.25 M) in each of THF and ACN for 1 h. (Note: shorter equilibration times are likely to be equally effective.) A solution of halide (0.11 mmol, 1.0 equivalent., 0.45 mL, 0.25 M) was added to each of the reaction vessels followed by 1 mL of either THF or ACN to make up a total volume of 2 mL. Reactions in THF were performed at 50 °C for 16 h and reactions carried out in ACN were performed at room temperature for 16 h. To each of the vessels was then added MP-Isocyanate scavenger (0.99 mmol, 10 equivalents, 570 mg, 1.73 mmol/g) and the reactions agitated at room temperature for a further 16 h and filtered. The filtrate was concentrated and the purities determined by GC and structures confirmed by ^{1}H NMR.

Alkylation of Phenols Using PS-TBD Resin

PS-TBD resin (0.34 mmol, 3.0 equivalents, 240 mg, 1.4 mmol/g) was incubated with a solution of phenol (0.12 mmol, 1.1 equivalent, 0.49 mL, 0.25 M) in each of THF and ACN for 1 h. A solution of halide (0.11 mmol, 1.0 equivalent, 0.45 mL, 0.25 M) was added to each of the reaction vessels, followed by 1 mL of either THF or ACN, to make up a total volume of 2 mL. Reactions in THF were carried out at room temperature for 16 h and reactions in ACN were carried out at 55 °C for 16 h. The reaction solutions were filtered, the filtrate was concentrated and the purities determined by GC and structures confirmed by ^{1}H NMR.

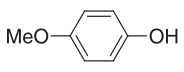
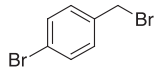
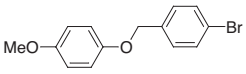
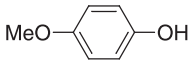
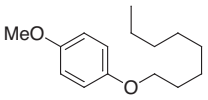
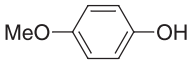
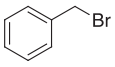
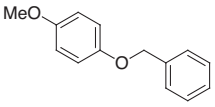
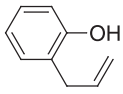
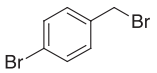
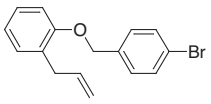
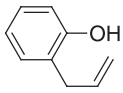
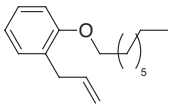
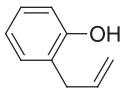
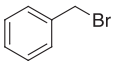
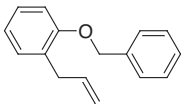
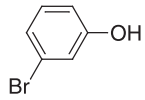
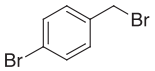
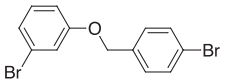
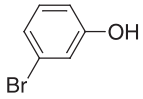
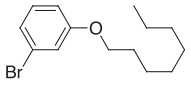
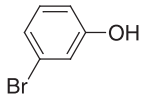
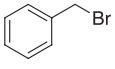
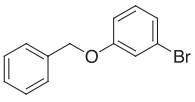
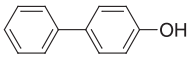
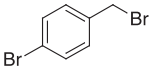
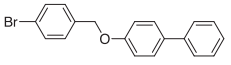
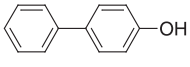
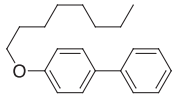
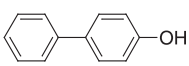
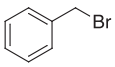
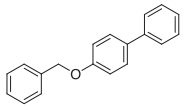
			ACN 55 °C 16 h		**THF RT 16 h**	
Phenol	**Electrophile**	**Product**	**% Yield**	**% Purity**	**% Yield**	**% Purity**
			89	100	87	100
			97	100	63	45
			91	100	90	100
			95	100	38	89
			94	100	88	100
			96	100	89	100
			90	100	45	17
			92	100	66	42
			91	100	77	100
			90	100	77	100
			85	100	91	100
			88	100	90	100

Table 2. Results of Williamson Ether Synthesis using PS-TBD

PS-TBD

Ordering Information

Part Number	Quantity
800513	3 g
800421	10 g
800422	25 g
800423	100 g
800424	1000 g

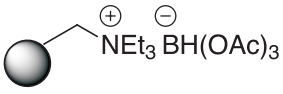
References

1. Morrissey, M. M.; Mohan, R.; Xu, W. *Tetrahedron Lett.* **1997**, 38, 7337.
2. (a) Iijima, K.; Fukuda, W.; Tomoi, M. *Pure Appl. Chem.* **1992**, A29(3), 249. (b) Organ, M. G.; Dixon, C. E. *Biotech. Bioeng. Comb. Chem.* **2000**, 71, 71.
3. (a) Tomoi, M.; Kato, Y.; Kakiuchi, H. *Makromol. Chem.* **1984**, 185, 2117. (b) Tomoi, M.; Watanabe, T.; Suzuki, T.; Kakiuchi, H. *Makromol. Chem.* **1985**, 186, 2473.
4. Boisnard, S.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1999**, 40, 7469.
5. Tamura, Y.; Fukuda, W.; Tomoi, M. *Synth. Commun.* **1994**, 24, 2907.

MP-TRIACETOXYBOROHYDRIDE

MP-Triacetoxyborohydride

Polymer-bound Reducing Agent



Resin Type: Macroporous polystyrene
Loading: Typical loading 2.0 mmol/g, minimum loading 1.8 mmol/g (based on hydrogen evolution in 1 M HCl)
Bead Size: 350–1250 µm, 18–52 mesh (95% within)
Chemical Name: Macroporous triethylammonium methylpolystyrene triacetoxyborohydride
Application: Reductive amination with primary and secondary amines
Typical Conditions for Reductive Amination: 1.0 mmol of carbonyl compound, 1.2 mmol of primary or secondary amine in THF, and 2.5 mmol of the resin stirred overnight at room temperature. For many of these reactions PS-Benzaldehyde or PS-Isocyanate may be added as scavengers for one-pot purification of the product.
Compatible Solvents: THF (2 mL/g), DMF (2 mL/g), N-methyl pyrrolidinone (NMP) (2 mL/g)
Composition: MP-Triacetoxyborohydride stabilized with 10% THF by weight
Storage: Should be stored in a closed container at 5 °C. However, the resin has been found to be stable at room temperature for up to 1 year.

MP-Triacetoxyborohydride is a macroporous polystyrene-bound equivalent of tetraalkylammonium triacetoxyborohydride. MP-Triacetoxyborohydride has primary applications in the reductive amination of aldehydes and ketones under neutral or mildly acidic reaction conditions. This resin was developed to perform in a manner similar to that of the well-established sodium triacetoxyborohydride, while simplifying reagent handling and product purification. Moreover, for many of these reactions, a scavenger resin may be added for one-pot purification of the product. MP-Triacetoxyborohydride contains approximately 10% tetrahydrofuran (THF) and is handled as free-flowing, low-static beads.

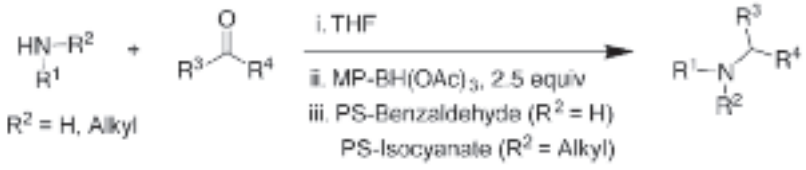
Sodium triacetoxyborohydride has emerged as one of the reagents used most frequently for carrying out reductive amination of carbonyl compounds, a reaction that is also known as reductive alkylation of amines.[1,2,3] This reagent has gained preference relative to other reducing agents as a result of its mild reaction conditions and broad scope of reactivity. The typical conditions for reductive amination reactions with sodium triacetoxyborohydride utilize 1.5–2.0 equivalents of reagent in THF or dichloroethane (DCE) in the presence of acetic acid. A disadvantage of sodium triacetoxyborohydride is its poor solubility, and that product isolation requires an aqueous quench followed by liquid-liquid extraction and column chromatography.

MP-Triacetoxyborohydride offers scope and reactivity similar to that of sodium triacetoxyborohydride with the additional convenience of a polymer-supported reagent for handling and purification. Typical conditions require 2.5 equivalents of resin relative to the limiting reagent in THF. Acetic acid is not required (Scheme 1). After the reaction is complete, a scavenger resin may be added for product purification. For example, in the case of reductive alkylation using an excess of primary amine, PS-Benzaldehyde may be used to scavenge the excess starting primary amine from the product secondary amine. Likewise, in the case of reductive alkylation of secondary amines, an excess of the starting secondary amine may be scavenged by PS-Isocyanate. The product is then isolated by simply filtering off the resins. Catch-and-release of the amines with MP-TsOH or ISOLUTE SCX-2 may also be employed to purify the reductive amination products when an excess of carbonyl compounds is used.[4]

Sodium triacetoxyborohydride is highly moisture-sensitive and sparingly soluble in common organic solvents, making it difficult to use in automated and parallel synthesis. The bound triacetoxyborohydride, on the other hand, may be used with resin dispensing systems. THF should be used as solvent in preference to DCE because of the incompatibility of reactive amines with DCE. This appears to be exacerbated by the presence of resin.

MP-Triacetoxyborohydride

Polar aprotic solvents, e.g., N,N-dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP), may be used for substrates with low solubility in THF. These solvents allow use of amine hydrochlorides directly without prior conversion to the free amine. The scope and reactivity of MP-Triacetoxyborohydride for secondary and tertiary amine synthesis are described in more detail in the following sections.



Scheme 1. Reductive alkylation of primary and secondary amines

Synthesis of Secondary Amines

The starting primary amine was used in 20% excess in order to control selectivity towards monoalkylation. Reductive amination reactions proceeded overnight at room temperature in THF under neutral reaction conditions. After the reaction was complete, PS-Benzaldehyde was added to the reaction mixture, selectively scavenging excess primary amine. The scavenging of primary amines proceeded to completion with no addition of acetic acid. Similar reactions using MP-Cyanoborohydride required 30% (vol.) acetic acid for complete scavenging of primary amines. We attributed the higher reactivity of the scavenger resin to the presence of excess MP-Triacetoxyborohydride, which acts as a dehydrating agent to drive imine formation with PS-Benzaldehyde. The product secondary amines were isolated as acetate salts by filtration of the resin and evaporation of the solvent. The free amine may be obtained by neutralization of the acetate salt with MP-Carbonate or by catch-and-release purification with MP-TsOH or ISOLUTE SCX-2 columns. We attributed the formation of the acetate salt to hydrolysis of an equivalent of triacetoxyborohydride by the water generated from imine formation prior to reduction.

The results for the reductive alkylation for a set of primary amines are summarized in Table 1. In most of the cases the products were isolated in excellent purity. Reaction of cyclohexanecarboxaldehyde afforded 16 and 4% overalkylated tertiary amine product with N-(3-aminopropyl)morpholine and 2-(aminomethyl)pyridine, respectively (Table 1, Entries 1 and 2). Acid-sensitive functional groups were tolerated, as exemplified by successful reductive amination of 1,4-cyclohexanedione mono-ethylene ketal with N-(3-aminopropyl) morpholine and 2-aminomethylpyridine (Table 1, Entries 3 and 4). Acetophenone underwent reductive amination in low to moderate yields, which is consistent with results obtained with sodium triacetoxyborohydride (Table 1, Entries 5 and 6).[1]

Reductive alkylation of hydrochloride salts of amino esters was carried out using DMF as the reaction solvent. Reactions were performed in the presence of 3.5 equivalents of MP-Triacetoxyborohydride with amine as the limiting reagent. The additional equivalent of resin was used for amine hydrochloride neutralization. Results are shown in Table 2. Isoleucine methyl ester hydrochloride underwent reductive alkylation with cyclopentanone and cyclohexanecarboxaldehyde, respectively, to afford the corresponding secondary amine products in high yield and purity (Table 2, Entries 1 and 2). Notably, over alkylation was not observed even though the carbonyl compound was in excess. Reductive alkylation of tyrosine methyl ester hydrochloride afforded analogous results (Table 2, Entries 3 and 4). NMP was equally effective as the solvent for these reactions. Since carbonyl compounds were used in excess, the products were purified by catch-and-release using MP-TsOH. This method effected convenient DMF removal from the product, since the MP-TsOH-amine complex can be washed with methanol prior to product release in ammonia/methanol.

MP-TRIACETOXYBOROHYDRIDE

Synthesis of Tertiary Amines

Reductive alkylation of secondary amines was carried out with carbonyl compounds as the limiting reagent. Similar to the reactions with primary amines, these reactions proceeded overnight at room temperature in dry THF. Upon completion of the reaction, PS-Isocyanate was added to the reaction mixture to selectively scavenge excess secondary amine. Tertiary amine product was isolated as a free amine by filtration and subsequent evaporation of the solvent. Reductive amination using secondary amines may also be carried out with the amine as the limiting reagent to drive the reaction to completion. In these cases, the product amines may be purified from non-basic impurities by catch-and-release using MP-TsOH.

The results from the reductive alkylation of a set of secondary amines are summarized in Table 3. The expected products were obtained for both cyclic secondary amines with aldehydes and ketones (Table 3, Entries 1-4). Alicyclic secondary amines (e.g., N-benzylmethylamine), also underwent smooth transformation to the corresponding tertiary amines (Table 3, Entries 5 and 6). In all cases the products were isolated in essentially pure form by simple concentration.

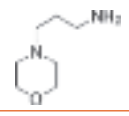
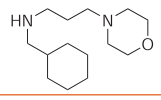
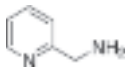
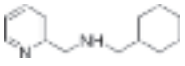
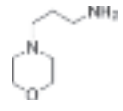
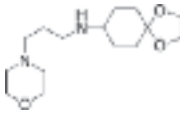
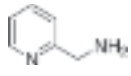
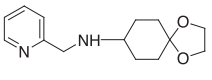
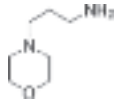
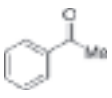
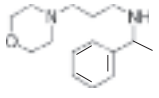
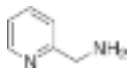
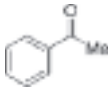
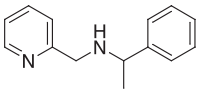
Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				77	84[a]
2				90	96[a]
3				77	100
4				91	100
5				69	98
6				76	27

Table 1. Reductive alkylation of primary amines using MP-Tricetoxyborohydride
[a] Dialkylated product present as the major impurity

Boron Impurities

The reductive amination products were analyzed for the presence of boron by elemental analysis. The level of Boron found was less than 100 ppm in all samples.

Capacity and Stability

The triacetoxyborohydride content of the resin is determined by hydrolyzing the resin with aqueous HCl (1 M). The capacity is calculated based on the amount of liberated hydrogen gas collected. The resin typically contains approximately 10% THF (as calculated from the ^{1}H NMR spectrum of a $CDCl_3$ extraction of the resin). The THF is required to stabilize the resin and it is important not to remove this by drying in vacuo. The resin is stable for at least 10 months at 4 °C in a closed container. Storage of samples for multiple months at room temperature does not affect the resin.

MP-Triacetoxyborohydride

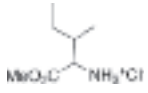
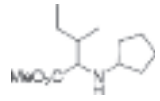
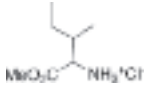
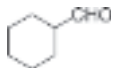
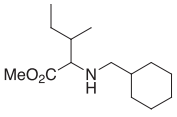
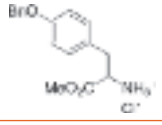
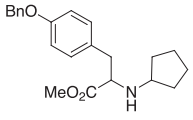
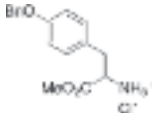
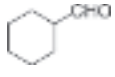
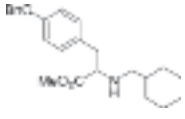
Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				59	98
2				93	99
3				60	93
4				74	98

Table 2. Reductive alkylation of amino ester hydrochlorides using MP-Triacetoxyborohydride in DMF

Representative Procedures

Reductive Alkylation of Primary Amines (Table 1, Entry 3)

A THF solution (0.50 M) of N-(3-aminopropyl)morpholine (1.2 mL, 0.60 mmol) was added to a THF solution (0.50 M) of 1,4-cyclohexanedione mono-ethylene ketal (1.0 mL, 0.50 mmol). MP-Triacetoxyborohydride (2.0 mmol/g, 0.625 g, 1.25 mmol) was then added and the mixture was agitated for 16 h at room temperature. When the reaction was complete, PS-Benzaldehyde (0.42 g, 0.5 mmol) and THF (2 mL) were added and the mixture was further agitated for 6 h. The resin was filtered and washed with THF (2 x 4 mL). The combined solution was concentrated to afford the product secondary amine as the acetate salt in 77% yield and 100% purity. The secondary amine was characterized by gas chromatography and ^{1}H NMR.

Reductive Alkylation of Primary Amine Hydrochlorides (Table 2, Entry 3)

A DMF solution (0.25 M) of HCl-Tyr(OBn)-OMe (2 mL, 0.5 mmol) was added to a DMF solution (0.5 M) of cyclopentanone (1.2 mL, 0.60 mmol). MP-Triacetoxyborohydride (2.3 mmol/g, 0.760 g, 1.75 mmol) was then added and the mixture was agitated for 16 h at room temperature. The resin was filtered with a 6 mL fritted polypropylene cartridge into a scintillation vial containing MP-TsOH (1 g, 1.5 mmol). The MP-Triacetoxyborohydride resin was rinsed with DMF (3 x 2 mL) and the combined filtrate was agitated with MP-TsOH for 45 min. The mixture was transferred to a polypropylene cartridge fitted with a PTFE stopcock to control the flow rate to approximately 0.5–1.5 mL/min. The MP-TsOH resin was washed with MeOH (4 x 8 mL) to remove nonbasic impurities. The product was released by washing with 2 M NH_3 /MeOH, and MeOH (2 x 8 mL). The combined solution was concentrated to afford the secondary amine product in 60% yield and 93% purity. The secondary amine was characterized by gas chromatography and ^{1}H NMR.

MP-Triacetoxyborohydride

Reductive Alkylation of Secondary Amines (Table 3, Entry 1)

A THF solution (0.5 M) of N-methylpiperazine (1.2 mL, 0.60 mmol) was added to a THF solution (0.5 M) of cyclohexanecarboxaldehyde (1.0 mL, 0.50 mmol). MP-Triacetoxyborohydride (2.0 mmol/g, 0.625 g, 1.25 mmol) was then added and the mixture was agitated for 16 h at room temperature. When the reaction was complete, PS-Isocyanate (0.4 g, 0.5 mmol) and THF (2 mL) were added and the mixture was further agitated for 6 h. The resin was filtered and washed with THF (4 mL x 2). The combined solution was concentrated to afford the tertiary amine product in 92% yield and 99% purity. The tertiary amine was characterized by gas chromatography and ^{1}H NMR.

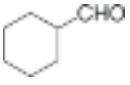
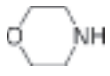
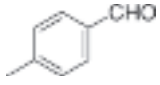
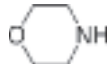
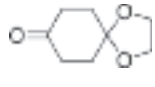
Entry	Starting Amine Carbonyl	Compound Product	Amine % Yield	% Purity
1			92	99
2			85	100
3			63	100
4			69	100
5			82	100
6			76	100

Table 3. Reductive alkylation of secondary amines using MP-Triacetoxyborohydride

Ordering Information

Part Number	Quantity
800517	3 g
800413	10 g
800414	25 g
800415	100 g
800416	1000 g

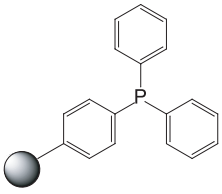
References

1. For synthetic applications of sodium triacetoxyborohydride, see: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R.S. *J. Org. Chem.* **1996**, 61, 3849-3862.
2. Gribble G. W. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed., John Wiley: NY **1995**; Vol. 7, p. 4649.
3. Abdel-Majid, A. F. In *Reductions in Organic Synthesis*, ACS Symposium Series, Abdel-Majid, A. F. ed., American Chemical Society: Washington, DC **1996**, p. 201.
4. MP-TsOH, MP-TsOH(65) or MP-TsOH cartridges technical information (pages 183, 184, 185, respectively). Removal in vacuo will lead to loss of activity.

PS-TRIPHENYLPHOSPHINE

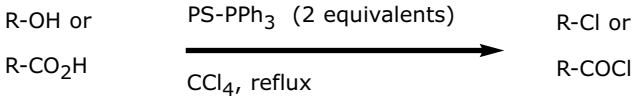
PS-Triphenylphosphine

Resin-bound Phosphine

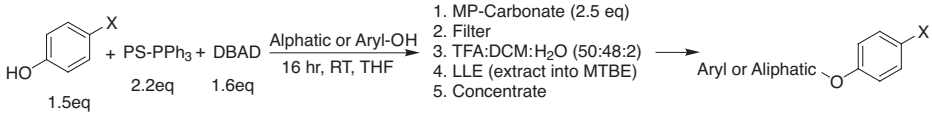


Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 2.2 mmol/g, minimum loading 1.8 mmol/g (based on uptake of benzyl bromide)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Diphenylphosphino-polystyrene
Application: Chlorination of acids and alcohols, Wittig and Mitsunobu reactions, scavenging of alkyl halides
Typical Chlorination Conditions: 0.5 equivalent of acid or alcohol in CCl_4, 3 h, reflux
Typical Mitsunobu Reaction Conditions: 1.0 equivalent of alcohol, 1.5 equivalent of phenol, 2.2 equivalents of resin, and 1.6 equivalent of di-tert-butyl azodicarboxylate (DBAD) at room temperature for 16 h
Typical Wittig Reaction Conditions: 2.0 equivalents of ylide resin, 8.0 equivalent of sodium bis (dimethylsilyl)amide/tetrahydrofuran (NaHMDS/THF), resin washed with THF, followed by 1.0 equivalent of carbonyl compound in THF at room temperature for 16 h
Typical Alkyl Halide Scavenging Conditions: 3.0 equivalent of resin, DMF, 10 mL/g resin, 20 °C, 16 h
Storage: Cool, dry location

PS-Triphenylphosphine is a diphenylphosphinated polystyrene resin that is a resin-bound equivalent of triphenylphosphine. The capacity of the resin is determined by the quantitation of benzyl bromide uptake in DMF (GC, internal standard method). The resin can readily convert alcohols or carboxylic acids to the corresponding chlorides or acid chlorides in carbon tetrachloride (Scheme 1).[1-3] Reaction conditions are relatively mild and the products are formed in high yield and purity (Table 1, pg 104).



Scheme 1. Chlorination using PS-Triphenylphosphine



Scheme 2. Mitsunobu reaction using PS-Triphenylphosphine

PS-Triphenylphosphine can also be used in Mitsunobu reactions to prepare aryl ethers in good-to-excellent yields and in high purities (Scheme 2).[4] The procedures described provide pure products without the need for laborious silica gel chromatography. Removal of excess phenol is accomplished with MP-Carbonate, while removal of excess DBAD (di-tert-butyl azodicarboxylate)-based hydrazide by-products may be accomplished by addition of TFA, followed by separation with silica SPE cartridge[5] or by liquid-liquid extraction (LLE). Reactions may be carried out at room temperature. Comparative studies suggest that there is no significant advantage to degassing the reaction mixture with nitrogen contrary to previous recommendations.[6] However, the order of addition of the substrates is critical in minimization of side products.

PS-Triphenylphosphine resin can also be used to synthesize olefins via the Wittig reaction (Scheme 3)[7,8] or as a scavenger for alkyl halides (Scheme 4, page 106).

PS-Triphenylphosphine

Representative Procedures

Chlorination (Table 1, Entry 4)

To a suspension of PS-Triphenylphosphine resin in CCl_4 (1 g, 2.12 mmol in 8 mL) was added a solution of piperonyl alcohol in CCl_4 (152 mg, 1 mmol in 2 mL). The reaction was heated at reflux for 3 h after which the mixture was filtered and the filtrate concentrated to give pure piperonyl chloride in 100% theoretical yield and purity.

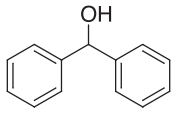
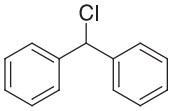
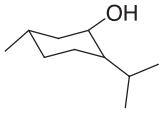
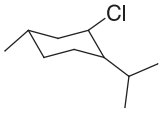
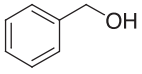
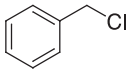
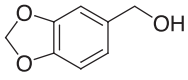
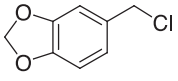
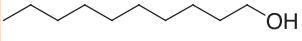
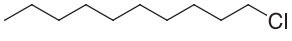
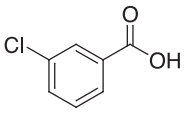
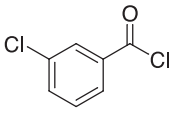
Entry	Alcohol	Product	% Isolated Yield	% Purity[a]
1			98	95
2			74[b]	64[c]
3			100	100
4			100	100
5			100	100
6			73	95

Table 1. Chlorination of acids and alcohols using PS-Triphenylphosphine
[a]GC analysis: HP-5 phenylmethylsilicone column 100–250 ºC, 15 ºC/min, 10 min hold
[b]Not isolated

[c]Rate of reaction slower for hindered aliphatic secondary alcohols, 28% conversion after 3 h, 64% conversion after 16 h reflux. Determined by ^{1}H NMR.

PS-Triphenylphosphine

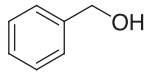
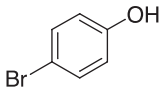
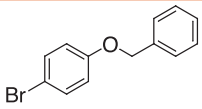
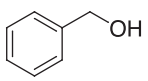
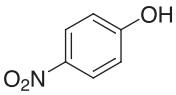
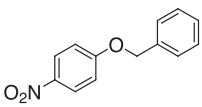
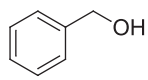
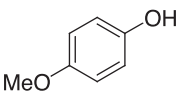
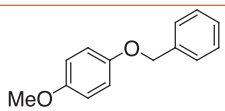
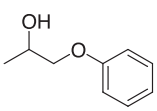
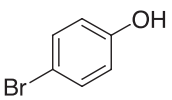
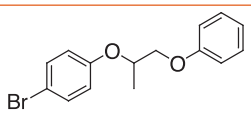
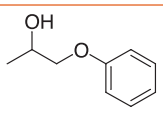
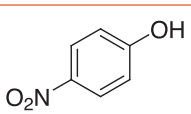
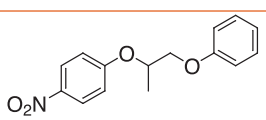
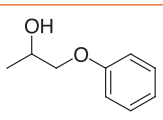
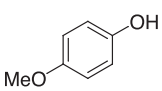
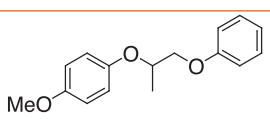
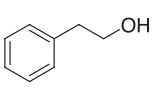
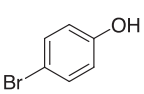
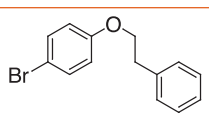
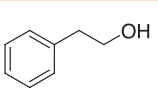
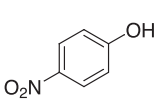
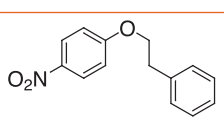
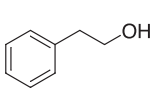
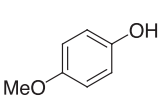
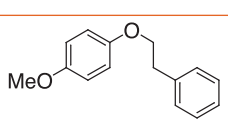
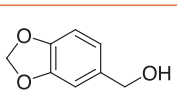
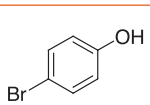
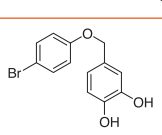
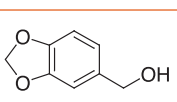
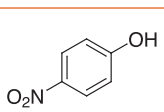
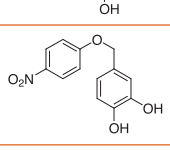
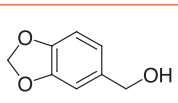
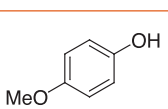
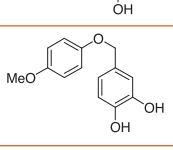
Entry	Alcohol	Phenol	Aryl ether	% Yield	% Purity
1				80	100
2				73	98
3				81	100
4				87	97
5				92	100
6				84	100
7				81	100
8				76	100
9				91	96
10				86	100[a]
11				94	100[a]
12				92	100[a]

Table 2. Mitsunobu reaction using PS-Triphenylphosphine resin
[a]Conversion 100%. The product was comprised of a mixture of hydrolyzed and un-hydrolyzed acetal protecting group. The product may be purified by LLE using aqueous base and MTBE.

PS-TRIPHENYLPHOSPHINE

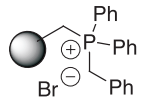
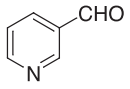
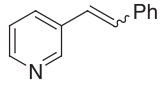
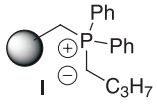
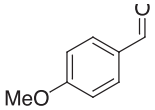
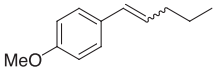
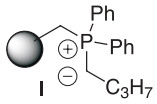
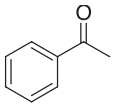
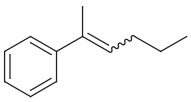
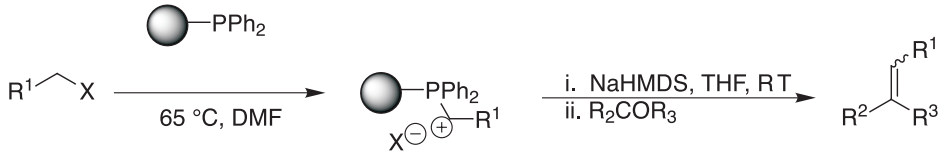
Entry	Phosphonium Resin	Carbonyl Compound	Olefin	% Isolated Yield (cis:trans)[a]	% GC Purity[b]
1				81 (5:1)	95
2				94 (2:3)	91
3				88 (2:1)	94

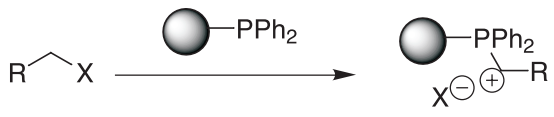
Table 3. Wittig reaction using PS-Triphenylphosphine
[a]Ratio determined by ^{1}H NMR analysis
[b]GC analysis: HP-5 phenylmethylsilicone column 100-250 ºC, 15 ºC/min, 10 min hold



Scheme 3. Wittig reaction using PS-Triphenylphosphine

Entry	Material Scavenged	Solvent	Temp °C	% Scavenged[a]	Time (h)
1	Ethyl bromoacetate	DMF	20	100	6 h
2	Benzyl bromide	DMF	20	100	16 h
3	Cinnamyl chloride	THF:DMF	50	100	10 h
4	Cinnamyl bromide	DMF	20	100	16 h

Table 4. Scavenging of alkyl halides with PS-Triphenylphosphine resin (3.0 equiv)
[a]GC analysis: HP-5 phenylmethylsilicone column 100–250 ºC, 15 ºC/min, 10 min hold



Scheme 4. Scavenging of alkyl halides using PS-Triphenylphosphine

PS-Triphenylphosphine

Mitsunobu Reaction (Table 2, Entry 3)

To a reaction vessel containing PS-Triphenylphosphine resin (311 mg, 0.66 mmol) was added a solution of p-methoxyphenol (0.45 mmol in 1 mL anhydrous THF). The suspension was allowed to stand for 5 minutes and then a solution of DBAD (di-tert-butyl azodicarboxylate) (1 mL, 0.48 mmol in anhydrous THF) was added. A further 0.5 mL of THF was added and the solution agitated at room temperature for 30 min. A solution of benzyl alcohol (1 mL, 0.3 mmol in anhydrous THF) was added and the reaction stirred overnight. In order to scavenge any excess phenols, MP-Carbonate resin (274 mg, 0.75 mmol) was then added and the mixture was stirred for a further 2 h. The resin was filtered and washed with THF (2 x 2 mL). To the filtrate was added 5 mL of a TFA/DCM/water (50:48:2) solution, and the mixture was stirred at RT for 2 h. The product was then extracted with MTBE, washed with water, and the MTBE layer concentrated to afford the product in 81% yield and 100% purity.

Wittig Reaction (Table 3, Entry 2)

1-Iodobutane (0.53 mL, 8.52 mmol) was added to a suspension of PS-Triphenylphosphine (3.0 g, 4.26 mmol) in 30 mL DMF and the reaction was stirred for 48 h at 65 ºC. The resulting phosphonium resin was washed with DMF (4 x 40 mL), toluene (4 x 40 mL), DCM (4 x 40 mL), and diethyl ether (4 x 40 mL) and dried in vacuo for 12 h. The dried phosphonium resin (0.2 g, 0.2 mmol) was added to a reaction vessel, followed by the addition of THF (2 mL). To the suspension of phosphonium resin was added a solution of sodium bis(dimethylsilyl)amide (2.0 M NaHMDS in THF, 0.4 mL, 0.8 mmol) at room temperature and the reaction stirred for 1 h. The ylide resin was washed with THF (5 x 4 mL) to remove excess base. To the suspension of ylide resin in anhydrous THF (2 mL) was added a solution of p-methoxybenzaldehyde (0.2 mL, 0.1 mmol) in THF (2 mL) and the mixture was stirred for 16 h. The reaction mixture was diluted with 2 mL hexane and directly applied to a silica SPE cartridge[9] followed by washing with hexane/ether (2:1, 2 x 4 mL). The solvent was concentrated to provide the olefin in 94% yield (GC purity 91%).

Scavenging of Alkyl Halide (Table 4, Entry 2)

PS-Triphenylphosphine (3.0 equivalents) was added to a solution of benzyl bromide (1.0 equivalent) in DMF (10 mL/g resin added) and the reaction stirred at room temperature for 5–16 h. Results by GC analysis indicate >80% scavenging after 6 h and 100% scavenging after 16 h.

Ordering Information

Part Number	Quantity
800510	3 g
800378	10 g
800379	25 g
800380	100 g
800381	1000 g

References

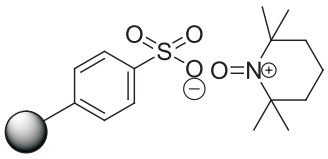
1. Relles, H. M.; Schluenz, R. W. *J. Am. Chem. Soc.* **1974**, 96, 6469.
2. Regen, S. L.; Lee, D. P. *J. Org. Chem.* **1975**, 40, 1669.
3. Landi, J. J. Jr.; Brinkman, *H. R. Synthesis* **1992**, 1093.
4. Tunoori, A. R.; Dutta, D.; Georg, G. I. *Tetrahedron Lett.* **1998**, 39, 8951.
5. Part Number 440-0200-C.
6. Vasudevan, A.; Park, D. C.; Wodka, D.; Gentles, R. G. *J. Comb. Chem.* **2002**, 4, 442.
7. Bernard, M.; Ford, W. T. *J. Org. Chem.* **1983**, 48, 326.
8. Bolli, M. H.; Ley, S. V. *J. Chem. Soc., Perkin Trans.* 1. **1998,** 15, 2243.
9. Part Number 440-0100-C.

Compatible Solvents: DMF (3.5 mL/g), THF (4.1 mL/g), DCM (5 mL/g), benzene (3.1 mL/g)

MP-TsO-TEMPO

MP-TsO-TEMPO

Polymer-bound Oxidizing Agent

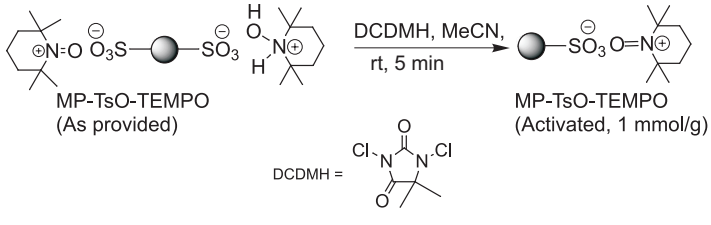


Chemical Name: Macroporous polystyrene-2,2,6,
6-tetramethylpiperidin-1-oxoammonium-p-toluenesulfonate
Resin Type: Macroporous poly(styrene-co-divinylbenzene)
Loading: Typical loading 1.0 mmol/g, minimum loading 0.8 mmol/g
(oxidation of bromobenzyl alcohol)
Bead Size: 400–500 µm
Application: Oxidation of activated primary and secondary
alcohols to their respective aldehydes and ketones under mild reaction conditions
Typical Reaction Conditions: 2.0 equivalents of resin relative to the
substrate in DCM or ACN, room temperature, 16 h
Compatible Solvents: ACN (3.0 mL/g), DCM (3.0 mL/g)
Storage: Store at 4 °C

MP-TsO-TEMPO is a macroporous polystyrene-bound equivalent of oxoammonium p-toluenesulfonate. The resin has primary applications in the oxidation of activated primary and secondary alcohols to their corresponding aldehydes and ketones under mild reaction conditions. MP-TsO-TEMPO has been found to be highly selective for oxidation of allylic, benzylic, and alicyclic hydroxy compounds. Oxidations with MP-TsO-TEMPO are very clean and the product is isolated by filtration of the solution followed by solvent removal.

The small molecule 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)[1-4] is widely used in oxidation of primary and secondary alcohols to their corresponding carbonyl compounds. The reaction typically uses stoichiometric amounts of a strong acid such as sulfonic acid, perchloric acid, or hydrochloric acid to generate the corresponding oxoammonium salt from TEMPO. These oxoammonium salts are the active species in this type of oxidation reaction. The method is generally selective in controlling the oxidation of primary alcohols to the corresponding aldehydes without any over-oxidation to carboxylic acids. Another major advantage of this class of reagent is that, unlike many other oxidants, it does not involve any toxic heavy metals such as chromium, osmium, or lead. The isolation of the product, however, routinely requires an aqueous workup and chromatographic separation of the spent reagent.

MP-TsO-TEMPO resin is provided as the mixture of active oxoammonium and the reduced hydroxylamine species in equal proportions (Scheme 1). The resin is activated to its full capacity with dichlorodimethylhydantoin (DCDMH) prior to use. Activation is very rapid, requiring treatment of the resin with a solution of DCDMH in acetonitrile (ACN) for 5 min. The resulting MP-TsO-TEMPO has a loading of approximately 1.0 mmol/g and is utilized for subsequent oxidation.



Scheme 1. Activation of MP-TsO-TEMPO

MP-TsO-TEMPO

The reactivity of the resin toward a substrate may be determined by performing a test reaction in an NMR tube with $CDCl_3$ as the solvent using ^1H NMR spectral analysis.[5] Typical reaction conditions require 2.0 equivalents of resin relative to the substrate. Oxidation reactions may be performed in ACN or dichloromethane (DCM) at ambient temperature for 16 h. The use of ACN is generally preferred, as its lower vapor pressure offers additional convenience in handling for both manual and automated synthesis. DCM should be used in preference to ACN for reactions generating volatile products.

After the reaction is complete, the product is isolated by simple filtration of the resin followed by evaporation of the solvent. As compared with the small molecule TEMPO, the use of the polymer-supported MP-TsO-TEMPO avoids aqueous workup, allows for product isolation by simple filtration of the solution, and may permit a subsequent reaction in the same reaction vessel.

The ease of product isolation when using MP-TsO-TEMPO facilitates generation of aldehydes for immediate use. Many reactive aldehydes used as building blocks in organic synthesis are unstable to storage. MP-TsO-TEMPO allows the preparation of such activated aldehydes from more stable alcohol precursors for subsequent use in a multi-step synthesis. Isolation of the product requires only simple filtration of the solution without any aqueous workup or chromatographic purification.

Results

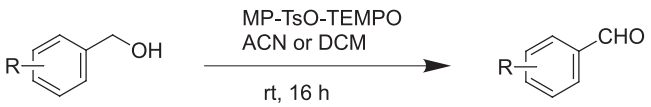
The scope and reactivity of MP-TsO-TEMPO were evaluated on a varied set of benzylic, allylic, acetylenic, and alicyclic alcohols. The product aldehydes and ketones were isolated by filtration of the solution and evaporation of the solvent. For alicyclic and unsaturated alcohols with low molecular weights, the reactions were performed in DCM to avoid any loss of product during evaporation of the solvent. The results are summarized in Tables 1–3. In most cases the products were isolated in excellent purity and high yield. The reactions were highly controlled in that no over-oxidation to carboxylic acid was observed. Aliphatic primary and acyclic secondary alcohols were unreactive towards MP-TsO-TEMPO. This is in contrast to a number of conditions using small molecule TEMPO, indicative of attenuated reactivity for the polymer-supported reagent.

As shown in Table 1, a range of differently substituted benzylic alcohols was successfully oxidized to the corresponding aldehydes and ketones. Electronic factors appeared to have little effect as exemplified by high conversion of benzylic alcohols containing both electron donating and withdrawing groups (Table 1, Entries 1–7). Most of the reactions afforded the oxidized products in high yield and purity when performed in ACN, although DCM appeared to be a better solvent with some of the substrates. For example, the oxidation of 3-nitrobenzyl alcohol (Table 1, Entry 3) proceeded to completion only when the reaction was performed in DCM. The oxidation of 1-phenyl-1-propanol (Table 1, Entry 5) and indan-1-ol (Table 1, Entry 6) also afforded higher conversions when performed in DCM. With ACN as the solvent, 80–90% conversions were observed with these substrates. The diol, hydrobenzoin (Table 1, Entry 9) was converted to a 1:1 mixture of benzil and benzoin using 4 equivalents of MP-TsO-TEMPO.

Table 2 summarizes the results for the oxidation of α,β-unsaturated alcohols. The reactions were performed in DCM as most of the substrates generate volatile products. The substrates included both allylic (Table 2, Entries 1–4) and acetylenic alcohols (Table 2, Entry 5). In all the cases studied, the starting alcohols were completely converted to their carbonyl compounds. The oxidation of geraniol (Table 2, Entry 1) and trans, trans-farnesol (Table 2, Entry 2) to their respective aldehydes proceeded with some isomerization around the 2,3-double bond. There is ample literature precedence[6] for such isomerization during the oxidation of these systems. Hydroquinone was successfully oxidized to 1,4-benzoquinone in high yield and purity using 4 equivalents of the resin (Table 2, Entry 6).

MP-TsO-TEMPO

Alicyclic alcohols are another class of hydroxy compounds that undergo smooth oxidation with MP-TsO-TEMPO. The results with a set of carbocyclic alcohols containing a secondary hydroxy group are summarized in Table 3. The oxidation of sterically hindered systems adamantanol and isoborneol to their respective ketones (entries 4 and 5) is particularly noteworthy. 2-Phenylcyclohexanol (Table 3, Entry 3) did not react under these conditions.



Scheme 2. Oxidation of activated alcohols

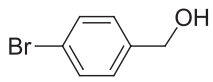
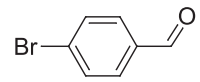
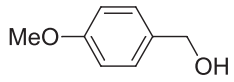
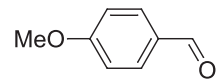
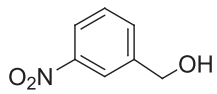
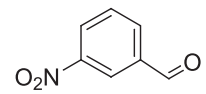
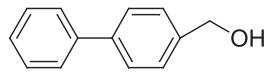
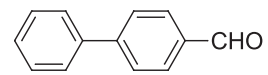
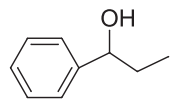
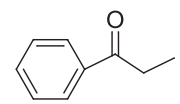
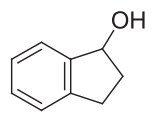
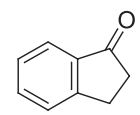
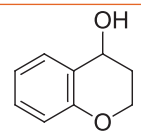
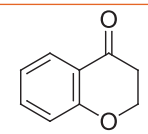
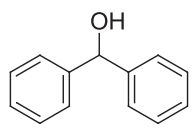
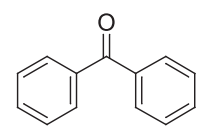
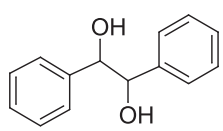
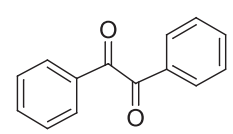
Entry	Benzylic Alcohol	Product	% Yield	% Purity
1			95	99
2			95	99
3			99	95[a]
4			95	98
5			98	99[a]
6			69	89[a]
7			70	97
8			97	95
9			99	50[b]

Table 1. Oxidation of benzylic alcohols in ACN
[a]Reactions were performed in DCM.
[b]The product mixture contained 50% of the monoketone along with the desired diketone.

MP-TsO-TEMPO

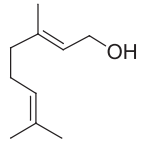
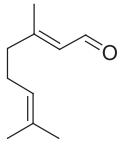
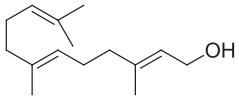
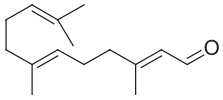
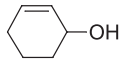
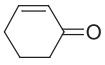
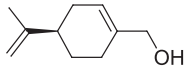
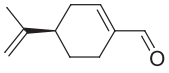
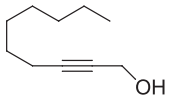
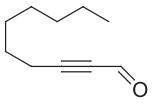
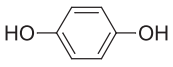
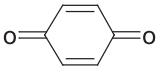
Entry	Starting Alcohol	Product	% Yield	% Purity
1			99	Isomeric Mixture
2			70	Isomeric Mixture
3			70	98
4			77	91
5			90	99
6			96	99

Table 2. Oxidation of α,β unsaturated alcohols in DCM

MP-TsO-TEMPO

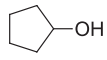
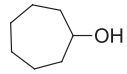
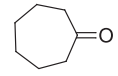
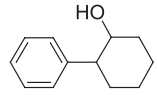
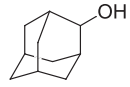
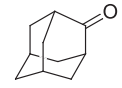
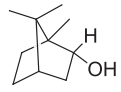
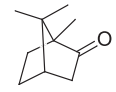
Entry	Starting Alcohol	Product	% Yield	% Purity
1			50	99
2			74	99
3		No Reaction	—	—
4			95	99
5			100	99

Table 3. Oxidation of cyclic alcohols in DCM

Activation and Recycling

MP-TsO-TEMPO is supplied as a mixture of active oxoammonium and hydroxylamine salt and requires activation to its full capacity (ca. 1 mmol/g) before use. Activation is a simple process of treating the resin with DCDMH (10% wt with respect to the resin) in ACN for 5 min. The resin is then washed with ACN and used for the oxidation reaction. The spent resin may be recycled up to three times by treating with DCDMH (20% wt with respect to the resin).

Loading and Stability

The pre-activated form of the resin is stable for at least several months at 4 °C in a closed container. The fully activated resin should be used within seven days and stored at 4 °C.

Experimental

Resin Handling

The resin is stored in a refrigerator at 4 °C and may be weighed out on the bench using regular weighing methods. Given its uniform density, the resin may also be dispensed by automated filling devices or manual dispensing systems such as the ArgoScoop resin dispenser (Part Number 300427). Static electric charge may make handling difficult in dry conditions. Avoiding plastic weighing tools minimizes this effect.

MP-TsO-TEMPO

Equipment List

The resin can be used in regular glass round-bottom flasks with magnetic stirrer, and also in polypropylene cartridges[7] and 96-well plates (Part Number 121-5203). Agitation by rotary wheel devices (VWR Part Number 62404-006) or orbital shakers is feasible during the course of these reactions. Filtration of the reaction solutions may be carried out in cartridges, and the filtrates collected into round-bottom flasks or scintillation vials ready for concentration.

Procedure for Small-Scale Activation

To a 6 mL ISOLUTE cartridge (Part Number 120-1113-C) fitted with a stopcock (Part Number 121-0009) was added MP-TsO-TEMPO (1.0 g), dichlorodimethylhydantoin (DCDMH, 0.1 g) and ACN (3 mL). The mixture was manually shaken a few times at room temperature for 5 min and the orange solution discarded. The light orange resin was washed with ACN (5 x 3 mL, or until the wash was colorless). The wet resin can be used directly for oxidation of alcohols.

Procedure for Bulk Activation for Parallel Synthesis

The procedure for small scale activation can be scaled up to prepare a larger batch of activated resin using a beaker as a reactor and a fritted glass funnel for suction filtration and washing. The mixture was agitated with a spatula occasionally. After washing with ACN, the resin was suction dried until the beads separated and was then dried under low vacuum (<20 Torr) overnight at room temperature. The dried, activated resin can be divided out for parallel reactions.

Representative Procedures

Oxidation of Benzylic Alcohol (Table 1, Entry 2)

A mixture of freshly activated MP-TsO-TEMPO (1.0 g, ca. 1.0 mmol) and 4-methoxybenzyl alcohol in ACN (3 mL, 0.5 mmol) was agitated for 16 h at room temperature. The resin was filtered and washed with ACN (3 x 1 mL). The combined solution was concentrated to afford 4-methoxybenzaldehyde in 95% yield and 99% purity.

Oxidation of α,β-Unsaturated and Alicyclic Alcohol (Table 3, Entry 4)

A mixture of freshly activated MP-TsO-TEMPO (1.0 g, ca. 1.0 mmol) and 2-adamantanol in DCM (3 mL, 0.5 mmol) was agitated for 16 h at room temperature. The resin was filtered and washed with DCM (3 x 1 mL). The combined solution was concentrated to afford 2-adamantanone in 95% yield and 99% purity.

Ordering Information

Part Number	Quantity
800518	3 g
800482	10 g
800483	25 g
800484	100 g
800485	1000 g

References

1. Bobbitt, J. M. *J. Org; Chem.* **1998**, 63, 9367 and references therein.
2. Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J-L. *J. Org. Chem.* **1996**, 61, 7452.
3. Nooy, A. E. J.; Besemer, A. C.; Bekkum, H. V. *Synthesis,* **1996**, 1153.
4. Bobbitt, J. M.; Flores, M. C. L. *Heterocycles*, **1988**, 27, 509.
5. Test reaction in NMR tube: To a clean NMR tube is added MP-TsO-TEMPO (ca. 0.1 g) and a $CDCl_3$ solution of the substrate (ca. 0.05 mmol, 1 mL). The septum-capped NMR tube is rotated on a rotary shaker at low speed and ambient temperature for 16 h. The reaction mixture is then analyzed by its ^1H NMR spectrum. Alternatively, the progress of the reaction may be monitored by taking ^1H NMR spectra at different time intervals. The resin does not interfere with running of NMR as it floats on the top of the $CDCl_3$ solution.
6. Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, 56, 6110 and references therein.
7. Parts needed for cartridge applications include: ISOLUTE empty reservoirs (Part Number 120-1113-C), universal stopcocks (Part Number 121-0009), and column caps (Part Number 1201-0123-C).

Toolbox and Kits

Solution-Phase Toolbox and Kits for Organic Synthesis

Solution-Phase Toolbox II

- 10 gram quantities of each: PS-Carbodiimide, MP-Carbonate, PS-DIEA, PS-HOBt(HL), PS-Isocyanate, PS-TBD, PS-Triphenylphosphine, PS-Trisamine, PS-$TsNHNH_2$, MP-TsOH
- Product information and procedure cards
- ArgoScoop calibrated scoop for convenient resin measuring

Reductive Amination Toolkit

- 10 gram quantities of: MP-Triacetoxyborohydride, MP Cyanoborohydride, PS-Isocyanate, PS-Benzaldehyde, MP-TsOH(65)
- Product information and procedure cards

Amidation kit

- 10 gram quantities of: PS-Carbodiimide, PS-HOBt(HL), RGT-ACTU, PS-Isocyanate, MP-Carbonate

Scavenger Kit

- 10 gram quantities of PS-Trisamine, PS-Thiophenol, PS-Isocyanate, PS-$TsNHNH_2$, MP-Carbonate, PS-TsCl(HL), PS-Benzaldehyde

Polymer Tosyl Kit

- 10 gram quantities of PS-Isocyanate, MP-Carbonate, PS-TsCl

Base Kit

- 10 gram quantities of MP-Carbonate, PS-DMAP, PS-DIEA, PS-NMM

Card Set, Solution-Phase Toolbox II

- Product information and procedure cards

Card Set, Reductive Amination Toolkit

Card Set, Amidation Toolkit

Ordering Information

Item	Quantity	Part Number
Solution-Phase Toolbox II	1	800429
Reductive Amination Toolkit	1	800487
Amidation Kit	1	800489
Scavenger Kit	1	800368
Polymer Tosyl Kit	1	800293
Base Kit	1	800294
Card Set, Solution-Phase Toolbox II	1	800460
Card Set, Reductive Amination Toolkit	1	800486
Card Set, Amidation Toolkit	1	800488

ArgoScoop® Resin Dispenser

ArgoScoop® resin dispenser

ArgoScoop® resin dispenser is a variable volume resin scoop designed for convenient dispensing of polymer scavengers and reagents. The table below is a guide for estimating fill weights (in milligrams rounded to the nearest 10 mg) for each resin when using a specific setting. Repetitive fill weights are typically within 10% of one another and show greater precision at larger settings. It is recommended that at least one test weight should be measured for the desired setting.

Part Number: 300427

Chart for Estimating Fill Weights

ArgoScoop Settings	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6
Scavengers (Weight in mg)											
PS-Benzaldehyde	80	150	220	290	360	430	500	570	640	710	780
MP-Carbonate	40	90	150	200	250	310	360	420	470	520	580
PS-DEAM	70	110	160	200	250	290	340	380	430	470	520
PS-Isocyanate	40	80	120	160	200	250	290	330	370	410	450
MP-Isocyanate	50	90	130	170	210	240	280	320	360	400	440
PS-NH_2	50	100	150	200	250	300	350	400	450	500	550
PS-Thiophenol	60	90	130	170	200	240	280	320	350	390	430
MP-TMT	40	70	100	130	160	200	230	260	290	320	360
PS-Triphenylphosphine	90	150	210	270	330	390	450	510	570	630	700
PS-Trisamine	20	80	130	180	230	290	340	390	440	500	550
MP-Trisamine	30	60	90	120	150	180	220	250	280	310	340
PS-TsCl(HL)	90	150	220	290	350	420	480	550	620	680	750
PS-$TsNHNH_2$	40	110	170	230	300	360	430	490	550	620	680
Resin-Bound Reagents											
MP-Borohydride	60	120	180	240	290	350	410	470	520	580	640
PS-Carbodiimide	80	130	180	240	290	350	400	460	510	570	620
MP-Carbonate	40	90	150	200	250	310	360	420	470	520	580
MP-Cyanoborohydride	60	120	170	230	280	340	390	450	500	560	620
PS-DES	70	130	190	250	320	380	440	500	560	620	680
PS-DIEA	80	150	220	290	360	430	500	570	640	710	790
PS-DMAP	40	100	150	200	250	300	350	400	460	510	560
PS-HOBt(HL)	70	110	160	200	250	300	340	390	440	480	530
PS-NMM	50	90	120	160	190	230	260	300	330	370	400
PS-PPh_3-Pd	50	100	140	180	220	260	310	350	390	430	470
PS-TBD	60	110	160	200	250	300	350	390	440	490	530
MP-Triacetoxyborohydride	60	110	150	200	250	290	340	390	430	480	530
PS-Triphenylphosphine	90	150	210	270	330	390	450	510	570	630	700
PS-TsCl	50	110	170	240	300	360	430	490	550	620	680
MP-TsOH	70	130	180	240	300	350	410	460	520	580	630
MP-TsOH(65)	50	90	140	190	240	280	330	380	430	480	520
MP-TsO-TEMPO	60	120	170	220	280	330	380	440	490	540	600
ACTU	80	160	240	310	390	460	540	620	690	770	840
Si-Scavengers (wt mgs)*											
Si-Carbonate	84	142	208	272	345	403	461	529	602	648	701
Si-Thiol	92	166	243	306	386	440	514	601	663	724	812
Si-Triamine	90	152	217	278	356	416	473	556	621	690	746
Si-Tosylhydrazine	100	172	251	320	395	476	549	624	697	785	832
Si-TsOH (SCX-3)	95	167	241	323	391	465	544	602	684	751	848
Si-Propylsulfonic acid (SCX-2)	91	151	220	284	353	422	487	556	623	681	759

*standard deviation ~ 10-20 mgs

Biotage Microwave Vials

Migrate From mg to g Without Re-optimization

Biotage Microwave Vials

Four Different Microwave Vial Sizes Support Microwave Synthesis from Milligrams to Grams, Without the Need for Re-optimization

Using microwave energy is quickly becoming the most popular way to perform synthetic organic reactions. Reagents are added to a vessel, which is sealed and irradiated with a focused beam of microwaves. During microwave synthesis, the temperature and pressure build-up inside the reaction vessel can reach significant levels. To make this procedure efficient and safe, Biotage has reaction vials made specifically for microwave applications.

Constructed from Type I, Class A borosilicate glass, these premium vials have very low metals content, extremely important to glass quality and compatibility with microwave chemistry. Unlike standard vials, Biotage microwave vials are optimized for use in microwave synthesizers.

Biotage microwave vials are manufactured in four sizes to accommodate reaction volumes from as low as 200 µL to as much as 20 mL and reaction scales from milligrams to grams, without method re-optimization. These vials are engineered to withstand operating pressures up to 300 psi (20 bars) and are packaged with caps and stir bars for each vial.

Choose the Vial Size that Works Best for Your Reaction:
Biotage recommends that reaction volumes do not fall below or exceed specified vial volumes. If the volume is too low, the temperature reading may be inaccurate, and if the volume is exceeded, insufficient space is left for pressure buildup.

0.2-0.5 mL*

0.5-2 mL

2-5 mL

10-20 mL*

*Only with EXP system

Biotage Microwave Vials

Features and Benefits

- All Biotage microwave vials withstand pressures up to 300 psi (20 bars).
- The Reseal™ septum design reseals after it has been penetrated, allowing repeated additions of reagents or in situ sampling.
- Manufactured from contaminant-free microwave-safe Type I, Class A glass for robustness and inertness.
- Magnetic stirring bars (included) promote even temperature distribution throughout the entire reaction mixture, including heterogeneous mixtures.
- Available in four sizes: 0.2-0.5 mL, 0.5-2.0 mL, 2.0-5.0 mL and 10-20 mL to accommodate reaction scales of milligrams to grams, without method re-optimization.

Ordering Information

Item	Description	Part Number
Microwave Vials*	0.2-0.5 mL, Qty 100	355458
Microwave Vials*	0.2-0.5 mL, Qty 300	355627
Microwave Vials*	0.2-0.5 mL, Qty 500	355628
Microwave Vials*	0.5-2 mL, Qty 100	352016
Microwave Vials*	0.5-2 mL, Qty 300	354625
Microwave Vials*	0.5-2 mL, Qty 500	355629
Microwave Vials*	2-5 mL, Qty 100	351521
Microwave Vials*	2-5 mL, Qty 300	354624
Microwave Vials*	2-5 mL, Qty 500	355630
Microwave Vials*	10-20 mL, Qty 50	354833
Microwave Vials*	10-20 mL, Qty 100	355631
Microwave Vials*	10-20 mL, Qty 250	355632
*Microwave vial caps and stir bars included with vial order		
Accessories		
Vial Caps	Include Reseal septa, Qty 100	352298
Crimper	Manual cap crimper	353671
Decapper	Manual cap remover	353913
Vial Adapter	0.2-0.5 mL, Qty 10	355459
Vial Adapter	10-20 mL, Qty 12	355367
O-rings	10-20 mL adapter, Qty 10	354838
Cavity Air Guide	Initiator, Qty 1	354974
Vial Rack	Initiator 8, holds (4) 0.2-5 mL vials	355391
Vial Rack	Initiator 8, holds (2) 10-20 mL vials	355390
Vial Rack	Initiator 60, holds (30) 0.2-5 mL vials	353478
Vial Rack	Initiator 60, holds (12) 10-20 mL vials	354836
Stir Bars	0.2-0.5 mL, Qty 30	355545
Stir Bars	0.5-2 mL, Qty 30	355544
Stir Bars	2-5 mL, Qty 30	355543
Stir Bars	10-20 mL, Qty 5	353930


Initiator
Biotage

Initiator™ Microwave Synthesis Systems

Fast, Safe, and Scalable Microwave Synthesis

INITIATOR™

Initiator™

The Initiator microwave synthesizer enables medicinal chemists to quickly synthesize compounds using microwave heating. In addition to speed, microwave synthesis offers other advantages such as simplicity and broader exploration. Through superior heating features, the Initiator is able to quickly achieve temperatures and pressures beyond the traditional reflux heating. This allows chemists to perform complex reactions formerly not possible and is, therefore, the fastest growing technology in the pharmaceutical research laboratory.

Initiator Eight

The 8-position sample bed provides automation to medicinal chemists for rapid optimization of reaction conditions and analog synthesis. The ability to use both large and small vials, in combination at any time and in any order without manual intervention, provides the medicinal chemist flexibility and the ability to rapidly scale-up compounds of interest.

Initiator Sixty

The 60-position sample bed supports the production of focused libraries, multi user environments and scale-up by scale-out. Flexible operation enables the use of both large and small vials in combination at any time and in any order without manual intervention.

Features and Benefits

Compact footprint
The Initiator is 45% smaller than its predecessor, fitting easily into any standard fume-hood space.

Touch Logic control
Load and run your samples using a touch-screen monitor for simple and intuitive navigation without the need for an external computer, keyboard, or mouse.

0.2 to 20 mL without system modifications
With the EXP function, use four different vial sizes in any order or combination at any time without system modifications for greater flexibility and direct scale-up of milligrams to grams.

Modular design
Easily upgrade from a single-sample manual format to an automated 8- or 60-position system.

Enhanced heating performance
The new single-mode applicator with the proven Dynamic Field Tuning™ feature offers faster heating of a broader range of solvents.

Best-in-class safety
All Biotage microwave synthesizers are designed for safe operation at elevated temperatures and pressures. The Initiator triple-tier safety-lock feature ensures maximum operator safety at all times.

Improved heating performance
Better regulation and more powerful heating. Lower limit is now set to 40 ºC, while the instrument can apply an unmatched 400 watts of power during processing.

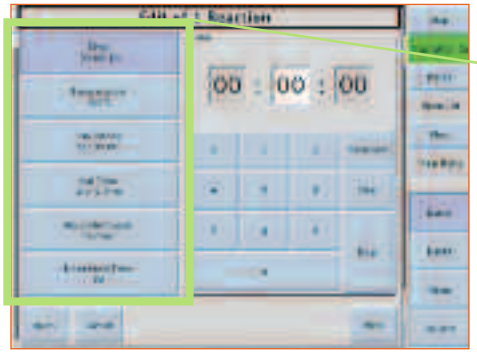
USB port at the front of the instrument
Allows for easy downloading of logfiles to USB stick.

1-Point Support™
Biotage's world-class field service organization serves customers on site to provide the highest quality personalized support.

Intuitive Touch Logic Control™—as simple as 1-2-3

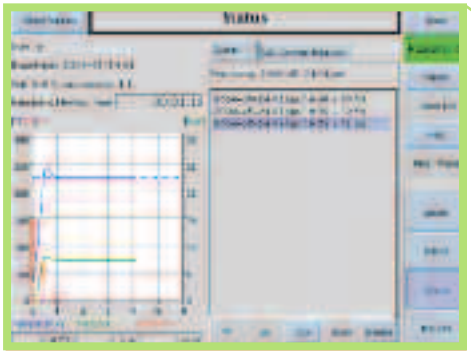
Step 1

Experiment Editor
Select Rack type. Select the number of reactions and vial position(s) to load.
Enter conditions for each vial.
View experiment, select user and run.



Step 2

Edit Your Method
Specify reaction time, temperature, vial size, and select absorption properties of your sample. Select to use fixed hold time if needed.



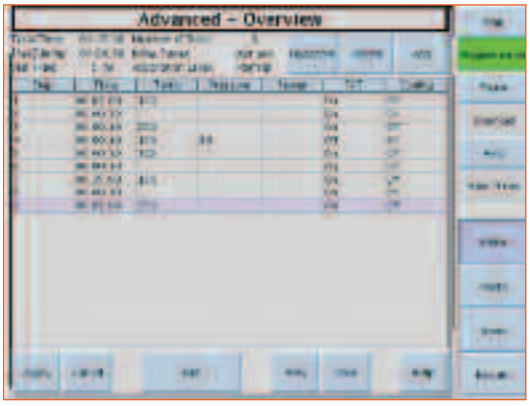
Step 3

Status
Check run status, remaining processing time, and queue status. View temperature, pressure, and power profile for the reaction being processed. Edit the run on-the-fly, change parameters as needed.

Initiator

Advanced Edit

Control pressure and power. Set individual pressure and power thresholds for each reaction. Build step or pulse sequences of up to 99 steps using all available control parameters; time, temperature, pressure, power, fixed hold time, and cooling.

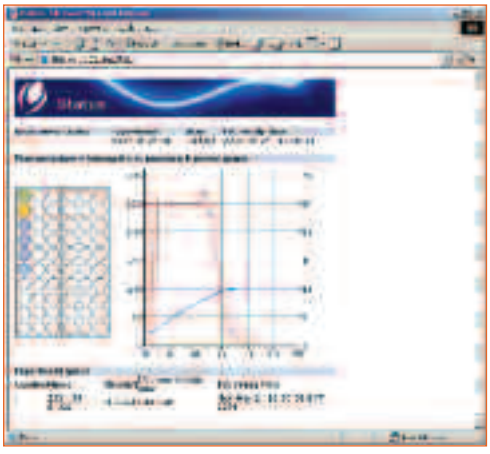


Racks with Track Overlay—Vial Type

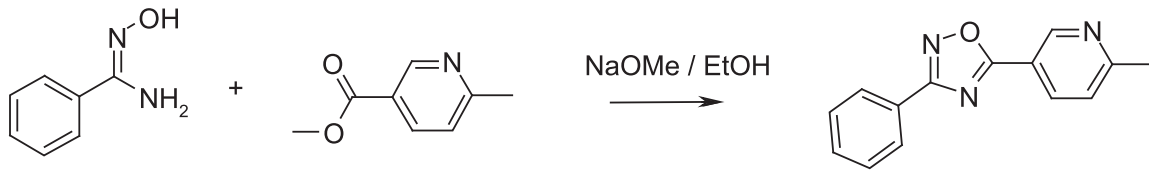
Check the specific parameters used and find the result for any given reaction on the tray. Display the parameter of choice for all reactions and remove performed experiments.

Remote Viewer

View the status of the instrument and the progress of your reaction from a remote location (your office). View, save, and print results.



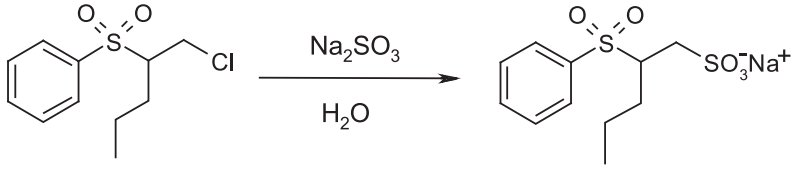
Faster Reactions and Higher Yields for Synthesis of 1,2,4 Oxadiazoles



	Temp	Time	Yield
Conventional	78 ºC	18 to 24 hours	7% to 63%
Microwave	160 ºC	5 minutes	80%

An early example from our in-house work illustrates how reaction times can be shortened while improving yields: Conventionally, the condensation of aldoximes with esters required 18 to 24 hours at reflux to provide the 1,2,4-oxadiazoles in yields of 7-63% (depending on what substrates were used). Using microwaves, it took 5 minutes at 160 °C to provide the product at 80% yield.

Broader Exploration Using Unconventional Solvents



	Temp	Time	Yield
Conventional	reflux	16 hours	<10%
Microwave	185 ºC	6 minutes	99%

Data courtesy of: Michael H. Howard, DuPont® Crop Protection Products

Using microwave synthesis, uncommon solvents such as water can be used. When water is heated to a very high temperature, the dielectric constant decreases as the temperature increases. Water has a dielectric constant, which decreases from 78 at 25 °C to 20 at 300 °C; this latter value is comparable to that of solvents such as acetone at ambient temperature. This molecular mutation promotes the solubility of organic substances in water not only because of the elevated temperatures but also due to the change in dielectric properties. Therefore, water acts as a pseudo-organic solvent in the microwave synthesis process.

This example was performed at DuPont Crop Protection. The product was used as a key intermediate in the synthesis of potential metallo-enzyme inhibitors. While reflux in water gave <10% yield, the microwave technique provided the desired product in 99% yield.

Specifications

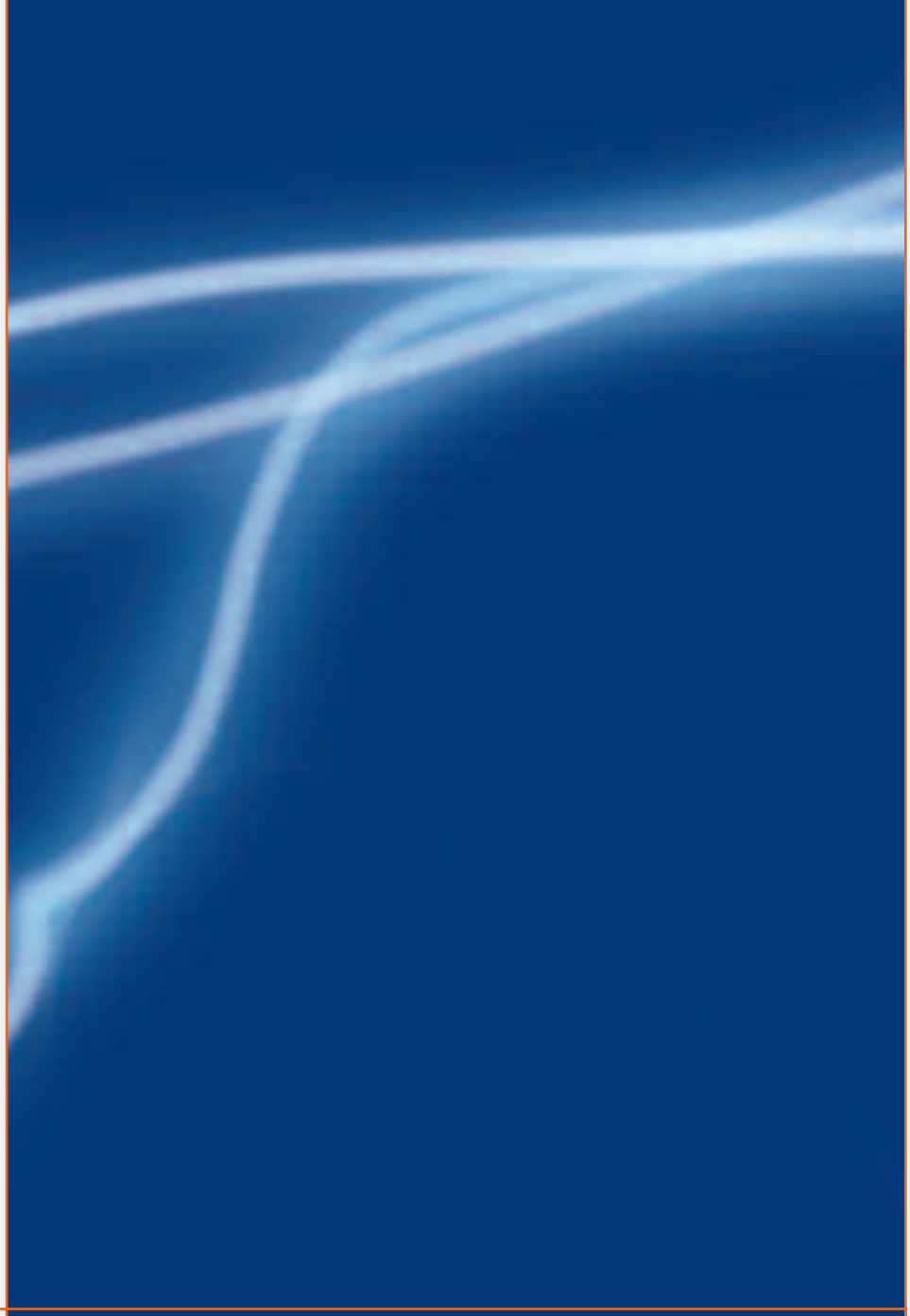
Heating Process	
Temperature	40-250 °C (104-482 °F)
Temperature increase	2-5 °C/sec (36-41 °F/sec)
Pressure range	0-20 bar (2 MPa, 290 PSI)
Power range	0-400 W at 2.45 GHz
Agitation	Magnetic stirrer, optional speed (300-900 RPM)
Sample Processor	
Reaction vials	4 vial sizes: 0.2-0.5 mL (EXP); 0.5-2 mL; 2-5 mL; 10-20 mL (EXP)
Reaction volumes	0.5-5 mL (0.2-20 mL with EXP function)
System Requirements	
Temperature	18-32 °C (65-90 °F)
Humidity	20-95% RH
Electrical supply	EU:220-240 V, 50 Hz (5 A); US: 120 V, 60 Hz (10 A); JP: 100V, 50/60 Hz (10 A)
Maximum power consumed	1100 VA
Cooling (post-processing)	Pressurized air supply >60 L/min (2.1 cubic feet/min), 2.5-4 bar (0.25-0.4 Mpa, 36-58 PSI)
Weight	22.2 kg (48.9 lb)
Dimensions	365 x 405 x 415 mm W x D x H (14.4 x 15.9 x 16.3”)
Interfaces	
Touch screen	6.4”
Ethernet LAN	complies with IEEE 802.3 (ANSI 8802.3) MII
Archiving, Backup and Printing	Via the LAN, Biotage HUB, USB memory stick, or direct connection with PostScript printer
Upgrade Path	The Initiator system can be upgraded to an 8 or 60-position system. Visit Biotage.com or contact your local Biotage sales office for more information
Certifications	CE, CSA certified
Initiator Eight	
Rack capacity	4 vials in rack for 0.2-5 mL vials; 2 vials in rack for 10-20 mL vials
Dimensions	400 x 500 x 580 mm W x D x H (15.7 x 19.7 x 22.8”)
Weight	29 kg (64 lb)
Initiator Sixty	
Rack capacity	30 vials in rack for 0.2-0.5, 0.5-2 and 2-5 mL vials 12 vials in rack for 10-20 mL vials
Dimensions	625 x 405 x 470 mm W x D x H (24.6 x 15.9 x 18.5”)
Weight	34.9 kg (77 lb)

Initiator Ordering Information

Item	Description (Country)	Part Number
Systems		
Initiator	EU	355230
Initiator	US	355286
Initiator	JPN	355287
Initiator EXP	EU	355301
Initiator EXP	US	355302
Initiator EXP	JPN	355303
Initiator Eight	EU	355522
Initiator Eight	US	355524
Initiator Eight	JPN	355526
Initiator Eight EXP	EU	355521
Initiator Eight EXP	US	355523
Initiator Eight EXP	JPN	355525
Initiator Sixty	EU	355435
Initiator Sixty	US	355437
Initiator Sixty	JPN	355439
Initiator Sixty EXP	EU	355434
Initiator Sixty EXP	US	355436
Initiator Sixty EXP	JPN	355438
Upgrade Modules		
Initiator Robot Eight		355380
Initiator Robot Sixty		355381
Initiator EXP Upgrade		355420
Biotage PathFinder	Web Subscription	355239
Accessories		
Initiator Waste Tray Inserts	Initiator, Qty 5	355366
Microwave Vials*	0.2-0.5 mL, Qty 100	355458
Microwave Vials*	0.2-0.5 mL, Qty 300	355627
Microwave Vials*	0.2-0.5 mL, Qty 500	355628
Microwave Vials*	0.5-2 mL, Qty 100	352016
Microwave Vials*	0.5-2 mL, Qty 300	354625
Microwave Vials*	0.5-2 mL, Qty 500	355629
Microwave Vials*	2-5 mL, Qty 100	351521
Microwave Vials*	2-5 mL, Qty 300	354624
Microwave Vials*	2-5 mL, Qty 500	355630
Microwave Vials*	10-20 mL, Qty 50	354833
Microwave Vials*	10-20 mL, Qty 100	355631
Microwave Vials*	10-20 mL, Qty 250	355632
Microwave Vial Caps	For 0.2-20 mL vials, Qty 100	352298
Crimper	Manual cap crimper	353671
Decapper	Manual cap remover	353913
Vial Adapters	0.2-0.5 mL, Qty 10	355459
Vial Adapters	10-20 mL, Qty 12	355367
O-rings for Vial Adapters	10-20 mL, Qty 10	354838
Initiator Cavity Air Guide	Initiator, Qty 1	354974
Vial Rack	Initiator 8, holds (4) 0.2-5 mL vials	355391
Vial Rack	Initiator 8, holds (2) 10-20 mL vials	355390
Vial Rack	Initiator 60, holds (30) 0.2-5 mL vials	353478
Vial Rack	Initiator 60, holds (12) 10-20 mL vials	354836
Magnetic Stir Bars	10-20 mL, Qty 5	353930
Venting Screw Replacement		354878

*Microwave vial caps and stir bars included with vial order

KNOWLEDGE



Biotage PathFinder

Web-based Resource for Microwave Synthesis Methods

Biotage PathFinder

Maximize the Benefits of Microwave Synthesis with Biotage PathFinder Web

Biotage PathFinder

Biotage PathFinder is the world's largest database of established methods for microwave synthesis. The new web-based format offers chemists worldwide access to more than 5,200 diverse microwave methods. Using simple keyword and/or substructure search, it is fast and easy to find microwave conditions for your reactions of interest along with experimental details and information needed to perform the reactions.

Additional Features

Ask-a-Chemist

In addition to the database, Biotage PathFinder includes an Ask-a-Chemist feature, which allows chemists to have a dialogue on microwave-synthesis methods and get quick answers to their questions directly from a Biotage chemist experienced in microwave synthesis.

Vapor-Pressure Calculator

This software allows chemists to automatically calculate the vapor pressure for some common solvents at various temperatures.

Biotage PathFinder Cookbook

A free feature that introduces all users to a sample of the valuable information available on PathFinder. Chemists may quickly browse through a selection of popular reactions and obtain reaction details.

Data Content

The data content is continually updated with new chemistries and currently contains reactions from Biotage's chemists contributions from our Scientific Partnership Program (SPP) and data from published material.

To experience the benefits firsthand, visit www.biotagepathfinder.com.

Figure 1. Enter a simple substructure search.

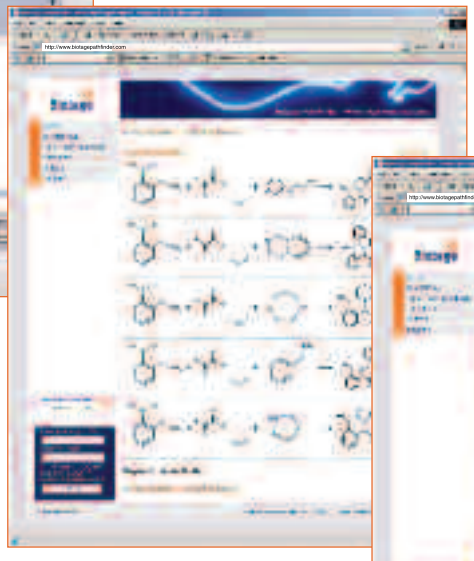


Figure 2. Search results are displayed in an easy-to-browse format.

Figure 3. Reaction details needed to perform reactions are listed in an easy-to-read format.

Ordering Information

Item	Description	Part Number
Biotage PathFinder Web	Single Seat-Annual Subscription	355239

ISOLUTE C

Work-up Solutions and Optimization

Solutions and Optimization

Work-up Solutions

Scavenger Resins

Scavenger resins selectively react with excess reagents and reaction by-products to quench reactions and allow removal of bound chemicals by simple filtration. Using scavenger resins, chemists can save time and achieve compound purities exceeding 85% for many frequently used reactions.

(See pg 136 for work-up optimization with scavengers)

IST Products for Reaction Mixture Work-up

Biotage offers a range of products for reaction mixture work-up. The solutions include a range of techniques and also address throughput requirements.

Techniques

- Solid Phase Extraction (SPE) formats for target compound isolation
- Catch & Release SPE
- Scavenging SPE
- Separation of chlorinated solvent and aqueous systems
- Water soluble impurity removal, water removal, and LLE
- Variety of filtration products

Formats

Flow-through columns and plate options:

- Columns for manual processing
- High throughput formats for manual and automated processing
    - ISOLUTE-96 fixed-well plate for routine high throughout applications
    - ISOLUTE Array modular plate for variable throughput requirements
    - ISOLUTE Array-24 system for applications requiring higher capacity in a microplate format

(See page 140 for guidelines on selecting the correct technique and format.)

Formats for Manual Work-up Applications

Biotage offers the following formats for manual work-up applications:

ISOLUTE™ Work-up Columns

ISOLUTE columns are available in a range of configurations to meet all reaction scale requirements for work-up applications. Working volumes (limited by the collection vessel volume) range from 3 to 150 mL. ISOLUTE columns are available in a range of sorbent masses for work-up of 1 mg to 70 g of target compound. Process up to 10 or 20 columns in parallel using the FlashVac Sample Processing Manifolds (see below).

FlashVac™ Sample Processing Manifolds

FlashVac-10 and -20 Sample Processing Manifolds are used to process standard Luer tipped ISOLUTE work-up columns. Constructed from glass or high density polyethylene, the FlashVac manifolds are compatible with commonly used reaction and work-up solvents.

(See page 222 for details)

Work-up Solutions

Formats for High Throughput Applications

Biotage offers four formats for high throughput applications:

ISOLUTE-96

Industry standard 1-piece 96-well plate used for high throughput applications. Working volumes (limited by the collection plate volume) up to 2 mL per well. SPE plates are available in a range of sorbent masses for work-up of 1 to 500 mg of target compound.

ISOLUTE Array

Modular 96-well format with removable wells. User can populate the plate as necessary, therefore a cost-effective format for method development or variable throughput requirements. Working volumes (limited by the collection plate volume) up to 2 mL per well. ISOLUTE Array plates and wells are available in a range of sorbent masses for workup of 1 mg to 500 mg of target compound.

ISOLUTE tab-less columns

ISOLUTE tab-less columns offer increased capacity in a microplate format. Tab-less 3 and 6 mL columns can be arranged in 48- and 24-well plate arrangements respectively. The tab-less 6 mL columns are compatible with the ISOLUTE Array-24 system. Applications include Catch & Release and scavenging SPE, filtration, phase separation, and supported liquid extraction. Both columns are compatible with commonly used synthesis and work-up instruments (e.g. Mettler Toledo MiniBlock® System).

ISOLUTE Array-24

ISOLUTE Array-24 base plate accommodates up to 24 ISOLUTE tab-less 6 mL columns in a 4 x 6 arrangement. Working volumes (limited by the collection plate volume) are up to 10 mL per well. ISOLUTE tab-less columns are available in a range of sorbent masses for workup of 1 mg to 1 g of target compound.

VacMaster-96 Sample Processing Manifold

All high throughput formats are compatible with the VacMaster-96 Sample Processing Manifold, a versatile manifold which can be used for manual processing or with liquid handling systems.

Scavenger Selection

Resin Selection

Solvent Compatibility

Lightly cross-linked polystyrene resins typically require the use of solvents that will swell the resin to allow reagents from the bulk solution to gain access to the resin-bound functional groups. If the reaction solvent does not swell the resin, it may be necessary to add a co-solvent that is compatible with the resin. In this catalog, the names of lightly cross-linked polystyrene resins have a "PS-" prefix.

The resin-bound functional groups of the more highly cross-linked macroporous resins come in contact with reagents by diffusion through the pore network and do not require the use of a solvent that will swell the resin. Macroporous resins are effective in any solvent that is not reactive with the resin functionality and do not swell or undergo significant volume changes in the presence of solvents that swell PS resins, such as DCM and THF. In this catalog, the names of macroporous resins have an "MP-" prefix.

Electrophile Scavengers	Nucleophile Scavengers	Metal Scavengers
PS-Trisamine	PS-Isocyanate	MP-TMT
MP-Trisamine	MP-Isocyanate	PS-DEAM
PS-Tosyl hydrazide	PS-Benzaldehyde	PS-TBD
PS-Thiophenol	PS-TsCl(HL)	MP-Trisamine
MP-Carbonate	MP-TsOH	PS-Triphenylphosphine
PS-Triphenylphosphine		

Table 1. Scavenger resin applications require an excess of scavenger resin, ca. 3-5 equivalents relative to the excess reagent or by-product to be scavenged. Scavenging of less reactive substrates can be accelerated by using two sequential treatments with scavenger resin.

Acids	Bases
MP-TsOH	MP-Carbonate
	PS-DIEA
	PS-NMM
	PS-TBD

Table 2. MP-Carbonate is effective for neutralization and for reactions requiring a mild inorganic base. Bound tertiary amines PS-DIEA and PS-NMM are used as acid acceptors which can be removed by filtration and are useful analogs to small molecule amines. Typical reactions include esterifications, amidation, mesylate, and sulfonamide formation. For reactions requiring stronger bases than tertiary amines, the bound guanidine base PS-TBD is available. PS-TBD is sufficiently basic to deprotonate moderately acidic hydrogens, such as phenolic and activated methylenes.

Scavenger Selection Guide

Which Compounds to Scavenge?		Recommended Scavengers
Scavengers for electrophiles		
Carbonyls		PS-$TsNHNH_2$ PS-Trisamine MP-Trisamine
Alkylating agents	Alkyl halides, Mesylates, Tosylates, ∂-bromoesters, ∂-bromoketones	PS-Thiophenol PS-Triphenylphosphine
Acid chlorides		PS-Trisamine MP-Trisamine PS-NH_2
Sulfonyl chlorides		PS-Trisamine MP-Trisamine PS-DMAP PS-NH_2
Isocyanates		PS-Trisamine MP-Trisamine PS-NH_2
Scavengers for Metals		
Expoxides		PS-Thiophenol
Oxophilic inorganic organometallic complexes, Lewis acid (B, Ti, Sn)		PS-DEAM
Lewis acids, e.g., Ti(IV), Sn(IV)		PS-DEAM
Transition metals, e.g. palladium		MP-TMT, PS-TBD, PS-PPh_3, MP-Trisamine
Scavengers for Nucleophiles		
Alcohols		PS-TsCI(HL)
Amines	Primary, secondary	PS-Isocyanate MP-Isocyanate MP-TsOH MP-TsOH cartridges PS-TsCI(HL)
	Selective for primary	PS-Benzaldehyde
	Anilines (aromatic)	PS-TsCI(HL) MP-TsOH MP-TsOH cartridges PS-Isocyanate MP-Isocyanate
Hydrazines		PS-Benzaldehyde PS-TsCI(HL)
Enolates		PS-Benzaldehyde
Thiol/thiolates		PS-Isocyanate MP-Isocyanate PS-Thiophenol
Alkoxides		PS-TsCI(HL) PS-Isocyanate MP-Isocyanate
Organometallics		PS-Benzaldehyde PS-TsCI(HL)
Reducing agents		PS-Benzaldehyde
Acid/acidic phenols	HOBt Pentafluorophenol 4-Nitrophenol Carboxylic acid Phenol	MP-Carbonate PS-Trisamine MP-Trisamine

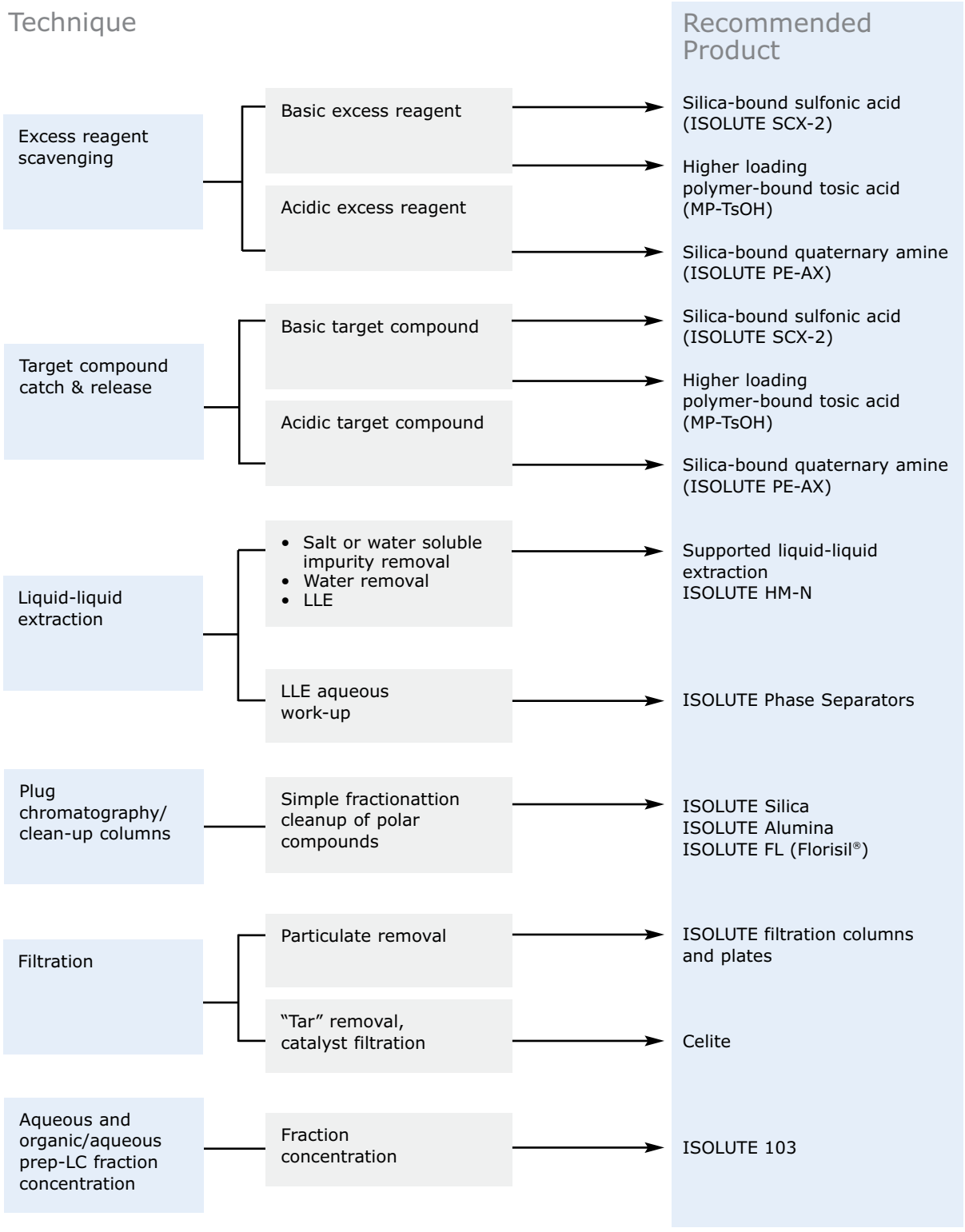
Glossary

24-well plate	4 x 6 position "microplate" format. Tab-less 6 mL columns can be arranged in a 4 x 6 microplate footprint for high throughput applications.
48-well Plate	6 x 8 position "microplate" format. Tab-less 3 mL columns can be arranged in a 6 x 8 microplate footprint for high throughput applications.
96-well Plate	8 x 12 position "microplate" format. 96 wells can be arranged in an 8 x 12 microplate footprint for high throughput applications.
Array (ISOLUTE Array)	Modular 96-well format with removable wells. User can populate the plate as necessary, therefore a cost-effective format for method development or variable throughput requirements.
Catch & Release SPE	Mode of SPE where the compound of interest is retained on the SPE column; the SPE column is rinsed to remove impurities, then the target compound is eluted using a suitable solvent.
Celite®	Modified form of diatomaceous earth.
Clean-up columns	Polar SPE columns for removal of polar impurities from the reaction mixture.
Column equilibration	Removal of excess solvent from an SPE column following column solvation. This "normalizes" the sorbent bed prior to loading reaction mixture.
Column solvation	Solvation is required to "wet" the sorbent, which ensures efficient interaction of the target compound or impurities with the sorbent.
Diatomaceous earth	Inert support material used in many applications including filtration and flash column pre-loading. See (ISOLUTE HM-N).
Flow-through technique	Flow-through workup uses polypropylene column or plate formats, unlike workup using a batch process. Liquids are passed through the column containing an SPE sorbent or filtration device using vacuum or positive pressure and collected at the Luer tip of the column. See SPE column.
Frits	Sintered particles (e.g. polyethylene (PE) or PTFE), which are compressed to form a porous material. Frit materials are relatively thick (>1 mm) and pores run in a multidirectional channel system. This enables the material to act as a filter. Frits are used to retain sorbents in SPE columns or as filtration devices.
Fixed-well plate	One piece 96-well plate with the industry standard footprint. Used for high throughput applications.
High throughput	Processing of up to 24, 48, or 96 samples in parallel.
ISOLUTE-96	Industry standard one-piece 96-well plate used for high throughput applications. Packed with ISOLUTE SPE sorbents and some filtration materials.
Functional groups	Bonded onto silica or resin-based sorbents to give the chemistry of the sorbent surface. See Retention Mechanisms and Sorbent (SPE sorbent).
HM-N (ISOLUTE HM-N)	Modified form of diatomaceous earth.
Liquid-liquid extraction	Partitioning of target compounds or impurities between two immiscible solvents.
Microplate footprint	Industry standard footprint for 24-, 48-, and 96-well plates. Refers to the exact dimensions of the plate, originating from the 8x12 formation of fixed-well 96-well plates for high throughput applications.
MP-TsOH	Resin-based sorbent functionalized with a tosic acid group, used to isolate basic compounds from reaction mixtures in Catch & Release and scavenging SPE.

Glossary

Parallel work-up	Catch & Release and scavenging SPE, filtration, or other work-up techniques processed in parallel, for example, a 24-, 48-, or 96-well plate format.
PE-AX (ISOLUTE PE-AX)	ISOLUTE PE-AX is a silica-based sorbent functionalized with a quaternary amine* group and can be used to isolate acidic compounds from reaction mixtures in catch and release and scavenging SPE. * This sorbent is pre-equilibrated with an acetate counter ion.
Phase separators	Flow-through columns and plates for the separation of aqueous and chlorinated solvents in reaction mixture workup.
Plug chromatography	See polar column cleanup.
Polar SPE column clean-up	SPE using polar columns; used to remove polar impurities from reaction mixtures.
Pre-treatment	Primary goal is to create an environment that promotes target compound or impurity retention onto the SPE sorbent. Sample pre-treatment often involves dilution to reduce sample viscosity, solvent polarity, or ionic strength.
Retention mechanisms	Retention mechanisms in SPE are based on non-polar (Van der Waals forces), polar (hydrogen bonding and dipole-dipole forces), or ionic (cation or anion) interactions between the compound of interest or impurities and the sorbent. These interactions are not covalent. For example, ISOLUTE SCX-2 is a silica-based sorbent functionalized with a sulfonic acid group and can be used to isolate basic compounds from reaction mixtures in Catch & Release and scavenging SPE.
Resin-based	Backbone of this sorbent is a carbon-hydrogen-based polymer.
Scavenging SPE	Mode of SPE where the impurities are retained on the SPE column while the compounds of interest pass straight through the SPE column and are collected.
Scrubbing	Removal of water-soluble components from a reaction mixture. See HM-N (ISOLUTE HM-N).
SCX-2 (ISOLUTE SCX-2)	ISOLUTE SCX-2 is a silica-based sorbent functionalized with a sulfonic acid group and can be used to isolate basic compounds from reaction mixtures in Catch & Release and scavenging SPE.
Silica-based	Backbone of this sorbent is a silica gel.
Solid phase extraction (SPE)	Flow-through technique where target compounds are separated from impurities by selective partitioning of the compounds between a solid phase (sorbent) and a liquid phase (solvent).
SPE column	Consists of a tube (or well in a 96-well plate) containing a sorbent held between two frits. See Flow-through technique. See page 143 for a diagram showing a typical SPE column format.
Sorbent (SPE Sorbent)	Silica or resin-based polymer that can be functionalized with a variety of functional groups with different retention properties. See Retention mechanisms.
Supported-liquid extraction	Liquid-liquid extraction achieved on a solid support called diatomaceous earth. See HM-N (ISOLUTE HM-N).
Tar	Gelatinous or viscous material that can be difficult to remove from crude reaction mixtures.
Tab-less columns	For high throughput applications only. Tab at the mouth of the SPE or filtration column is removed to allow columns to be fitted into a microplate footprint. Tab-less 3 mL columns for 48-well arrangements and tab-less 6 mL columns for 24-well arrangements.
Target compound elution	Elution of a target compound or compounds from an SPE column using a suitable solvent.
Well	Individual column in a 24-, 48-, or 96-well plate.

IST Product Selection Guide



Introduction to Solid Phase Extraction (SPE) for Reaction Work-up

Solid phase extraction (SPE) is a flow-through technique using column or 96-well plate formats. SPE can be used to selectively retain products (Catch & Release SPE) or impurities (scavenging SPE) from solutions onto a solid functional medium. Figure 1 shows a typical SPE column format.

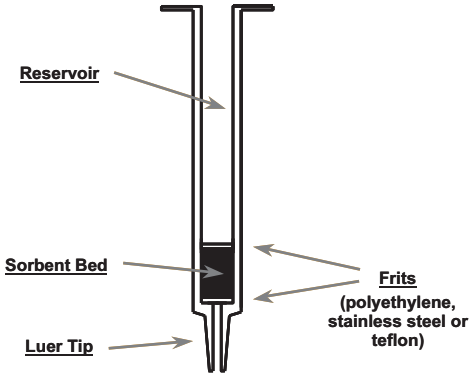


Figure 1. Typical SPE column format

Retention Mechanisms

The retention mechanism can be ionic, polar, or non-polar. Unlike resin scavengers, SPE interactions are relatively nonselective, reversible, and are not based on specific chemical reactions between compounds and functionalized sorbents. SPE columns and 96-well plates can be used in both Catch & Release and scavenging SPE modes.

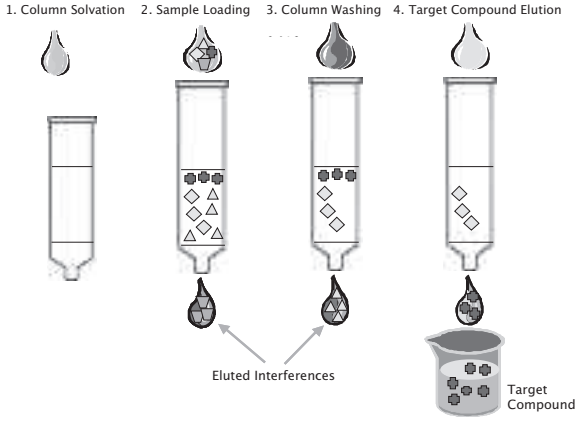


Figure 2. Catch & Release SPE procedure

Catch & Release SPE

In Catch & Release SPE, the sorbent bed "catches" the compound of interest along with some impurities. Rinsing the column or well removes impurities, leaving the compound of interest on the column for subsequent elution in an appropriate solvent or solvent mixture.

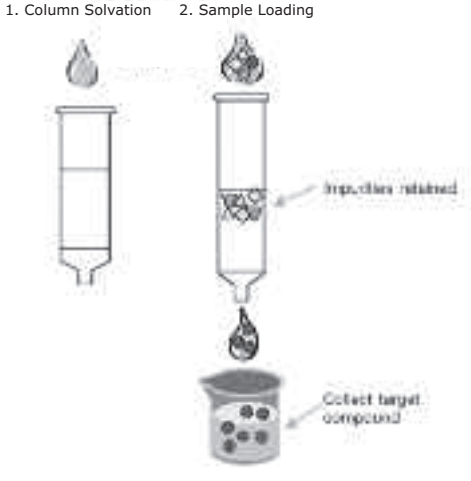


Figure 3. Scavenging SPE procedure

Scavenging SPE

In scavenging SPE, the sorbent bed retains impurities and allows the compound of interest to pass straight through the column or well. Compound isolation is achieved through interaction between the sorbent and the impurities, which are retained on the column.

Column Sizes

SPE columns are available in a range of sizes and formats. The traditional syringe barrel format is most convenient for processing up to 20 samples at a time. For higher throughput, a tab-less SPE column format allows column arrangement in a microplate footprint. This provides options for 24- and 48-well workup. Fixed well and modular 96-well formats are also available for high throughput applications.

(See page 200 for more information on formats)
(See the selection guide on page 140 for a guide on choosing the correct SPE column)

SPE Column Capacity

The amount of material that can be isolated using SPE depends on the capacity of the sorbent bed. As a general guideline, non-polar and SPE columns can retain approximately 5% w/w of the total sorbent bed. For example, a 1 g sorbent mass will retain 50 mg of target compound or impurities.

The capacity of ion exchange SPE columns is measured in milliequivalents (meq) per gram of sorbent. An SPE column packed with 500 mg of strong cation exchange sorbent (sulfonic acid functional group), with an exchange capacity of 0.6 meq/g, can retain up to 70 mg of a typical basic compound with a molecular weight of 250 g/mol.

SPE Column Materials

ISOLUTE SPE column reservoirs and 96-well plates are made of polypropylene. Frits are made of polyethylene. Both have a high degree of solvent resistance and are compatible with all commonly used solvents, acids, and bases.

Processing

SPE columns and plates can be processed manually using a vacuum manifold or using automated liquid handling systems for high throughput applications.

- FlashVac-10 & -20 Sample Processing Manifolds for processing columns manually (See pg 224)
- VacMaster-96 Sample Processing Manifold for processing 24- and 96-well plates manually (See pg 220)

Guidelines for ISOLUTE SPE Column Use

Follow these steps to ensure correct use of ISOLUTE SPE columns.

Column Processing

1. Do not pass liquids through the SPE column too quickly, particularly when performing ion-exchange procedures. Excessive solvent flow rates can lead to target compound breakthrough (where compounds pass unretained through the column). For guidelines on sample loading flow rates see (Table 2, pg 144).

2. Filter or remove particulates to prevent column plugging. Ensure that target compound(s) are not adsorbed to particulates removed from the sample prior to extraction.

3. If the sample contains precipitated or particulate matter on which the compounds adsorb, desorb the compounds from the particulates prior to extraction. This can be accomplished in a variety of ways, such as adding acid or base, or an organic solvent. Alternatively, extract solids with a solvent prior to SPE.

Choosing the Correct SPE Sorbent

Application	Product to Use	Columns	Plates
Organic Solvent Systems		**Page Number**	**Page Number**
Basic target compound	Silica-based sulfonic acid (ISOLUTE SCX-2)	204	204
Basic target compound	Higher loading resin-based tosic acid (MP-TsOH)	205	N/A
Acidic target compound	Silica-based quaternary amine (ISOLUTE PE-AX)	202	202
Basic excess reagent	Silica-based sulfonic acid (ISOLUTE SCX-2)	204	204
Basic excess reagent	Higher loading resin-based tosic acid (MP-TsOH)	205	N/A
Acidic excess reagent	Silica-based quaternary amine (ISOLUTE PE-AX)	202	202
Acidic and basic impurities, neutral compound	Silica-based quaternary amine and sulfonic acid (ISOLUTE PE-AX/SCX-2)	203	203
Simple fractionation clean-up of polar compounds	Polar columns: ISOLUTE Si II ISOLUTE AL-N ISOLUTE FL	207	N/A
Aqueous Solvents and Organic/ Aqueous Mixtures			
Prep-LC fractions	Resin-based, non-polar sorbent (ISOLUTE 103)	208	N/A

Table 1. Sorbent selection with product page numbers

Guidelines for Catch & Release SPE

A Typical Catch & Release SPE Method Involves:

1. Reaction mixture pre-treatment
2. Column solvation
3. Column equilibration
4. Sample loading
5. Column washing (impurity elution)
6. Target compound elution

Sample Pre-treatment

The primary goal of sample pre-treatment in Catch & Release SPE is to create an environment that promotes target compound retention on the chosen SPE column. Sample pretreatment often involves dilution to reduce sample viscosity, solvent polarity, or ionic strength.

Reduce the solvent polarity by diluting the reaction mixture using a less polar solvent (ensuring that target compounds do not precipitate). Alternatively, evaporate the sample and re-dissolve the remaining compounds in an appropriate polar solvent.

Column Solvation

Solvation is required to ensure efficient interaction of the target compound with the SPE sorbent. Pass methanol, acetonitrile, or other organic solvent through the column to "wet" the sorbent and ensure interaction with the optimized reaction mixture. A typical volume for solvation solvent is 5–10 mL/g of sorbent.

Column Equilibration

Equilibration is required to "normalize" the column after solvation, and maximize retention efficiency at the sample load stage. Equilibrate the column by treating it with a solvent that is as "sample-like" as possible. If the sample is an organic solvent or mixture, equilibrate the column with the same organic solvent. If sample pre-treatment involves dilution with a less polar solvent, the equilibration solvent should match the pre-treated sample. A typical volume of solvent is 10 mL/g of sorbent.

Sample Loading

Apply the sample to the equilibrated column. Establishing the optimum flow rate is an important part of the method procedure. Flow rates that are too fast will compromise recoveries. Gravity loading may be suitable.

Column	Non-polar Retention Mechanism	Polar Retention Mechanism	Ion Exchange Retention Mechanism
3 mL	2 mL/min	2 mL/min	1 mL/min
6 mL	4 mL/min	4 mL/min	2 mL/min
15 mL	6 mL/min	6 mL/min	3 mL/min
25 mL	10 mL/min	10 mL/min	4 mL/min
70 mL	30 mL/min	30 mL/min	7 mL/min
150 mL	50 mL/min	50 mL/min	15 mL/min

Table 2. Suggested flow rates for use with ISOLUTE SPE columns

Column Washing (Impurity Removal)

One or more wash steps are used to selectively remove impurities from the sorbent without eluting the target compound(s). Solvents in which the target compound is insoluble are often very good choices for wash solvents. The flow rate should allow enough contact time for impurities to dissolve efficiently. Flow rates in Table 2 can be used as a guide.

Target Compound Elution

Recover compounds by washing the column with a solvent that will elute the target compound from the sorbent into a suitable collection vessel. Choose an elution solvent in which the target compound is highly soluble. Elution solvent selection may be influenced by the ease of solvent evaporation or other subsequent procedures. The typical minimum elution volume is 2.5 mL/g sorbent. Flow rates in Table 2 can be used as a guide.

Guidelines for Scavenging SPE

A Typical Scavenging SPE Method Involves:

1. Sample pre-treatment
2. Column solvation
3. Column equilibration
4. Sample loading

Sample Pre-treatment

Unlike Catch & Release SPE, sample pre-treatment for scavenging SPE is performed to promote retention of impurities, not the target compound, on the chosen SPE column. Sample pre-treatment often involves dilution to reduce sample viscosity, solvent polarity, or ionic strength.

Reduce the solvent polarity by diluting the reaction mixture using a less polar solvent (ensuring that target compounds do not precipitate). Alternatively, evaporate the sample and re-dissolve the remaining compounds in a less polar solvent.

Column Solvation

Solvation is required to ensure efficient interaction of the impurities with the SPE sorbent. Pass methanol, acetonitrile, or other organic solvent through the column to "wet" the sorbent and ensure interaction with the optimized reaction mixture. A typical volume for solvation solvent is 5–10 mL/g of sorbent.

Column Equilibration

Equilibration is required to "normalize" the column after solvation and maximize retention efficiency at the sample load stage. Equilibrate a column by treating it with a solvent that is as "sample-like" as possible. If the sample is an organic solvent or mixture, equilibrate the column with the same organic solvent. If sample pre-treatment involves dilution with a less polar solvent, the equilibration solvent should match the pre-treated sample. A typical volume of solvent is 10 mL/g of sorbent.

Sample Loading

Apply the sample to the equilibrated column. Collect the sample as it passes through the column as this contains the isolated target compound.

Establishing the optimum flow rate is an important part of the method development procedure. Flow rates that are too fast will compromise purity. Gravity loading may be suitable. See Table 2 for guidelines on flow rates.

ISOLUTE Polar Clean-up/Plug Chromatography Columns

Simple, rapid cleanup of organic synthesis mixtures can be achieved using polar ISOLUTE SPE columns. There are two ways of using these columns.

- Polar target compounds are retained on the column while less polar impurities are removed (product Catch & Release SPE approach)
- Polar impurities are retained on the column while the less polar target compound(s) pass through the column (impurity scavenging SPE approach)

(The principles for product Catch & Release SPE and impurity scavenging SPE are discussed on pages 144-145)
(See page 206 for standard and tab-less column ordering information)

The success of polar SPE columns for this application relies on differences in polarity of the target compound and the impurities as well as the sorbent characteristics and solvents used. There are three different ISOLUTE polar SPE columns that can be used for this application:

- ISOLUTE AL-N
- ISOLUTE FL
- ISOLUTE Si II

ISOLUTE AL-N

This is an aluminum oxide-based support with retention mechanisms that include polar and acid-base interactions and can be used in a similar way to silica (above). Unlike silica, neutral alumina can be used for compounds with acid-sensitive functional groups such as acetals and ketals. See Table 3 on page 147 for solvent considerations.

ISOLUTE FL

Based on magnesium oxide silica gel (Florisil®), this product can be used to retain highly polar compounds such as amines, amides, and heterocylces. These compounds absorb less strongly on ISOLUTE FL compared to non-magnesium silica gels and may be eluted with less polar solvent mixtures. Florisil can also be used to remove polar impurities while allowing the less polar target compounds to pass through unretained. See Table 3 below for solvent considerations.

ISOLUTE Si II

This product is suitable for removing highly polar interferences from crude reaction mixtures. The reaction mixture is applied to the column, which retains the polar impurities. The target compounds are also initially retained but are washed off the column with a solvent of appropriate polarity (Table 3).

An example of this application is the work-up of arylimidazoles formed by Suzuki coupling using the palladium catalyst PS-PPh_3-Pd.[1]

Summary of Method Considerations When Using Polar Clean-up Columns for Reaction Work-up

ISOLUTE Si II, ISOLUTE AL-N, and ISOLUTE FL can be used in Catch & Release and scavenging SPE modes (Table 3).

	Catch & Release SPE	Scavenging SPE
Reaction Mixture Pre-treatment	Non-polar solvent (e.g. hexane)	Medium polarity solvent in which the target compound is soluble (e.g. THF)
Column Solvation	Non-polar solvent that allows retention of the target compound(s) (e.g. hexane)	Medium polarity solvent in which the target compound is soluble (e.g. THF)
Column Equilibration	N/A	N/A
Sample Loading	Gravity or vacuum – see page 144	Gravity or vacuum – see page 145 COLLECT ELUENT AS THIS CONTAINS THE TARGET COMPOUND
Column Washing (impurity elution)	Non-polar solvent with some polar modifier; ensure target compound(s) remains on the column (e.g. hexane containing DCM)	N/A
Target Compound Elution	Polar solvent or solvent mixture that overcomes the polar interactions (e.g. DCM)	N/A

Table 3. Summary of polar column clean-up approaches

References

1. Page 90.

ISOLUTE 103

ISOLUTE 103 Columns for Concentration of Organic/Aqueous Prep-LC Fractions

Packed with a hydroxylated polystyrene-divinylbenzene co-polymer, ISOLUTE 103 columns allow simple and rapid transfer of compounds dissolved in aqueous-based LC mobile phase fractions into pure organic solvent. This approach negates the need for lengthy solvent evaporation processes.

This approach uses a Catch & Release SPE technique (described on page 143), but as the sorbent has a wettable surface, it is not necessary to condition and equilibrate the sorbent surface before sample application.

Column Selection Guidelines

Select a column with a bed mass that is at least five times the mass of the compound to be isolated. For example, a fraction containing 30 mg of product may require a 200 mg ISOLUTE 103 column. Factors which can reduce the effective capacity of the column include target compound polarity and concentration of organic component.

Sample Pre-Treatment

Dilution of the fraction may be necessary to reduce the level of organic solvent. The maximum concentration of organic solvent present should be 30% v/v.

Column Solvation/Equilibration

NA – the sorbent is water-wettable.

Sample Loading

Apply the sample to the dry column at a flow rate of 10-50 mL/min using vacuum or positive pressure.

Column Washing (Impurity Elution)

Rinse off any remaining salts with water (1 mL per 100 mg of sorbent).

Target Compound Elution

In most cases, this can be achieved using a water-miscible organic solvent (acetonitrile or methanol). If using a water-immiscible solvent, remove excess water from the column before compound elution using vacuum or positive pressure.

It may be necessary to add 2-5% v/v of a volatile acid or base modifier to ensure full recovery of acidic or basic compounds, respectively. As a guideline, use between 0.5-1 mL of solvent per 100 mg of ISOLUTE 103.

ISOLUTE HM-N for Rapid Aqueous Work-up and Removal of Water-soluble Impurities from Reaction Mixtures

Packed with a diatomaceous earth support, ISOLUTE HM-N columns and 96-well plates provide a simple and rapid approach to aqueous work-up. This hydrophilic inert support can be used instead of traditional liquid-liquid extraction (LLE) protocols, eliminating emulsion formation and improving reproducibility.

ISOLUTE HM-N products are available in a variety of formats to match the reaction scale.

Format	Reaction Mixture Volume	Maximum buffer Volume	Page
Standard columns	5-40 mL	0.3 to 20 mL	211
Tab-less 3 and 6 mL columns for use with 48 and 24-well automation formats	3-6 mL	0.3 to 1 mL	211
Bulk ISOLUTE HM-N	> 500 mL	2 mL/g	211

Table 5. A range of formats to suit reaction scales

ISOLUTE HM-N can be used for the following applications:

- Removal (scrubbing) of water soluble impurities
- Residual water removal
- Workup of an aqueous reaction mixture using supported liquid extraction (LLE on the column)

Solvents

Typical solvents are those used in traditional LLE, such as DCM, chloroform, ethyl acetate, hexane, butyl acetate, and toluene. If the solvent contains a water-miscible polar modifier such as isopropyl alcohol or acetone, dilute to less than 10% v/v polar modifier.

Selecting the Appropriate Column Size

ISOLUTE HM-N columns are described by their capacity for aqueous systems. For example, an ISOLUTE HM-N 1 mL sample volume column can absorb up to 1 mL aqueous solvent.

(See page 211 for ordering information)

ISOLUTE HM-N

Principles of Removal (Scrubbing) of Water-soluble Impurities

1. Load aqueous buffer using gravity flow. This will absorb onto the column. Allow 5-15 minutes for complete aqueous absorption to take place.
    - To scrub bases, add 1M HCl or similar acid
    - To scrub acids, add 1 M NaOH or similar base

2. Load the water-immiscible reaction mixture using gravity flow.

3. Collect the mixture as it passes through the column. The reaction mixture is now ready for concentration or further work-up.

Principles of Water Removal

For reaction mixtures containing trace amounts of water, ISOLUTE HM-N can be used to dry the solution. ISOLUTE HM-N can absorb up to 750 µL of water per g of material. This capacity may vary depending on the solvent used.

1. Load the reaction mixture onto the column using gravity flow. Residual moisture will be absorbed onto the support material.

2. Collect the dried reaction mixture as it passes through the column.

ISOLUTE Sodium Sulfate Drying Cartridge can also be used for water removal. See page 212 for more information.

Principles of Supported Liquid Extraction

For aqueous solvent mixtures, ISOLUTE HM-N can be used to transfer target compounds into water-immiscible solvents.

1. Load the aqueous reaction mixture onto the appropriate-size column using gravity. Maximize extraction of ionizable compounds by neutralizing the ionizable groups. For basic compounds, adjust the pH to two units above the lowest pK value. For acidic compounds, adjust the pH to 2 units below the lowest pK value.

2. Allow to stand for 5-15 minutes for complete absorption.

3. Load a suitable water-immiscible organic solvent under gravity and collect the filtrate, which contains the target compound(s).

ISOLUTE Phase Separators for Rapid Aqueous Work-up

Separation of aqueous and halogenated solvent phases can be achieved easily using ISOLUTE Phase Separator columns and 96-well plates. ISOLUTE Phase Separators contain a selectively permeable frit that allows the organic solvent to pass through the column but retains the aqueous phase.

The synthesis mixture is loaded onto the column and the two phases separate out with the more dense organic phase forming the bottom layer.* The organic solvent passes through the frit under gravity, while the aqueous phase is retained above the frit for up to 24 hours without breakthrough.

Note: *ISOLUTE Phase Separators are only suitable for organic solvents more dense than water.*

General Procedure

1. Select the appropriate column size according to the total volume of the two-phase mixture.

2. Add the two-phase mixture to the ISOLUTE Phase Separator column.*

3. Allow the two solvents to separate out under gravity. The organic solvent should start to penetrate the frit within a few seconds.

4. Collect the organic solvent in a suitable collection vessel.

5. The ISOLUTE Phase Separator will hold up the aqueous layer for up to 24 hours. Hold-up time may be reduced if the aqueous layer contains high levels of dissolved salts or low volumes of miscible organic solvent.

* To ensure removal of trace amounts of water, attach an ISOLUTE Sodium Sulfate Drying Cartridge to the Luer outlet of the column before applying the two-phase mixture. See page 212 for more information on this product.

ISOLUTE Accessories for Reaction Work-up

Biotage offers a range of accessories for use with filtration, Catch & Release, and scavenging SPE columns in organic synthesis work-up schemes.

ISOLUTE Filtration Columns and Plates

- For all filtration applications
- Polypropylene tubes fitted with 20 µm polyethylene frits – excellent solvent resistance
- Standard columns from 1-150 mL volumes for manual processing
- Includes a 50 mL wide-mouth filtration column for easy access to filtered material
- 24-, 48-, and 96-well formats for high throughput applications
- Seal with column caps and Luer tip cap for carrying out room temperature reactions

(See page 214 for standard and tab-less column ordering information)
(See page 214 for 96-well plate ordering information)

ISOLUTE Frits

- Use when sample pre-loading on ISOLUTE flash columns, constructing filtration, Catch & Release, and scavenging SPE columns
- 10 and 20 µm PE for 1-150 mL reservoirs
- 20 µm PTFE for 1-70 mL reservoirs

(See page 217 for ordering information)

Celite® Columns for "Tar" and Catalyst Removal

- Filtration device for the removal of "tars" from crude reaction mixtures
- Catalyst removal from reaction mixtures
- Pre-packed columns containing an inert Celite material with an optimized particle size for rapid cleanup

(See page 215 for standard column ordering information)

ISOLUTE Empty Reservoirs

- Constructed of polypropylene and available in 1-150 mL reservoir volumes
- Attach to ISOLUTE columns used on any work-up application to extend the volume that can be applied in one aliquot
- Seal with column caps and Luer tip cap for carrying out room temperature reactions

(See page 213 for ordering information)

ISOLUTE SPE Column Adaptors

- For stacking empty reservoirs and filtration columns above Catch & Release and scavenging SPE columns
- Available in polyethylene and PTFE for all column sizes

(See page 217 for ordering information)

ISOLUTE SPE Column Caps and Luer Tip Cap

For sealing column inlets or Luer tips to allow:

- Liquid-filled ISOLUTE columns to be transported from one location to another
- Room-temperature reactions in empty reservoirs or filtration columns

(See page 217 for ordering information)

PTFE Stopcocks and Needles

- PTFE stopcock and stopcock needle unit options allows individual column flow control
- Provide excellent solvent resistance for use on FlashVac Sample Processing Manifolds

(See page 224 for ordering information)

Scavenger Resins

Save Time & Achieve Higher Purities

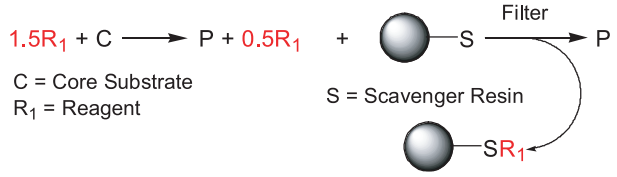
Scavenger Resins

Scavenger Resins

Scavenger resins selectively react with excess reagents and reaction by-products to quench reactions to purification by simple filtration. Using scavenger resins, chemists can save time and achieve compound purities exceeding 85% for many frequently used reactions.

Scavenger resins can be used as an alternative to extractions and chromatography, or to greatly speed initial cleanup of large reagent excesses prior to chromatography. Biotage makes scavengers for a variety of electrophiles, nucleophiles and metals. Since the reactive functionality is resin-bound, combinations of scavengers that would be incompatible in solution, such as acids with bases, can be used simultaneously to remove mixtures of impurities.

Biotage determines resin capacity by measuring the uptake of a model substrate. This provides a better measure of scavenging capacity than determinations based on elemental analysis. Scavenger resin applications typically require the addition of a two- to five-times excess of scavenger resin relative to the excess reagent or by-product to be scavenged. Scavenging of weakly reactive substrates can be accelerated by two sequential treatments with scavenger resin.



Polymer Scavengers

Polymer-Supported Acids and Bases

Bound acids are effective reagents in organic synthesis for catalyzing reactions and as purification aids. MP-TsOH acts as a bound analog of p-toluenesulfonic acid with the advantage of product purification by filtration. It is also useful in Catch-and-Release purification of amines and basic heterocycles.

Polymer-Supported Nucleophile Scavengers

- PS-TsOH; MP-TsOH
- Ps-TsCl, PS-TsCl(HL)
- PS-Benzaldehyde
- PS-Isocyanate; MP-Isocyanate

Polymer Scavengers (cont...)

Bound acids are effective as both reagents, for catalyzing reactions, and as nucleophile scavengers. MP-TsOH acts as a bound analog of p-toluenesulfonic acid. It has been used in acid catalyzed protecting group cleavage as well as for purifiying amines using its Catch-and-Release properties. MP-TsCl, an excellent scavenger of nucleophiles, also aids alkylating amines with alcohols, via a catch-and-release protocol.

Polymer-Supported Electrophile Scavengers

- PS-TBD
- PS-DMAP
- PS-Thiophenol
- MP-Carbonate
- PS-NH_2
- PS-Trisamine
- PS-DIEA
- PS-NMM
- PS-$TsNHNH_2$

Bound bases are effective scavengers of acids, acid chlorides, carbonyls, and isocyanates. These agents have also been employed effectively during a reaction to quench any acidic by-products that are generated in situ. Since polymer-supported functionalities do not interact with each other, a cocktail consisting of polymer-supported acid and bases, incompatible in free form, can be utilized effectively in one pot for scavenging a range of functional groups.

Polymer-Supported Metal Scavengers

- MP-TMT
- PS-DEAM
- PS-Trisamine
- Si-Thiol
- Si-Trisamine
- PS-PPh_3
- Si-TsOH (SCX-3)
- MP-Trisamine
- Si Triamine
- PS-Thiophenol

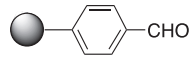
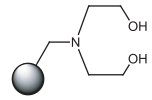
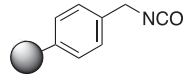
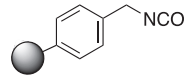
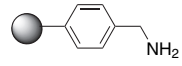
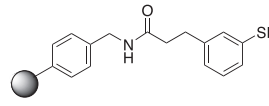
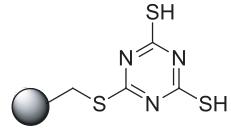
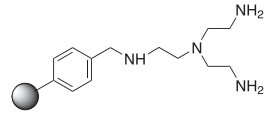
Bound metal chelators are effective in reducing the residual-free metal content of products derived from organometallic reactions. MP-TMT effectively reduces the concentration of palladium in both aqueous and non-aqueous solutions to acceptable levels. PS-DEAM has been shown to scavenge both titanium and tin from reaction mixtures.

Abbreviations

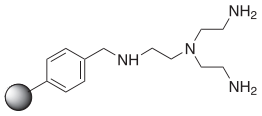
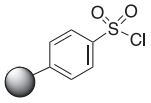
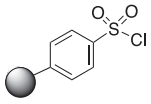
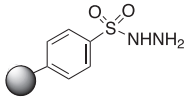
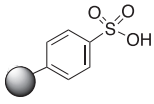
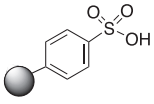
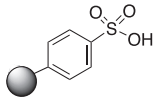
ACN	—	acetonitrile
DBAD	—	di-tert-butylazodicarboxylate
DCE	—	1,2 dichloroethane
DCM	—	dichloromethane
DEAD	—	diethylazodicarboxylate
DIC	—	diisopropylcarbodiimide
DIEA	—	diisopropylethylamine
DMA	—	dimethylacetamide
DMAP	—	dimethylaminopyridine
DMF	—	dimethylformamide
EtOH	—	ethanol
HOAc	—	acetic acid
HOAt	—	N-hydroxy-9-azabenzotriazole
HOBt	—	N-hydroxybenzotriaole
MeOH	—	methanol
PEG	—	polyethylene glycol
Py	—	pyridine
TBAF	—	tetrabutylammonium fluoride
TEA	—	triethylamine
TFA	—	trifluoroacetic acid
THF	—	tetrahydrofuran

Scavenger Resins

Scavenger Selection Table

Product	Class	Structure	Function	Part Numbers	Page
PS-Benzaldehyde	Nucleophile Scavenger		Scavenging nucleophiles, including primary amines, hydrazines, reducing agents	3 g - 800502 10 g - 800360 25 g - 800361 100 g - 800362 1000 g - 800363	160
PS-DEAM	Metal Scavenger		Scavenging titanium(IV) chloride, titanium(IV) isopropoxide,boronic acids	3 g - 800515 10 g - 800430 25 g - 800431 100 g - 800432 1000 g - 800433	161
PS-Isocyanate	Nucleophile Scavenger		Scavenging nucleophiles, including amines and alkoxides	3 g - 800495 10 g - 800260 25 g - 800261 100 g - 800262 1000 g - 800311	165
MP-Isocyanate	Nucleophile Scavenger		Scavenging nucleophiles, including amines and alkoxides	3 g - 801504 10 g - 801409 25 g - 801410 100 g - 801411 1000 g - 801412	167
PS-NH_2	Electrophile Scavenger		Scavenging acid chlorides, sulfonyl chlorides, isocyanates, and other electrophiles	3 g - 800491 10 g - 800263 25 g - 800264 100 g - 800265 1000 g - 800307	169
PS-Thiophenol	Electrophile Scavenger		Scavenging alkylating agents	3 g - 800500 10 g - 800273 25 g - 800274 100 g - 200275 1000 g - 800310	170
MP-TMT	Palladium Scavenger		Scavenging palladium	3 g - 801506 10 g - 801469 25 g - 801470 100 g - 801471 1000 g - 801472	172
PS-Trisamine	Electrophile Scavenger		Scavenging acid chlorides, sulfonyl chlorides, isocyanates and other electrophiles	3 g - 800501 10 g - 800228 25 g - 800229 100 g - 800230 1000 g - 800309	175

Scavenger Selection Table

Product	Class	Structure	Function	Part Numbers	Page
MP-Trisamine	Electrophile Scavenger		Scavenging acid chlorides, sulfonyl chlorides, isocyanates, and other electrophiles	3 g - 801505 10 g - 801397 25 g - 801398 100 g - 801399 1000 g - 801400	176
PS-TsCl	Electrophilic Activation		Loading of alcohols followed by nucleophilic displacement (catch-and-release), scavenging of nucleophiles	3 g - 800490 10 g - 800276 25 g - 800277 100 g - 800278 1000 g - 800316	178
PS-TsCl(HL)	Nucleophile Scavenger		Scavenging alcohols, amines and other nucleophiles	3 g - 800503 10 g - 800364 25 g - 800365 100 g - 800366 1000 g - 800367	181
PS-TsNHNH$_2$	Electrophile Scavenger		Scavenging aldehydes and ketones	3 g - 800497 10 g - 800270 25 g - 800271 100 g - 800272 1000 g - 800317	182
MP-TsOH	Resin-bound Acid		Acid catalysis, scavenging and catch-and-release of amines	3 g - 800498 10 g - 800461 25 g - 800462 100 g - 800463 1000 g - 800464	183
MP-TsOH(65)	Resin-bound Acid		Scavenging and catch-and-release of amines, acid catalysis	3 g - 800499 10 g - 800478 100 g - 800480 125 g - 800479 1000 g -800481	185
MP-TsOH Cartridge	Resin-bound Acid		Catch-and-release amine purification, scavenging basic range of impurities, purification of compounds with basic sites	Available in a range of sizes from 100 mg - 2.5 g	183

PS-BENZALDEHYDE

PS-Benzaldehyde

Nucleophile Scavenger

Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 1.3 mmol/g, minimum capacity 1.1 mmol/g (based on nitrogen analysis of the 2,4 DNP derivative)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Polystyrene carboxaldehyde
Application: Scavenging nucleophiles including primary amines, hydrazines, reducing agents
Typical Scavenging Conditions: 3 equivalents relative to nucleophile, DCE, 1–16 h
Compatible Solvents: DCM (8.1 mL/g), DCE (7.4 mL/g), THF (7.3 mL/g), toluene (7.0 mL/g), and other solvents that swell gel-type polystyrene
Storage: Cool, dry location

PS-Benzaldehyde[1,2] is the resin-bound equivalent of benzaldehyde. This resin is useful for scavenging various nucleophiles, including primary amines (selectively compared with secondary amines), hydrazines, and carbon-based nucleophiles such as Meldrum's acid and organometallics. The capacity of the resin is typically about 1.2 mmol/g, based on uptake of phenylhydrazine. Scavenging reactions typically use 3 equivalents of resin per equivalent of substrate to be scavenged. Various solvents can be used, including DCE, DCM, and DMF with a temperature range from 20 to 50 °C. PS-Benzaldehyde is stable at room temperature with no loss of activity observed.

Representative Procedure

Phenylhydrazine Scavenging

PS-Benzaldehyde resin (3 equivalents) in DCE was allowed to react with phenylhydrazine (1 equivalent) in the presence of a catalytic amount of glacial HOAc. The reaction was monitored by TLC and was complete after stirring for approximately 1 h at room temperature. The reaction may also be run without HOAc by heating for 1 h at 50 °C.

Scavenging Various Substrates

PS-Benzaldehyde (3 equivalents) was added to a solution of the substrate in DCE along with a catalyst if necessary. The mixture was stirred for the specified time and temperature, and the filtrate was analyzed by TLC for disappearance of the substrate by comparison with standards.

Material Scavenged	Equiv	Solvent	Additive	Temp °C	% Scavenged*	Time (h)
Phenylmagnesium chloride	1.0	THF	None	20	100	0.5
p-Toluenesulfonylhydrazide	1.0	DCE	Acetic acid	50	100	2.0
Meldrum's acid	1.0	DCE or DMF	TEA	50	100	1.0
Phenylhydrazine	1.0	DCE or DMF	Acetic acid	20	100	1.0
Phenylhydrazine	1.0	DCE	None	50	100	1.0
Tryptamine	1.0	DCM	MeOH	20	100	18

Table 1. Comparative scavenging of nucleophiles with PS-Benzaldehyde

* Reactions were judged complete when substrate was no longer observable by TLC. Merck silica gel 60 F254 plates were used and detection was by short-wave UV or iodine. Scavenging of phenylmagnesium chloride was monitored by quenching an aliquot with benzophenone, followed by TLC analysis and comparison with an authentic tri-phenylmethanol sample.

Ordering Information

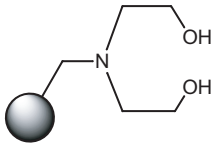
Part Number	Quantity
800502	3 g
800360	10 g
800361	25 g
800362	100 g
800363	1000 g

References

1. Kaldor, S. W.; Seigel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, 37, 7193.
2. Frechet, J.M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, 93, 492.

PS-DEAM

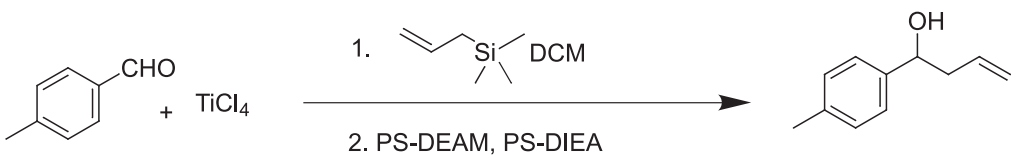
Metal Scavenger



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 1.8 mmol/g, minimum capacity 1.5 mmol/g (based on nitrogen analysis)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: N,N-Diethanolaminomethyl polystyrene
Application: Scavenging metal complexes, including boronic acids, titanium(IV) chloride, titanium(IV) isopropoxide, and tin(IV) chloride
Typical Boronic Acid Scavenging Conditions: 2–3 equivalents of PS-DEAM relative to boronic acid at room temperature for 4 h
Typical Titanium(IV) Chloride Scavenging Conditions: 4.5 equivalents each of PS-DEAM and PS-DIEA relative to $TiCl_4$ at room temperature for 4 h
Typical Titanium(IV) Isopropoxide Scavenging Conditions: 2 equivalents of PS-DEAM relative to $Ti(OiPr)_4$ at room temperature for 16 h
Compatible Solvents: THF (7.5 mL/g), DCM (4.0 mL/g), MeOH (3.0 mL/g), DMF (6.7 mL/g). PS-DEAM can also be used in THF-EtOH, THF-MeOH mixtures.
Storage: Storage in closed container at room temperature is recommended. Drying resin in a vacuum desiccator is recommended before use in titanium scavenging applications.

PS-DEAM is a polymer-supported diethanolamine, which is a resin-bound equivalent of the tridentate (N, O, O) N-alkyldiethanolamine ligand. PS-DEAM is an effective scavenger for a variety of organometallic and inorganic metal complexes. The resin can be used to quench reactions and remove metallic reagents, catalysts, or by-products, allowing the purified product to be isolated by filtration. Boronic acids are scavenged by PS-DEAM. This has been exploited in the purification of Suzuki reactions through the removal of excess boronic acid and coupling by-products.[1, 2]

PS-DEAM is also effective at removing common Lewis acids, including Ti(IV) and Sn(IV) complexes. PS-DEAM has been found to scavenge titanium(IV) chloride from Sakurai[3] and related reactions. Titanium(IV) chloride and its alkoxide derivatives are widely used as Lewis acid catalysts in a number of important organic reactions. Particularly noteworthy are 1,2 and 1,4 additions of allylsilanes to carbonyl and enone compounds (Sakurai reaction, Scheme 1), the Mukaiyama aldol reaction, and the Knoevenagel condensation. These reactions require an aqueous workup and filtration of TiO_2 precipitate. This can be problematic. We have found that a cocktail of PS-DEAM (4.5 equivalents) and PS-DIEA (4.5 equivalents) effectively quenches and removes titanium tetrachloride from Sakurai reactions, thereby eliminating the aqueous work-up step (Table 1, page 163). Purification by resin scavenging overcomes the problem of separating the gelatinous titanium hydroxide and oxide salts that are formed when aqueous workup is employed. By analogy, tin(IV) tetrachloride can also be removed from organic solutions by the PS-DEAM/PS-DIEA mixture. PS-DIEA should be used in conjunction with PS-DEAM in cases where coordination of diethanolamine with the metal results in the release of hydrogen halides or other acidic species.

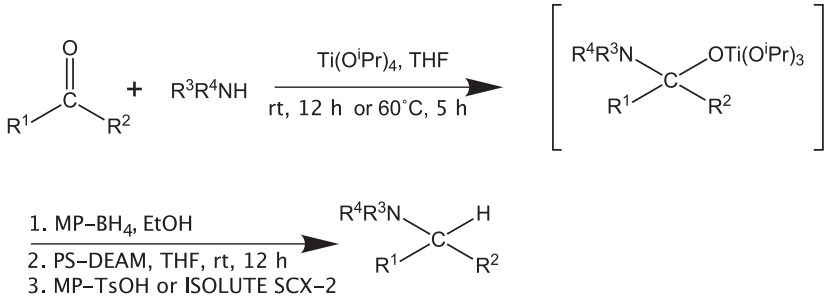


Scheme 1. Scavenging of $TiCl_4$ from 1,2 addition of allylsilane (Sakurai reaction)

PS-DEAM

The purification of titanium(IV) isopropoxide-mediated reductive amination reactions forms another important new application of PS-DEAM.[4] This methodology enables controlled reductive alkylation of primary amines to secondary amines and reductive amination of enolizable carbonyl compounds, acetophenones and sterically hindered carbonyl substrates. Moreover, the neutral reaction conditions are applicable to substrates containing acid-sensitive motifs.

The reaction workup for titanium isopropoxide-mediated reductive amination typically uses aqueous quenching to precipitate titanium as the gelatinous hydroxide and oxide solid, followed by filtration and liquid-liquid extraction. Purification of these reactions is simplified by using a polymer-supported reducing agent, MP-Borohydride,[5] in conjunction with PS-DEAM to scavenge titanium(IV) isopropoxide (Scheme 2).



Scheme 2. Scavenging of $Ti(OiPr)_4$ with PS-DEAM in Reductive Amination Reactions

This improved process was demonstrated for a series of reductive aminations using carbonyl compounds with a wide reactivity profile (Table 2, p 164). A 1:1 ratio of amine:carbonyl was used and the products were purified using PS-DEAM, followed by catch-and-release using MP-TsOH cartridges[6] or SCX cartridges.[7] The procedure afforded the desired secondary and tertiary amines in high purity and very good yield. In contrast to our results with MP-Cyanoborohydride, over-alkylation was suppressed when primary amines were reacted with the very reactive cyclohexane carboxaldehyde (Table 2 [p 164] entries 1 and 2). Notably, sterically hindered adamantyl methyl ketone was reactive with primary amines under these conditions (Table 2 [p 164] entries 7 and 8). A secondary amine, 1-methylpiperazine, underwent reductive amination with cyclohexane carboxaldehyde and cyclopentanone (Table 2 [p 164] entries 3 and 6). It was, however, not reactive with adamantyl methyl ketone. Reactions with 4-(3-aminopropyl)morpholine did not proceed to complete conversion and scavenging traces of unreacted 4-(3-aminopropyl)morpholine with PS-Benzaldehyde was required (Table 2 [p 164] entries 2, 5, 8). Product amines had titanium levels that were less than the detection limit of 10 ppm, and boron levels were ≤ 20 ppm as measured by elemental analysis.

PS-DEAM is hygroscopic and water present in the resin can cause precipitation of titanium(IV) oxide when used for scavenging titanium(IV) complexes. It is recommended that the resin be dried under vacuum or in a drying oven (to constant weight) before use in these applications. Once dried, the resin can be stored in a closed container.

Capacity and Stability

The capacity of the resin was calculated from nitrogen elemental analysis. The resin is stable indefinitely at room temperature in a closed container.

Representative Procedure

Scavenging of Titanium(IV) Chloride from Sakurai Reactions (Table 1, Entry 2)

To a solution of cyclohexane carboxaldehyde (56 mg, 0.50 mmol) in DCM (2 mL) was added a solution of titanium(IV) chloride (95 mg, 0.50 mmol) in DCM (2 mL) at room temperature with magnetic stirring under an atmosphere of nitrogen. The mixture was stirred for 5 min and a solution of allyltrimethylsilane (57 mg, 0.60 mmol) in DCM (2 mL) was added. After the resulting mixture was stirred for 10 min, PS-DEAM (1.26 g, 1.75 mmol/g, 2.2 mmol), PS-DIEA (0.6 g, 3.7 mmol/g, 2.2 mmol), and DCM (12 mL) were added and the mixture was agitated for 5 h to quench the reaction and scavenge titanium(IV) chloride. The resin was filtered and washed with DCM (10 mL x 2). The combined solution was passed through a short silica gel plug (0.5 g) and the filtrate was concentrated to obtain an oily residue. ^{1}H NMR analysis of the crude product indicated that it was an 80:20 mixture of the product homo-allylic alcohol and the starting aldehyde. A portion of the filtrate (2 mL) was treated with aqueous NaOH (1 M, 1 mL); no white precipitation was observed, indicating complete scavenging of titanium(IV) chloride.

Scavenging of Titanium(IV) Isopropoxide from Reductive Amination Reactions (Table 2, Entry 4)

A mixture of cyclopentanone (42 mg, 0.50 mmol), titanium(IV) isopropoxide (170 mg, 0.60 mmol), and 2-(aminomethyl)pyridine (54 mg, 0.50 mmol) in dry THF (3 mL) was allowed to stir at room temperature for 16 h (alternatively at 60 °C for 5 h). MP-Borohydride (410 mg, 3.0 mmol/g, 1.2 mmol) and dry EtOH (3 mL) were then added and the resulting mixture was stirred at room temperature for 8 h. PS-DEAM (1.2 mmol) and THF (4 mL) were added to scavenge titanium(IV) isopropoxide, and the mixture was agitated for 12 h and passed through a pre-conditioned (DCM) 0.7 g MP-TsOH cartridge.[6] The flow rate was adjusted to 1 mL/min and maintained at this rate for all subsequent elution steps. The cartridge was washed with DCM (15 mL) and the eluent discarded. The product amine was released using 2 M NH_3-MeOH (4 mL) followed by DCM (15 mL). Alternatively, an ISOLUTE SCX-2 cartridge[7] was used in place of the MP-TsOH cartridge. Concentration of the collected solution afforded the product amine. In cases where an excess of starting amine is still present, PS-Benzaldehyde[8] (for primary amines) or PS-Isocyanate[9] (for secondary amines) may be used as scavengers for purification in a subsequent step.

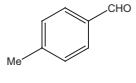
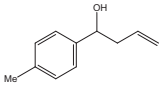
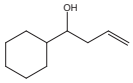
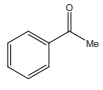
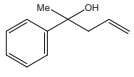
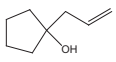
Entry	Carbonyl Compound	Product Alcohol	$TiCl_4$ mmol	PS-DEAM mmol	PS-DIEA mmol	% $TiCl_4$ Scavenged
1			0.5	2.2	2.2	100
2			0.5	2.2	2.2	100
3			0.5	2.2	2.2	100
4			0.5	2.2	2.2	100

Table 1. Scavenging of titanium(IV) chloride with PS-DEAM and PS-DIEA from titanium(IV) chloride-mediated 1,2 addition of trimethylallylsilane to carbonyl compounds.

PS-DEAM

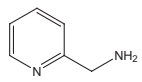
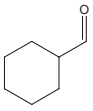
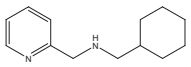
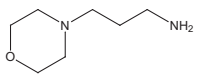
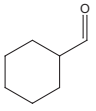
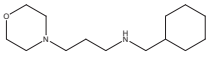
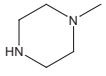
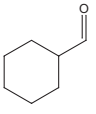
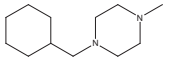
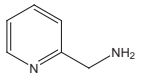
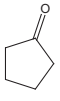
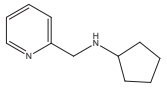
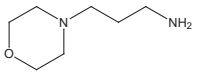
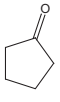
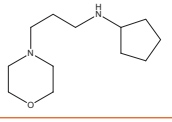
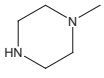
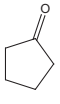
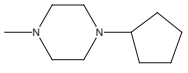
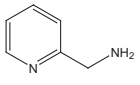
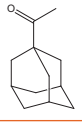
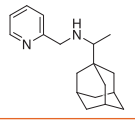
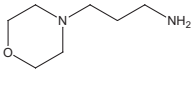
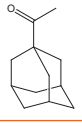
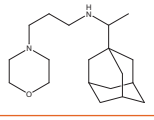
Entry	Starting Amine	Carbonyl Compound	Product Amine	Yield %	Purity GC %
1				95	93 mono 2 di-
2				90	99 mono 1 di-
3				97	100
4				89	100
5				60	100
6				95	100
7				86	94*
8				89	90*

Table 2. Reductive amination results using titanium(IV) isopropoxide and MP-Borohydride in conjunction with PS-DEAM purification
*The only impurity present was the starting carbonyl compound

Ordering Information

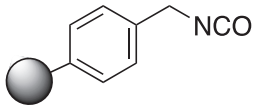
Part Number	Quantity
800515	3 g
800430	10 g
800431	25 g
800432	100 g
800433	1000 g

References

1. Bolton, G. L.; Booth, R. J.; Cresswell, M. W.; Hodges, J. C.; Warmus, J. S.; Wilson, M. W.; Kennedy, R. M. WO 97/42230 (**1997**).
2. Hall, D. G.; Tailor, J.; Gravel, M. *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 3064.
3. Sakurai, H. *Pure Appl. Chem.* **1982**, 54, 1.
4. Bhattacharyya, S. *J. Org. Chem.* **1995**, 60, 4928; Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans 1*, **1998**, 2527; Bhattacharyya, S.; Fan, L.; Vo, L.; Labadie, *J. Combinatorial Chemistry and High Throughput Screening* **2000**, 3, 117.
5. Part Numbers: 800401, 10 g; 800402, 25 g; 800403, 100 g.
6. The MP-TsOH column was prepared by adding 0.7 g of resin to a 6 mL ISOLUTE filtration column (Part Number 120-1113-C), fitted with a universal PTFE stopcock. Alternatively, MP-TsOH cartridges (Part Number 800477-0050-C) can be used.
7. ISOLUTE SCX-2, Part Number 532-0050-C
8. Part Numbers: 800502, 3 g; 800360, 10 g; 800361, 25 g; 800362, 100 g; 800363, 1000 g.
9. Part Numbers: 800495, 3 g; 800260, 10 g; 800261, 25 g; 800262, 100 g; 800311, 1000 g.

PS-Isocyanate

Nucleophile Scavenger



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 1.4 mmol/g, minimum capacity 1.1 mmol/g (based on benzylamine uptake)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Polystyrene methylisocyanate
Application: Scavenging nucleophiles, including amines and alkoxides
Typical Scavenging Conditions: 2–3 equivalents relative to nucleophile, 1–16 h, 20 °C
Compatible Solvents: DCM (9.5 mL/g), DCE (7.2 mL/g), THF (8.2 mL/g), toluene (7.8 mL/g)
Storage: Cool, dry location

PS-Isocyanate is a 1% cross-linked poly(styrene-co-divinylbenzene) which has pendent benzylisocyanate functionality. The resin is produced from aminomethyl resin by a superior process which gives high conversion with minimal urea formation as determined by IR spectroscopy (Figure 2). The resin can readily scavenge excess nucleophiles, which are often used to drive reactions to completion. This facilitates workup and purification.[1-5] The reaction of nucleophiles with the isocyanate moiety occurs without liberation of small molecule by-products.

Removal of nucleophiles from solution generally requires 2–3 equivalents of PS-Isocyanate depending on substrate reactivity. Comparative scavenging of amines (0.2–0.05 M) of varying reactivity was tested as a function of time and temperature (Table 1, p 166). Typical aliphatic amines are completely sequestered by three equivalents of PS-Isocyanate within 1 h. Three equivalents of PS-Isocyanate sequestered 100% aniline at room temperature over 16 h. A less reactive aromatic amine, 2-aminobenzophenone, was not completely sequestered even at elevated temperatures. The use of DIEA as a catalyst did not improve the scavenging efficiency of PS-Isocyanate towards aromatic amines. Alcohols were not reactive towards PS-Isocyanate at room temperature, suggesting that aliphatic amines can be selectively sequestered in the presence of alcohol functionality. More nucleophilic alcohols may be removed at elevated temperatures.

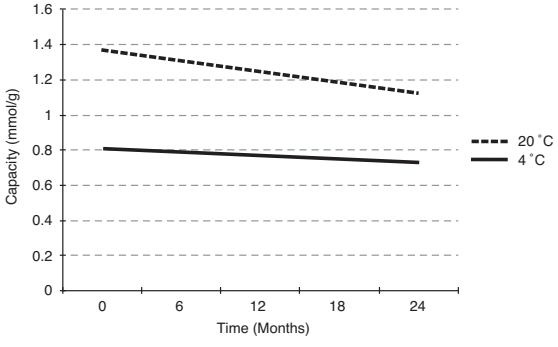


Figure 1. PS-Isocyanate stability at 4 and 20 °C

Upon completion of the scavenging, the product is washed away from the resin with a suitable solvent. Suitable solvents include those which dissolve the product and swell polystyrene but are not nucleophilic enough to react with the resin. DCM, dichloroethane, THF, and toluene are all good choices with DCM being preferred.

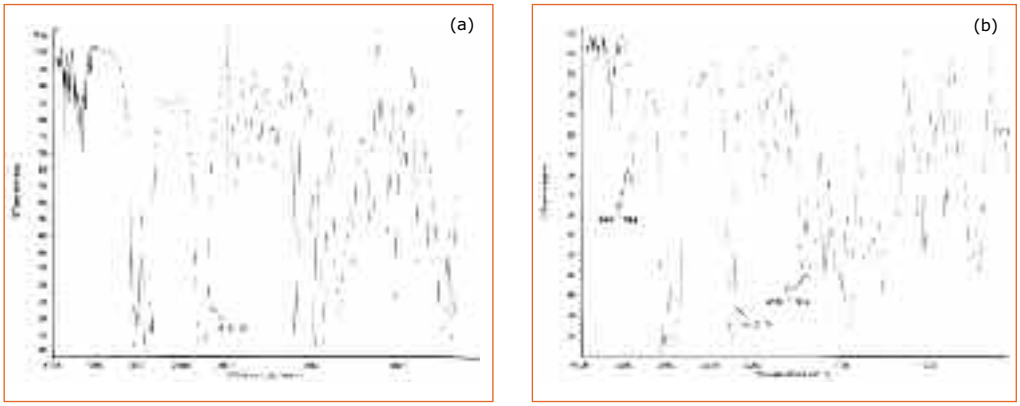
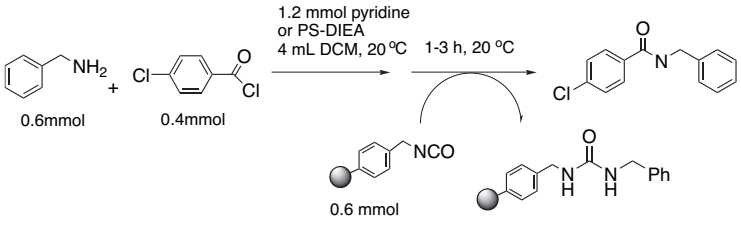


Figure 2. FT-IR Spectra of (a) PS-Isocyanate, 1.2 mmol/g; (b) polystyrene methylisocyanate, 0.9 mmol/g, prepared by the procedure described in reference 4.

PS-Isocyanate

PS-Isocyanate was tested in an amide bond-forming application where 4-chlorobenzoyl chloride was allowed to react with excess benzylamine in the presence of PS-DIEA resin as the base (Scheme 1 and Table 2). Upon completion of the reaction, the excess benzylamine was scavenged using three equivalents of PS-Isocyanate resin. The product was then isolated by rinsing it from the resin followed by concentration. The yields were determined gravimetrically and the purities by GC. PS-Isocyanate was also used to sequester excess secondary amines in the preparation of tertiary amines using PS-TsCl (see PS-TsCl product information on page 178).



Scheme 1. Amide synthesis followed by scavenging excess amide

Nucleophile Scavenged	PS-Isocyanate (equivalent)	Temp (˚C)	% Scavenged 1 h	16 h
Piperidine	3.0	20	100	-
Benzyl amine	3.0	20	100	-
Aniline	3.0	20	-	100
Aniline	3.0	60[a]	92	100
2-Aminobenzophenone	3.0	60[a]	-	81

Table 1. Comparative scavenging of nucleophiles in dichloromethane
[a]Dichloroethane solvent

Base	Scavenging Time	% Yield	% Purity
PS-DIEA	1 hr	87	97
PS-DIEA	3 hrs	87	95

Table 2. Amide synthesis

Representative Procedure

Amide Formation

4-chlorobenzoyl chloride was allowed to react for 1 h with 1.5 equivalent of benzylamine in DCM with 3 equivalents of PS-DIEA resin as the base.

Excess benzylamine was scavenged by adding PS-Isocyanate resin (3 equivalents relative to excess amine). Beads were removed by filtration, washed two times with DCM and the combined filtrate was concentrated to afford the benzyl 4-chlorobenzamide as the sole product in 87% yield.

Ordering Information

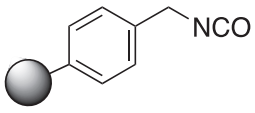
Part Number	Quantity
800495	3 g
800260	10 g
800261	25 g
800262	100 g
800311	1000 g

References

1. Rebek, J.; Brown, D.; Zimmerman, S. *J. Am.Chem. Soc.* **1975**, 97, 4407.
2. Kaldor, S. W.; Seigel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, 37, 7193.
3. Kaldor, S. W.; Fritz, J. E.; Tang, J.; McKenney, E. R. *Bioorg. Med. Chem. Lett.* **1996**, 6, 3041.
4. Booth, J. R.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, 119, 4882.
5. Creswell, M. W.; Bolton, G. L.; Hodges, J. C.; Meppea, M. *Tetrahedron* **1998**, 54, 3983.

MP-Isocyanate

Macroporous Nucleophile Scavenger



Chemical Name: Polystyrene methyl isocyanate
Resin Type: Highly cross-linked macroporous poly(styrene-co-divinylbenzene)
Capacity: 0.9-1.3 mmol/g (based on benzyl amine uptake)
Bead Size: 150-355 microns; 45-100 mesh (>90% within)
Application: Scavenging nucleophiles, including amines and alkoxides
Typical Scavenging Conditions: 2-3 equivalents relative to nucleophile, 1-16 h, 20 °C
Compatible Solvents: Non-acidic organic solvents and water
Swelling: 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)
Storage: Cool, dry location

MP-Isocyanate is a macroporous polystyrene-bound scavenger, for nucleophiles such as amines and alkoxides. Resin-bound scavengers are added after a reaction is complete in order to quench and react selectively with excess reactants and/or reaction by-products. The resulting resin-bound reactants are removed by simple filtration.

Biotage supplies two isocyanate scavenger resins: PS-Isocyanate and MP-Isocyanate. The resin backbone in PS-Isocyanate consists of 1% crosslinked polystyrene-co-divinylbenzene. Nucleophiles to be scavenged gain access to the isocyanate sites by diffusion through the polystyrene gel. The MP-base copolymer is a highly crosslinked a robust and low-swelling material, which makes it ideal for restricted volume environments (e.g. microwave vials and 96-well plates etc.). Its unique pore structure provides greater access to the reactive sites without the need for solvent swelling, resulting in faster reactions and higher recoveries. The abrasion-resistant matrix has better handling characteristics and reduced transfer losses.

I. Scavenging Amines using MP-Isocyanate and PS-Isocyanate in 1,2-Dichloroethane

This study compares the ability of PS-Isocyanate and MP-Isocyanate to scavenge four amines from solution in DCE. Three equivalents of scavenger were used relative to the amine.

At ambient temperature, the scavenging rates correlated directly with amine nucleophilicity (Table 1). Both resins were able to scavenge piperidine and benzylamine from solution within 1 h. Scavenging of aniline took place more slowly, reaching only 60-63% completion within 1 h. At 60 °C, PS-Isocyanate scavenged aniline to 92% completion, while MP-Isocyanate removed it completely from solution within 1 h. Scavenging of the highly hindered 2-aminobenzophenone was slow with both scavengers, even at 60 °C.

Electrophile	Temp (°C)	Resin	% Scavenged in 1h	% Scavenged in 3.3 h	% Scavenged in 18 h
Piperidine	RT	PS-Isocyanate	100	100	-
		MP-Isocyanate	100	100	-
Benzylamine	RT	PS-Isocyanate	100	100	-
		MP-Isocyanate	100	100	-
Aniline	RT	PS-Isocyanate	60	91	91
		MP-Isocyanate	63	85	100
Aniline	60 °C	PS-Isocyanate	92	-	100
		MP-Isocyanate	100	-	100
2-Aminobenzophenone	RT	PS-Isocyanate	13	30	83
		MP-Isocyanate	34	57	90
2-Aminobenzophenone	60 °C	PS-Isocyanate	13	-	77
		MP-Isocyanate	39	-	90

Table 1. Comparative scavenging of amines by PS-Isocyanate and MP-Isocyanate in 1,2-dichloroethane.

MP-Isocyanate

II. The Effect of Different Solvents on Scavenging by MP-Isocyanate and PS-Isocyanate

Scavenging in THF, which swells 1% cross-linked polystyrene, was compared with scavenging in acetonitrile and methyl tert-butyl ether (MTBE). Acetonitrile and MTBE are poor solvents for swelling 1% cross-linked polystyrene. MTBE was chosen as a method for other ethereal solvents commonly employed in organic synthesis.

Scavenging rates for both scavengers followed the order THF > Acetonitrile > MeOH > MTBE (Table 2). Benzyl amine was scavenged rapidly in THF reaching 93% and 98% completion within 2 h with PS-Isocyanate and MP-Isocyanate, respectively. MP-Isocyanate scavenged more rapidly and more completely in the three other solvents, demonstrating it to be the scavenger of choice in solvents that do not swell 1% cross linked polystyrene.

Reducing the amount of scavenger from 3.5 equivalents to 2 equivalents reduced the amount of benzyl amine scavenged within the given time. We recommend the use of 3.5 equivalents for complete scavenging.

Solvent	Time (h)	PS-Isocyanate % Scavenged	MP-Isocyanate % Scavenged
THF	2	93	98
	5.5	96	100
	20	97	100
THF[a]	2	-	79
	5.5	-	82
	20	-	88
Acetonitrile	1	69	100
	4	91	-
MTBE	1	0	84
	4	0	100
	20	0	-
MeOH	2	-	66
	5.5	8	75
	20	20	78
MeOH[a]	2	-	-
	5.5	-	46
	20	-	53

Table 2. Scavenging benzylamine by 3.5 equivalents of PS-Isocyanate or MP-Isocyanate in various solvents at ambient temperature in different solvents at room temperature. 2.0 equivalent of resin was used in these reactions

Summary

In comparison with PS-Isocyanate, MP-Isocyanate offers the following benefits:

- Scavenges effectively in solvents that do not swell 1% cross-linked polystyrene
- Limited swelling, so can be used where volume is restricted (e.g. 96 well plates, microwave vials)
- Faster scavenging rate than PS-Isocyanate
- For certain substrates MP-Isocyanate offers more complete scavenging than does PS-Isocyanate

Ordering Information

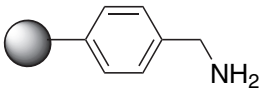
Part Number	Quantity
801504	3 g
801409	10 g
801410	25 g
801411	100 g
801412	1000 g

References

1. Booth, R. J., Hodges, J. C. *J. Am. Chem. Soc.* **1997**, 119, 4882
2. Gooding, O., Labadie, J.; Porco, J. *J. Comb. Chem.* **1999**, 1, 420-422

PS-NH_2

Electrophile Scavenger



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 1.6 mmol/g, minimum capacity 1.3 mmol/g (determined by coupling of Fmoc-Gly, followed by UV quantification of Fmoc chromophore)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Aminomethyl polystyrene
Application: Scavenging acid chlorides, sulfonyl chlorides, isocyanates, and other electrophiles
Typical Scavenging Conditions: 3–6 equivalents relative to acid chloride, 1–4 h, 20 °C. If an additional resin-bound base is present, only 1.5–3 equivalents required.
Compatible Solvents: DCM (9.1 mL/g), THF (7.7 mL/g), DMF (6.5 mL/g)
Storage: Cool, dry location

PS-NH_2 is useful as a scavenger for electrophiles, including acid chlorides, sulfonyl chlorides, and isocyanates.[1]

Ordering Information

Part Number	Quantity
800491	3 g
800263	10 g
800264	25 g
800265	100 g
800307	1000 g

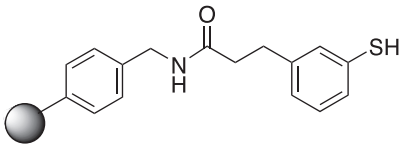
References

1. Kaldor, S. W.; et.al *Tetrahedron Lett.* **1996**, 37, 7193.

PS-THIOPHENOL

PS-Thiophenol

Electrophile Scavenger



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 1.5 mmol/g, minimum capacity 1.3 mmol/g (based on benzyl bromide uptake)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: 3-(3-mercaptophenyl)propanamidomethylpolystyrene
Application: Scavenging alkylating agents
Typical Scavenging Conditions: 2–3 equivalents relative to electrophile, 20 °C, DMF or THF:EtOH (1:1), 1–16 h. Scavenging requires conversion to the thiophenolate with potassium trimethylsilanolate (TMSOK) or use in conjunction with DIEA (DIEA, 2 equivalents) and MP-Carbonate (2 equivalents). The EtOH is added for the scavenging process and may provide benefits in solvents other than THF.
Compatible Solvents: DMF (7.0 mL/g), THF (7.0 mL/g), DCM (7.0 mL/g)

PS-Thiophenol is based on an aminomethyl resin with a tethered thiophenol functionality. The resin was designed for the scavenging of alkylating agents, e.g. alkyl halides. PS-Thiophenol was tested and found effective in scavenging alkylating agents ranging from octyl bromide to benzyl bromide. The scavenging effectiveness of PS-Thiophenol was found to be greater than a polymer-bound benzyl thiol towards octyl bromide, indicative of the higher nucleophilicity of the thiophenolate.

Effective scavenging of active halides requires the use of either the potassium thiolate salt (formed with potassium trimethylsilanolate) or the presence of DIEA and MP-Carbonate. The solvent used for the scavenging reaction is critical for good scavenging rates. Both 1:1 THF/EtOH mixtures and DMF were found to be effective solvents for the scavenging reaction. Scavenging in pure THF has been observed to be inefficient. Ethanol should be added to reactions performed in pure THF prior to scavenging excess alkyl halides with PS-Thiophenol. Addition of ethanol may also be necessary to accelerate scavenging in other solvents.

In the case of potassium trimethylsilanolate (TMSOK), two equivalent of base are incubated with the resin for 30 min in THF. The resin is then rinsed three times with THF to remove excess base. This can be carried out individually or in bulk and distributed. One equivalent of base can be used relative to PS-Thiophenol, which circumvents the need to post-wash the resin since the hexamethylsiloxane formed is volatile. However, a slight increase in the equivalent of resin used may be required for the scavenging step. Alternatively, DIEA (2 equivalents) can be added to PS-Thiophenol in the presence of MP-Carbonate (2 equivalents). The DIEA acts as a base and reacts with the hydrogen halide generated during thioether formation, and the amine hydrohalide formed is subsequently neutralized by the carbonate resin. Ultimate removal of the DIEA is performed by evaporation.

Alkylating Agent	PS-Thiophenol (equivalents)	Base	% Scavenged in DMF[a]		% Scavenged in THF:EtOH[b]	
			1 h	16 h	1 h	16 h
Benzyl Bromide	1.90	TMSOK	–	93	100	–
Benzyl Bromide	2.34	DIEA/MP-Carbonate[2]	–	–	92	100
Cinnamyl Cloride	2.25	TMSOK	100	–	100	–
Cinnamyl Cloride	2.18	DIEA/MP-Carbonate[2]	–	100	–	–
Octyl Bromide	1.87	TMSOK	–	92	79	100
Octyl Bromide	1.89	DIEA/MP-Carbonate[2]	–	86	–	–

Table 1. Scavenging of alkylating agents with PS-Thiophenol
[a] Conditions affording >80% scavenging can typically be driven to completion with additional 1–2 equiv of resin.
[b] Two equiv of DIEA and MP-Carbonate relative to PS-Thiophenol.

The scope of scavenging efficiency of PS-Thiophenol was tested for a set of electrophiles ranging in reactivity from octyl to benzyl bromide using both the TMSOK and DIEA/MP-Carbonate methods, and is given in Table 1. PS-Thiophenol was effectively used as a scavenger in Williamson ether synthesis as shown in Scheme 1. High yields and purities were achieved using either the TMSOK or DIEA/MP-Carbonate scavenging method.

Representative Procedure

Scavenging Excess Electrophiles from Williamson Ether Synthesis

Reaction: To a 0.2 M solution of phenol (57 mg, 0.60 mmol) in THF was added 0.41 mL of 1.61 M potassium t-butoxide (0.66 mmol). After 0.5 h, 0.11 mL of benzyl bromide (1.5 equivalent, 0.90 mmol) was added and the solution was heated at 65 °C with stirring for 5 h.

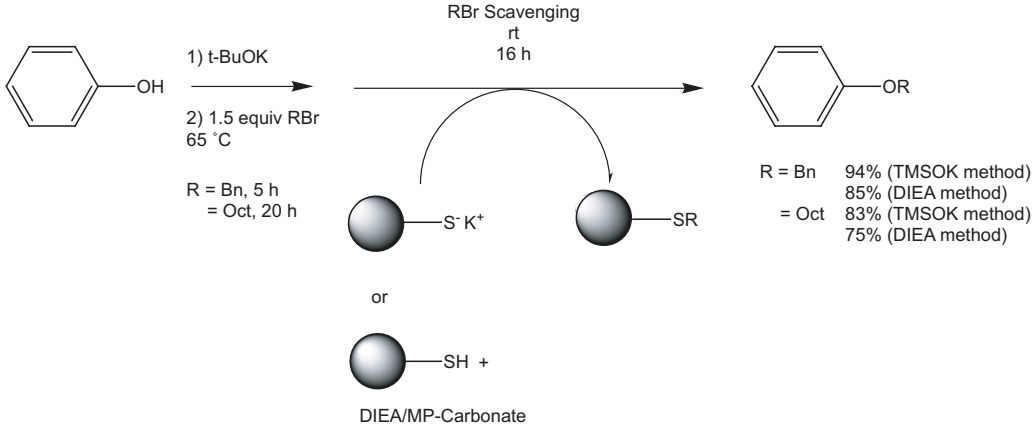
Reaction Work-up

Method A. TMSOK

PS-Thiophenol (692 mg, 0.87 mmol/g, 0.60 mmol, 2 equivalents) was treated with 7 mL of a deoxygenated 0.17 M TMSOK solution (154 mg, 1.20 mmol, 2 equivalents) in THF:EtOH (1:1) and allowed to react for 30 min. The solution was removed by filtration and the resin was washed three times with THF:EtOH (deoxygenated). The reaction mixture was added to the prepared bed of PS-Thiophenol, 3 mL of ethanol was added, and the mixture was stirred overnight. The solution was filtered through Celite and the beads were washed two times with THF:EtOH. The phenyl benzyl ether product was isolated in 94% yield after concentration.

Method B. DIEA/MP-Carbonate

The reaction solution was added to a mixture of 692 mg of PS-Thiophenol, 0.4 g of MP-Carbonate (2 equivalents), 3 mL of ethanol, and 0.210 mL of DIEA. After agitation for 16 h the phenyl benzyl ether product was isolated by analogy to Method A in 85% yield (depending on the product structure up to five times wash of the resin is employed with MP-Carbonate). An analogous procedure applied to a synthesis using octyl bromide as the electrophile required a 20 h reaction time and 4 equivalents of PS-Thiophenol to afford phenyl octyl ether in 83 and 75% yield by Method A and B, respectively.



Scheme 1. Scavenging alkylating agents with PS-Thiophenol after Willamson ether synthesis

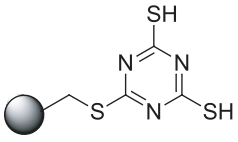
Ordering Information

Part Number	Quantity
800500	3 g
800273	10 g
800274	25 g
800275	100 g
800310	1000 g

MP-TMT

MP-TMT

Palladium Scavenger



Chemical Name: Macroporous polystyrene-2,4,6-trimercaptotriazine
Resin Type: Highly cross-linked macroporous poly(styrene-co-divinylbenzene)
Capacity: > 0.5 mmol/g (elemental nitrogen analysis)
Bead Size: 150-355 microns; 45-100 mesh (>90% within)
Application: Scavenging palladium from aqueous and nonaqueous solutions
Typical Scavenging Conditions: 5 equivalents Argoresin MP-TMT relative to palladium content, 16-24 h, room temperature
Compatible Solvents: THF (4.3 mL/g), dichloromethane (DCM) (3.8 mL/g), toluene (<4.9 mL/g), acetonitrile (ACN)(<4.6 mL/g), methanol (MeOH) (4.3 mL/g), water (3.7 mL/g)
Storage: Cool, dry location

MP-TMT is a macroporous polystyrene-bound trimercaptotriazine, a resin-bound equivalent of 2,4,6-trimercaptotriazine (TMT). The resin is designed to scavenge residual palladium from products derived from palladium-catalyzed reactions. The Argoresin MP-base copolymer has been re-designed to yield a more robust, low-swelling material, which makes it ideal for restricted volume environments (e.g. microwave vials and 96-well plates etc.). Its unique pore structure provides greater access to the reactive sites resulting in faster reactions and higher recoveries. The abrasion-resistant matrix has better handling characteristics and reduced transfer losses.

MP-TMT has been found to be highly effective in reducing the concentration of palladium in both aqueous and non-aqueous solutions. After treatment with Argoresin MP-TMT, the product is isolated by filtration of the solution followed by solvent removal.

Palladium-catalyzed reactions are widely practiced in organic synthesis.[1] A few important examples include Suzuki-type cross coupling reactions, Heck reaction, Buchwald amination, Wacker-type oxidation, hydrogenation, allylation, and indole formation. Despite the widespread use of palladium-mediated reactions, removal of residual palladium during workup and product isolation remains a major problem. Reducing the palladium content to the low parts per million (ppm) levels, as is required for active pharmaceutical ingredients, is particularly challenging.[2]

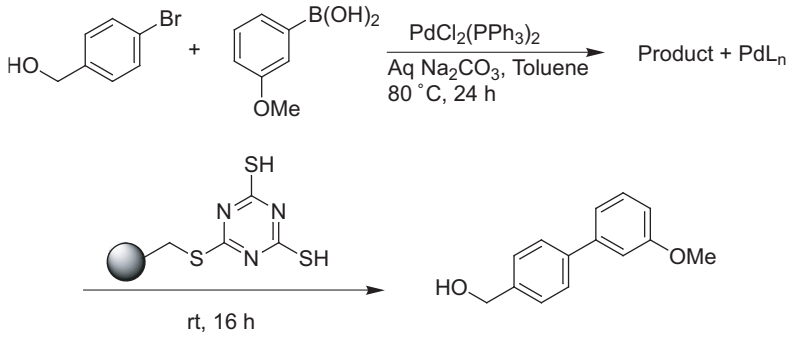
The small molecule 2,4,6-trimercaptotriazine has been used effectively to bind and precipitate palladium and other heavy metals from solution.[3] For example, palladium levels in an advanced pharmaceutical intermediate were reduced from approximately 625 ppm to approximately 40 ppm by employing a precipitation/filtration process. Unfortunately, the solubility of TMT–palladium complexes in polar organic solvents limits the effectiveness and generality of this approach. To address the solubility issue, a polymer-bound version of TMT was prepared by covalently attaching TMT to an insoluble gel-type polystyrene support.[4] This resin was demonstrated to effectively reduce palladium(II) acetate concentration in THF solution by a factor 1000.[5]

MP-TMT resin has a TMT loading >0.5 mmol/g. The base resin is a highly cross-linked macroporous polystyrene. This means that Argoresin MP-TMT is effective in both organic and aqueous solvents and is not dependent on solvent swelling. Typical conditions for palladium scavenging require 5 equivalents of resin relative to the palladium content for a period of 16–24 h (Table 1). Scavenging has been demonstrated in THF, dichloroethane (DCE), toluene, and acetonitrile (ACN).

MP-TMT (equivalents)	Pd Scavenged (%)
10	96
5	98
2	96
1.1	79

Table 1. Scavenging of $PdCl_2(PPh_3)_2$ from THF solution with various equivalents of MP-TMT[a]
[a] Initial Pd concentration = 0.0045. M, reaction time was 25 h at 20 °C.

In a practical application, the scavenging of palladium from the product of a Suzuki reaction was investigated (Scheme 1). After completing the reaction and work-up in a standard fashion, the resulting solution containing product and residual palladium was split into two portions. One portion was simply concentrated, while a second was treated with MP-TMT (5 equivalents) for 18 h prior to filtration and concentration. The untreated sample had a palladium content of 3.34% by weight while, in the MP-TMT-treated sample, the palladium content had been reduced to < 190 ppm.



Scheme 1. Palladium scavenging after Suzuki reaction using MP-TMT

Resin Handling

The resin may be weighed out on the bench using regular weighing methods. Given its uniform density, the resin may also be dispensed by automated filling devices or manual dispensing systems such as the ArgoScoop® calibrated resin dispenser (Part Number 300427). Static electric charge may make handling difficult in dry conditions. This effect is minimized by avoiding plastic weighing tools.

MP-TMT

Representative Procedure

Scavenging of Palladium from Suzuki Coupling Reaction Catalyzed by $PdCl_2(PPh_3)_2$

A mixture of 1-bromo-4-hydroxymethylbenzene (1.26 g, 6.7 mmol), 3-methoxyphenyl boronic acid (1.11 g, 7.3 mmol) and $PdCl_2(PPh_3)_2$ (0.5 g, 0.71 mmol) in toluene (110 mL), and aqueous Na_2CO_3 (6.7 mL, 0.5 M) was stirred at 80 °C for 24 h under an inert atmosphere. The mixture was cooled to room temperature and washed with brine (2 x 50 mL). The organic solution was dried over $MgSO_4$, and filtered through a small plug of celite yielding a yellow-orange solution. A portion of this solution was concentrated and found to contain 3.34% palladium by weight as determined by ICP analysis.[6] If necessary, excess boronic acid may be scavenged using PS-DEAM.[7] A portion of the above filtrate (15 mL) was transferred to an empty cartridge body with a 20-µm frit, a stopcock, and a cap.[8] It was treated with MP-TMT (0.6 g, 0.48 mmol, 5 equivalents relative to starting Pd) and agitated at room temperature for 18 h on an orbital mixer. The solution was filtered away from the resin and the resin was washed with toluene (2 x 10 mL). The combined filtrates were evaporated to give a light yellow oil. The residual palladium level in the product was determined to be < 190 ppm.[7]

Ordering Information

Part Number	Quantity
801506	3 g
801469	10 g
801470	25 g
801471	100 g
801472	1000 g

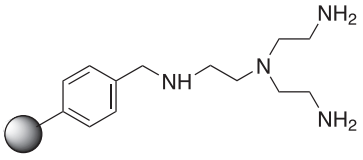
References

1. See, for example: Rylander, P. N. *Hydrogenation methods*; Academic Press: New York, **1985**; Hegedus, L. S. In *Comprehensive Organic Synthesis*, Trost. B. M.; Fleming, I. Eds; Pergamon, New York, **1991**,Vol 4, p. 551; *Handbook of Reagents for Organic Synthesis: Reagents,Auxiliaries and Catalysts for C-C Bond Formation*, Coates, R. M.; Denmark, S. E. Eds; Wiley, New York, **1999**.
2. Chen, C; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, 68, 2633.
3. Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res & Dev.* **1997**, 1, 311.
4. Ishihara, K.; Nakayama, M.; Kurihara, H.; Itoh, A.; Haraguchi, H. *Chem Lett.* **2000**, 1218.
5. Palladium(II) acetate concentration was reduced from 47 ppm to 45 ppb upon a single treatment.
6. Quantitative inductively coupled plasma (ICP) analysis was conducted by Galbraith Laboratories, Knoxville, TN.
7. Please refer to Technical Note: PS-DEAM.
8. Parts needed include: ISOLUTE® empty reservoirs (Part Number 120-113-C), universal stopcocks (Part Number 121-0009), and column caps (Part Number 1201-0123-C).

PS-Trisamine

PS-Trisamine

Electrophile Scavenger



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 3.8 mmol/g, minimum capacity 3.4 mmol/g (based on benzoyl chloride uptake)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Tris-(2-aminoethyl)aminomethyl polystyrene
Application: Scavenging acid chlorides, sulfonyl chlorides, isocyanates, and other electrophiles
Typical Scavenging Conditions: 3–6 equivalents relative to acid chloride, 1–4 h, 20 °C. If an additional resin-bound base is present: 1.5–3 equivalents
Compatible Solvents: DCM (7 mL/g), THF (6 mL/g), DMF (5.2 mL/g)

PS-Trisamine is an amine functional resin for the removal of excess electrophilic reagents during the quenching and purification of reaction mixtures.[1] PS-Trisamine resin has a scavenging capacity of 3.0–4.0 mmol/g based on reaction with an excess of benzoyl chloride. Scavenging of common electrophiles typically requires 3–6 equivalents of PS-Trisamine and occurs within 0.5–3 h at room temperature. The scope of PS-Trisamine as a scavenger for electrophilic reagents was investigated using 4-chlorobenzoyl chloride, 2-phenylbutyryl chloride, and 2,6-dimethoxybenzoyl chloride as a series of acid chlorides with decreasing reactivity. Acid chlorides were completely scavenged in 0.5 h using 3.5 equivalents PS-Trisamine (Table 1). The presence of a tertiary base (e.g. PS-DIEA or PS-NMM) reduces the amount of PS-Trisamine required in the reaction by removing the hydrogen chloride formed. In addition to acid chlorides, benzenesulfonyl chloride and 4-methoxyphenyl isocyanate were effectively scavenged in 0.5 h.

Representative Procedure

Acid Chloride Scavenging After Amide Synthesis

The application of PS-Trisamine for amide synthesis was tested by reacting an acid chloride (1.5 equivalents, 0.60 mmol) with benzylamine (44 µL, 0.40 mmol) in the presence of pyridine (97 µL, 1.2 mmol) in 2 mL of DCM for 1 h at RT. At the end of the reaction, 3.5 equivalents of PS-Trisamine, relative to excess acid chloride, was added to the reaction mixture, which was then agitated for 3 h. The resin was removed by filtration and washed three times with DCM. The filtrate was concentrated to afford the desired amide. This procedure was used to prepare benzyl 2,6-dimethoxybenzamide as the sole product in 97% yield.

Electrophile	PS-Trisamine (equivalent)*	% Scavenged
4-Chlorobenzoyl chloride	3.5	100
2-Phenylbutyryl chloride	3.5	100
2,6-Dimethoxybenzoyl chloride	3.5	100
4-Methoxyphenyl isocyanate	2	100
Benzenesulfonyl chloride	4	100

*Relative to electrophile, no additional base present

Ordering Information

Part Number	Quantity
800501	3 g
800228	10 g
800229	25 g
800230	100 g
800309	1000 g

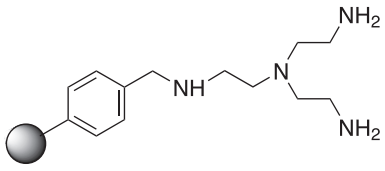
References

1. Booth, R. J.; Hodge, J. C. J. *Am. Chem. Soc.* **1997**, 119, 4882.

MP-TRISAMINE

MP-Trisamine

Electrophile Scavenger



Chemical Name: Tris-(2-aminoethyl)aminomethyl polystyrene
Resin Type: Highly cross-linked Macroporous poly(styrene-co-divinylbenzene)
Capacity: 2-3 mmol/g (based on benzoyl chloride uptake)
Bead Size: 150-355 µm; 45-100 mesh (>90% within)
Application: Scavenging acid chlorides, sulfonyl chlorides, isocyanates, and other electrophiles
Typical Scavenging Conditions: 3-6 equivalents relative to acid chloride, 1-4 h, 20 °C.
If an additional resin-bound base is present: 1.5-3 equivalents.
Compatible Solvents: Non-acidic organic solvents and water.
Swelling: 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)
Storage: Cool, dry location

MP-Trisamine is a macroporous polystyrene-bound scavenger, for electrophiles such as acid chlorides, sulfonyl chlorides, and isocyanates. Resin-bound scavengers are added after a reaction is complete in order to quench and react selectively with excess reactants and/or reaction by-products.

Biotage supplies three trisamine scavenger resins: Si-Trisamine, PS-Trisamine and MP-Trisamine. The resin backbone in PS-Trisamine consists of 1% cross-linked polystyrene-co-divinylbenzene. Electrophiles to be scavenged gain access to the trisamine sites by diffusion through the polystyrene gel. The MP-base copolymer is a highly cross-linked, robust, and low-swelling material, which makes it ideal for restricted volume environments (e.g. microwave vials, 96-well plates, etc.). Its unique pore structure provides greater access to the reactive sites without the need for solvent swelling, resulting in faster reactions and higher recoveries. The abrasion-resistant matrix has better handling characteristics and reduced transfer losses.

I. Scavenging by MP-Trisamine and PS-Trisamine in 1,2-Dichloroethane

The scavenging abilities of MP- and PS-Trisamine were tested with a series of five electrophiles, present at an initial concentration of 0.5 M in dichloroethane (Table 1). Under these conditions, four of the five electrophiles were scavenged within 0.5 h, using either of the two scavengers. PS-Trisamine was unable to scavenge 3-methoxyphenyl isocyanate to completion in this time.

Electrophile	Resin	Equivalents	% Scavenged in 0.5 h
4-chlorobenzoyl chloride	PS-Trisamine	3.5	100
	MP-Trisamine	3.5	100
2-phenylbutyryl chloride	PS-Trisamine	3.5	100
	MP-Trisamine	3.5	100
2,6-dimethoxybenzoyl chloride	PS-Trisamine	3.5	100
	MP-Trisamine	3.5	100
3-methoxyphenyl isocyanate	PS-Trisamine	3.0	92
	MP-Trisamine	3.0	100
Benzene sulfonyl chloride	PS-Trisamine	4	100
	MP-Trisamine	4	100

Table 1. Comparative scavenging of electrophiles by PS-Trisamine or MP-Trisamine in 1,2-dichloroethane at room temperature

II. The Effect of Different Solvents on Scavenging by MP-Trisamine and PS-Trisamine

Scavenging in THF, which swells 1% cross-linked polystyrene, was compared with scavenging in acetonitrile and methyl tert-butyl ether (MTBE). Acetonitrile and MTBE are poor solvents for swelling 1% cross-linked polystyrene. MTBE was chosen as a model for other ethereal solvents commonly employed in organic synthesis.

The results are shown in Table 2. MP-Trisamine scavenged effectively in all three solvents, capturing both substrates to 89-100% within 0.8 h. PS-Trisamine also scavenged 4-chlorobenzoyl chloride effectively in THF and acetonitrile, but these reactions occurred more slowly than with MP-Trisamine. MP-Trisamine also scavenged 3-methoxyphenyl isocyanate in acetontrile much faster than PS-Trisamine. In MTBE, MP-Trisamine sequestered both electrophiles to completion within 4 h, while PS-Trisamine was unable to scavenge either substrate in this nonswelling solvent.

Electrophile	Solvent	Time (h)	PS-Trisamine % Scavenged	MP-Trisamine % Scavenged
4-chlorobenzoyl chloride	THF	0.5	77	100
		2	100	100
	Acetonitrile	0.7	15	100
		1.8	45	100
		5.3	76	
		20	100	
	MTBE	0.8	0	100
		3.8	0	100
		20	0	
3-methoxyphenyl isocyanate	THF	0.5	89	89
		2	89	89
		4 days	88	89
	Acetonitrile	0.7	17	90
		1.8	47	90
		5.3	66	90
		20	84	100
	MTBE	0.8	0	95
		3.8	0	100

Table 2. Comparative scavenging of electrophiles by 3 equivalents of PS-Trisamine or MP-Trisamine in different solvents at room temperature

Summary

In comparison with PS-Trisamine, MP-Trisamine offers the following benefits:

- Scavenges effectively in solvents that do not swell 1% cross-linked polystyrene
- Limited swelling, so can be used where volume is restricted (e.g. 96 well plates, microwave vials)
- Faster scavenging rate than PS-Trisamine
- For certain substrates, Argoresin MP-Trisamine offers more complete scavenging than does PS-Trisamine

These advantages are offset to a certain degree by the higher capacity of PS-Trisamine (3-5 mmol/g, in comparison with 2-3 mmol/g for MP-Trisamine) Si-Trisamine also available.

Ordering Information

MP- Trisamine

Part Number	Quantity
801505	3 g
801397	10 g
801398	25 g
801399	100 g
801400	1000 g

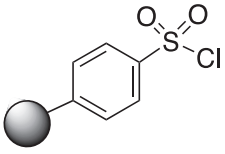
Si-Trisamine

Part Number	Quantity
9495-0010	10 g
9495-0025	25 g
9495-0100	100 g
9495-0500	500 g
9495-1000	1000 g

PS-TsCl

PS-TsCl

Electrophilic Activation

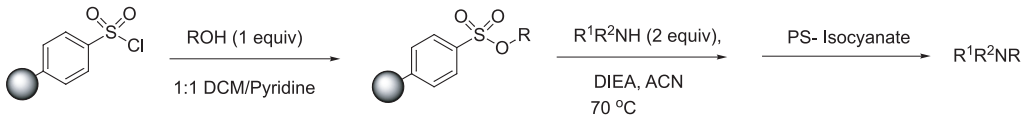


Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Loading: Typical loading 1.6 mmol/g, minimum loading 1.3 mmol/g (based on Volhard titration)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Polystyrene sulfonyl chloride
Application: Loading of alcohols followed by nucleophilic displacement (catch-and-release), scavenging of nucleophiles
Typical Alcohol-loading Conditions: 0.7–3 equivalents of alcohol in DCM/pyridine (1:1), 5–10 h, 20 °C
Compatible Solvents: DCM (12 mL/g), THF (8.6 mL/g), DMF (12.5 mL/g)

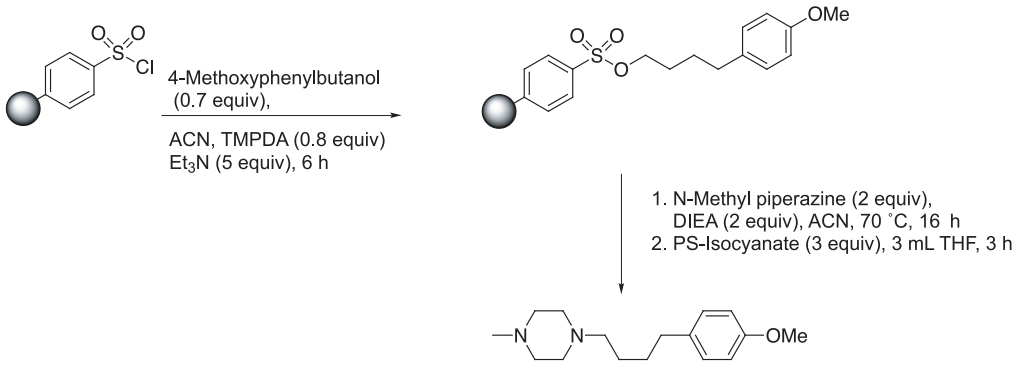
PS-TsCl is a chlorosulfonated polystyrene resin that is a resin-bound equivalent of tosyl chloride and has a capacity of 1.0–2.0 mmol/g based on sulfur analysis. The resin can readily react with nucleophiles to give a variety of sulfonyl functional polymers which can be used as polymeric supports, reagents, and catalysts in organic synthesis.[1-8]

PS-TsCl can be employed in Catch-and-Release applications, where the resin catches a compound to form an activated polymer intermediate, in this case a tosylate. After purification by washing, the resin-bound tosylate is subjected to a second transformation that releases a new product from the resin. Typically the second transformation is with a nucleophile (e.g. an amine, as described below). This process has been successfully applied to the synthesis of oxazolines[9] and spiperone analogs.[10] In these reactions, the resin is often used in excess relative to the alcohol to assure complete capture during the formation of the bound tosylate.

Loading of primary alcohols to PS-TsCl typically requires reaction with 0.7–3 equivalents of alcohol for 5 h at room temperature in 1:1 DCM/Pyridine (Scheme 1(a)). An alternative procedure for loading primary alcohols on PS-TsCl employs a mixture of TEA and tetramethylpropanediamine (TMPDA) as the base.[11] Bound tosylate formation is carried out at room temperature for 6 h in ACN with 1 equivalent of PS-TsCl, 0.7–1 equivalent of primary alcohol, 0.8 equivalents of TMPDA, and 4–6 equivalents of TEA (Scheme 1(b)). Increasing the amount of TEA or TMPDA beyond that recommended generally reduces the yield of bound tosylate.



Scheme 1(a). Reaction of alcohol with PS-TsCl using pyridine as base



Scheme 1(b). Reaction of alcohol with PS-TsCl using TEA and TMPDA

The sulfonate formation may be monitored using a simple bead-staining test. To check for residual sulfonyl chloride groups on the resin, a few beads may be sampled from the alcohol-loading reaction and the beads washed with DCM (3x), DMF (3x), DMF/H_2O (3:1, 3x), THF (3x). The resin is then treated with 5% ethylenediamine in DMF for 5 min to convert remaining sulfonyl chloride groups into a sulfonamide-linked primary amine. The beads are washed with DMF (3x), DCM (3x), THF (3x), then stained with a few drops of bromophenol blue (1% in DMA). The beads are further washed with DMF (5x). If the final color of the beads is white or off-white, the reaction is complete.

Sulfonate resins may be cleaved using secondary amines to produce tertiary amines. Cleavage of the sulfonate resin is accomplished using 2 equivalents of secondary amine in the presence of 6 equivalents of diisopropylethylamine in ACN at 70 °C for 18 h, or 80 °C for 8 h. Alternatively, cleavage using volatile secondary amines may be performed using 6 equivalents of secondary amine at 60 °C for 8 h.

The use of PS-TsCl was applied to a Catch-and-Release sequence for a series of alcohols and amines (Scheme 1[a]), with the results for representative examples given in Table 1. PS-Isocyanate was used to sequester excess secondary amine from the sulfonate displacement reaction. This expedited approach afforded tertiary amine products in high yield and purity while circumventing extractions and chromatography in product isolation and purification.

Representative Procedure

Pyridine as Base

To a reaction vessel containing 200 mg of PS-TsCl resin (1.49 mmol/g, 0.298 mmol) was added a solution of 1-(4-methoxy)phenylbutanol (51 mg, 0.30 mmol) in 4 mL of DCM/Py (1:1). The reaction was agitated for 6 h at room temperature. The resin was then washed with DCM (3 x 4 mL), DMF (5 x 4 mL), DMF/H_2O (3:1, 5 x 4 mL), THF (3 x 4 mL), and DCM (3 x 4 mL) and dried under vacuum. A solution of 1-phenylpiperazine (90 µL, 0.6 mmol) and DIEA (214 µL, 1.2 mmol) in 4 mL ACN was added to the resin and the mixture was heated at 70 ºC for 18 h. Finally, 740 mg of PS-Isocyanate resin (1.2 mmol/g, 0.89 mmol) was added with 3 mL of THF and the reaction was agitated. After 3 h, the resin was filtered and washed three times with THF. The filtrate was concentrated to give 1-methyl-4-(4-methoxyphenyl) butyl-piperazine in 90% yield (GC purity 100%).

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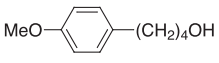
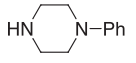
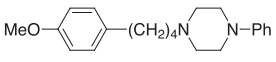
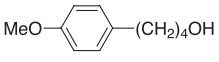
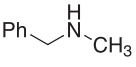
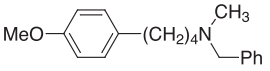
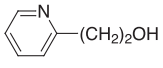
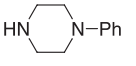
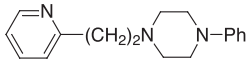
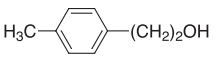
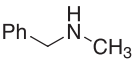
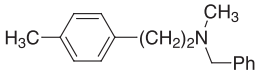
1				90	100
2				91	100
3				91	100
4				87	100

Table 2. Synthesis of tertiary amines from alcohols using PS-TsCl

PS-TsCl

TEA as Base with Tetramethylpropanediamine Additive

To 200 mg of PS-TsCl resin (1.47 mmol/g, 0.298 mmol) was added a solution of 1-(4-methoxy)phenylbutanol (37 mg, 0.201 mmol), TEA (120 mg, 1.192 mmol), and tetramethylpropanediamine (30 mg, 0.23 mmol) in 4 mL of ACN. The reaction was agitated for 6 h at room temperature. The resin was then washed with DCM (2 x 4 mL), DMF (2 x 4 mL), DMF/H_2O (3:1, 2 x 4 mL), THF (3 x 4 mL) and DCM (3 x 4 mL) and dried under vacuum. A solution of 1-phenylpiperazine (90 µL, 0.6 mmol) and DIEA (214 µL, 1.2 mmol) in 4 mL ACN was added to the resin and the mixture was heated at 70 ºC for 18 h. PS-Isocyanate resin (740 mg, 1.2 mmol/g, 0.894 mmol) was added together with 3 mL of THF. After 3 h, the resin was filtered and washed three times with THF. The filtrate was concentrated to give 1-methyl-4-(4-methoxyphenyl) butyl-piperazine in 83% yield (GC purity 100%).

Ordering Information

Part Number	Quantity
800490	3 g
800276	10 g
800277	25 g
800278	100 g
800316	1000 g

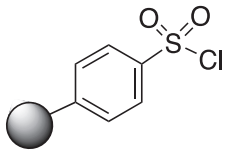
References

1. Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1998**, 39, 975.
2. Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, 39, 979.
3. Zhong, H. M.; Greco, M. N.; Maryanoff, B. E. *J. Org. Chem.* **1997**, 62, 9326.
4. For reviews on the use of polymer-supported aryl-sulfonyl chloride resin, see Huang, W.; He, B. Chin. *J. Reactive Polymers* (Engl.) **1992**, 1, 61.
5. Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, 118, 9998.
6. Takahashi, T.; Ebata, S.; Doi, T. *Tetrahedron Lett.* **1998**, 39, 1369.
7. Zhang, H.-C., Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Letters* **2000**, 2, 89.
8. A method for α-chlorination of ketones: Brummond, K. M.; Gesenberg, K. D. *Tetrahedron Lett.* **1999**, 40, 2231.
9. Pirrung, M. C.; Tumey, L. N. *J. Comb. Chem.* **2000**, 2, 675-680.
10. Hansen, H. C.; Olsson, R.; Croston, G.; Andersson, C. M. *Bioorg. Med. Chem. Lett.* **2000**, 10, 2435.
11. Yoshida, Y.; Shimonishi, K.; Sakakura, Y.; Okada, S.; Aso N.; Tanabe, *Y. Synthesis* **1999**, 9, 1633-1636.

PS-TsCl (HL)

PS-TsCl(HL)

Nucleophile Scavenger



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 2.2 mmol/g, minimum capacity 2.0 mmol/g (based on uptake of aniline and confirmed by Volhard titration)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Polystyrene sulfonyl chloride
Application: Scavenging of alcohols, amines, and other nucleophiles
Typical Scavenging Conditions: 3 equivalents relative to nucleophile, 20% pyridine or 6 equivalents of TEA, THF or DCE, 3–6 h
Compatible Solvents: DCM (4.5 mL/g), THF (9.9 mL/g), DMF (9.0 mL/g)
Storage: Cool, dry location

PS-TsCl(HL) is a functionalized 1% cross-linked polystyrene resin that is the resin-bound equivalent of tosyl chloride. This high-loaded resin is useful for the scavenging of various nucleophiles, including amines, hydrazines, alcohols, and organometallics. Various solvents may be used with a temperature range from 20 to 50 °C.

Representative Procedure

3-Phenylpropanol Scavenging

To a solution of 3-phenylpropanol (1 equivalent) in DCE/Py (20-50% Py, 10 mL/g resin added) is added PS-TsCl(HL) (3 equivalents), and the reaction is stirred at room temperature for 5–6 h. Results by GC analysis indicate >90% scavenging after 3 h and 96–99% scavenging after 5.5 h (heating for an additional 2 h at 50 °C achieved 100% scavenging). The pyridine hydrochloride generated was free-based by subsequent treatment with of MP-Carbonate resin (4 equivalents) for 2 h at room temperature. The reaction mixture was filtered and the filtrate collected.

Scavenging reactions may also be performed in THF or DMF. In these cases, THF was found to give lower scavenging efficiency when compared with DCE. Reactions done in DMF were successful; however, reaction mixtures became discolored. As an alternative to MP-Carbonate, solid potassium carbonate may be employed for free-basing amine hydrochloride salts in DMF.

Material Scavenged	Equiv	Solvent	Base	Temp (°C)	% Scavenged	Time (h)
3-Phenylpropanol	1.0	THF	20% pyridine	20	90[a]	5.5
3-Phenylpropanol	1.0	DCE	20–50% pyridine	20	96-99[b]	5.5
Cyclohexanol	1.0	DCE	50% pyridine	20	80[c]	5.5
3,5-Dimethylaniline	1.0	THF	6 equivalent NEt_3N or 20% pyridine	20	96-100	3
3,5-Dimethylaniline	1.0	DCE or DMF	6 equivalent NEt_3N or 20% pyridine	20	100	<3
PhMgCl[d]	1.0	THF	–	20	100[d]	1
Phenylhydrazine	1.0	DCE	1 equivalent NEt_3N	50	100	1

Table 1. Comparative scavenging of nucleophiles with PS-TsCl(HL) (3 equivalents)
[a]97% scavenged after an additional 2 hours at 50 °C. [b]100% scavenged after an additional 2 hours at 50 °C. [c]90% scavenged after an additional 2 hours at 50 °C. [d]Scavenging of PhMgCl was monitored by quenching of an aliquot of the reaction mixture with benzophenone, followed by TLC analysis and comparison with authentic triphenylmethanol.

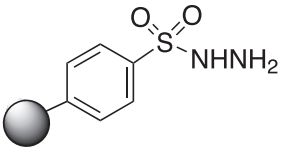
Ordering Information

Part Number	Quantity
800503	3 g
800364	10 g
800365	25 g
800366	100 g
800367	1000 g

PS-TsNHNH$_2$

PS-TsNHNH$_2$

Electrophile Scavenger



Resin Type: 1% Cross-linked poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 2.8 mmol/g, minimum capacity 2.3 mmol/g (based on benzaldehyde uptake)
Bead Size: 75–150 microns, 100–200 mesh (95% within)
Chemical Name: Polystyrene sulfonyl hydrazide
Application: Scavenging aldehydes and ketones
Scavenging Conditions: 3 equivalents relative to carbonyl, 1–3 h, 20 °C, DCM. Ketones and hindered aldehydes are accelerated by the addition of HOAc (~10%) and/or heat.
Compatible Solvents: DCM (7 mL/g), DCE (7 mL/g), THF (6.5 mL/g), DMF (7.2 mL/g)
Storage: Cool, dry location

PS-TsNHNH$_2$ is a resin-bound equivalent of p-toluenesulfonyl hydrazide and readily reacts with aldehydes and ketones. In contrast to reported sulfonyl hydrazide resins,[1–3] PS-TsNHNH$_2$ is a moderate capacity resin in which all sulfonyl hydrazide reaction sites display good accessibility to carbonyl reactants. Comparison with a polymeric benzyl hydrazide showed PS-TsNHNH$_2$ was a superior scavenger for carbonyls and much more stable to storage (the benzyl hydrazide resin decomposed on storage).

Removal of excess carbonyls from solution generally requires a threefold excess of PS-TsNHNH$_2$. Addition of a catalytic amount of HOAc (5–10%) may be required for ketones and hindered aldehydes. HOAc is also required for sequestering aldehydes in DMF. Complete removal of common aldehydes occurs in 0.5 to 3 h and removal of a ketone takes from 2 to 16 h. Elevated temperatures were required for hindered ketones (e.g. 2,6-dimethylcyclohexanone). Upon completion of the scavenging, the resin is rinsed with a suitable solvent (i.e. those which swell polystyrene), and the product is isolated by concentration. Representative aldehyde and ketone scavenging examples are presented in Table 1. PS-TsNHNH$_2$ was successfully used to work up the synthesis of alcohols by addition of a Grignard reagent to aldehydes.

PS-TsNHNH$_2$ is also potentially useful as a polymer-bound reagent. Bound sulfonyl hydrazones, formed by condensation with carbonyl compounds, can be utilized in further synthetic transformations. The high accessibility of tosyl hydrazide functional groups in PS-TsNHNH$_2$ should afford high synthetic fidelity relative to reported systems.[1-]

Carbonyl Substrates	PS-TsNHNH2	Additive	Time (h)	% Scavenged
Benzaldehyde	3	–	1	100
Hexanal	3	–	1	100
2,6-Dimethoxybenzaldehyde	3	–	1	100
Cyclohexanone	3	HOAc	1	100
Acetophenone	3	HOAc	8	100
2,6-Dimethylcyclohexanone[1,2]	3	HOAc (70 °C)	10	85

Table 1. Comparative scavenging times in DCM

Ordering Information

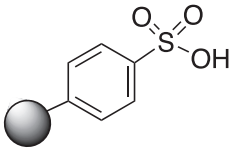
Part Number	Quantity
800497	3 g
800270	10 g
800271	25 g
800272	100 g
800317	1000 g

References

1. Emerson, D. W.; Emerson, R. R.; Joshi, S. C.; Sorensen, E. M.; Nrek, J. *J. Org. Chem.* **1979**, 44, 4634.
2. Kamogawa, H.; Kanzawa, A.; Kodoya, M.; Naito, T.; Nanasawa, M. *Bull. Chem. Soc. Jpn.* **1983**, 56, 762.
3. Galioglu, O.; Auar, A. *Eur. Polym. J.* **1989**, 25, 313.

MP-TsOH

Resin-Bound Acid



Resin Type: Macroporous poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 4.0 mmol/g, minimum capacity 3.7 mmol/g (based on uptake of benzylamine)
Bead Size: 375–575 microns, 25–40 mesh (mean value)
Chemical Name: Macroporous polystyrene sulfonic acid (0.5% inorganic antistatic agent)
Application: Scavenging and catch-and-release of amines, acid catalysis
Typical Scavenging Conditions: Approx. 2–3 equivalents of resin relative to amine, 0.5–1 h, 20 °C
Compatible Solvents: DCM (3.0 mL/g), THF (3.1 mL/g), DMF (3.1 mL/g), MeOH (3.05 mL/g)

MP-TsOH resin is a sulfonated macroporous polystyrene resin that is a resin-bound equivalent of p-toluenesulfonic acid (TsOH). The resin may be used as an equivalent to the strong cation-exchange resin, Amberlyst A-15 (Rohm and Haas).[1-4] MP-TsOH has been optimized for use as a bound reagent or scavenger resin for the synthesis of small molecules. The sulfonic acid groups in MP-TsOH are readily accessible for removal of basic compounds (e.g. primary, secondary, and tertiary amines) by quatenary salt formation. In addition, MP-TsOH does not contain dark leachable impurities derived from overoxidation of the polystyrene backbone observed in higher loading sulfonic acid resins.[5]

Representative amine scavenging examples (batch mode) as a function of time are provided in Table 1. MP-TsOH provides a useful alternative to quenching reactions with aqueous or soluble organic acids. MP-TsOH may also be used in cartridge applications to perform Catch-and-Release of amine derivatives in analogy to silica-derived SCX columns.[6-8] MP-TsOH circumvents the contamination of amine products with particulates that sometimes occur with silica-derived SCX columns. Representative amine-scavenging examples (cartridge mode) as a function of time are provided in Table 2.

Amine	MP-TsOH (equivalent)	% Scavenged 20 min	1 h
Propylamine	3	100	100
3-(morpholino)propylamine	3	100	100
Aniline	3	100	100
Nitroaniline	3	75	96
2-Aminothiazole	3	100	100

Table 1. Amine removal by MP-TsOH (batch mode)

Amine	MP-TsOH (equivalent)	% Scavenged (5 min)
Propylamine	5	100
3-(morpholino)propylamine	5	100
Aniline	5	100
2-Aminothiazole	5	98

Table 2. Amine removal by MP-TsOH (cartridge mode)

MP-TsOH

We have found catch-and-release purification of amines with MP-TsOH columns to be effective in retaining amines with a wide range of basicity, including N-methylmorpholine, aniline, aminothiazole, and nitroaniline. Full retention of weakly basic amines such as nitroaniline was achieved when DCM was used as the solvent, however, retention is less efficient in THF or DMF. The use of greater than three equivalents of resin is recommended for weakly basic amines in these solvents.

Representative Procedure

Catch-and-Release

The amine solution is incubated with MP-TsOH (3 equivalents relative to the amine) for 30 min. The resin is then filtered off followed by DCM washing to remove nonbasic impurities. Treating the resin with 2 M ammonia in methanol releases the amine as a free base. The same Catch-and-Release experiment can also be performed using MP-TsOH cartridges.[9] For details see page 205. This procedure can be used for purification of amines synthesized by reductive amination.[10]

Ordering Information

Part Number	Quantity
800498	3 g
800461	10 g
800462	25 g
800463	100 g
800464	1000 g

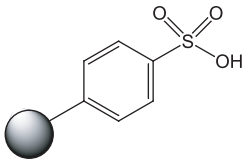
References

1. Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S. Woodard, S. S. *J. Am. Chem. Soc.* **1997**, 119, 4874.
2. Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, 38, 513.
3. Parlow, J. J.; Flynn, D. L. *Tetrahedron* **1998**, 54, 4013
4. Suto, M. J.; Gayo-Fung, L. M.; Palanki, M. S. S.; Sullivan, R. *Tetrahedron* **1998**, 54, 4141.
5. Stahlbush, J. R.; Strom, R. M.; Byers, R. G.; Henry, J. B.; Skelly, N. E. *Prediction and Identification of Leachables from Cation Exchange Resins*, Presented at the 48th Annual Meeting International Water Conference, Pittsburgh, PA Nov. **1987**, IWC-87-10.
6. Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett*. **1997**, 38, 3357.
7. Shuker, A. J.; Siegel, M. G.; Matthews, D. P.; Weigel, L. O. *Tetrahedron Lett.* **1997**, 38, 6149.
8. Lawrence, M. R.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553.
9. Part Number 800477-0050-C.
10. Reductive amination reactions are described in the MP-Cyanoborohydride and MP-Tricetoxyborohydride sections. (pages 73 and 98, respectively)

MP-TsOH (65)

MP-TsOH (65)

Resin-Bound Acid



Resin Type: Macroporous poly(styrene-co-divinylbenzene)
Capacity: Typical capacity 3.0 mmol/g, minimum capacity 2.5 mmol/g, 3.5–4.5 mmol/g (based on uptake of benzylamine)
Bead Size: 50–100 micron (95% within)
Chemical Name: Macroporous polystyrene sulfonic acid (0.5% inorganic antistatic agent)
Application: Scavenging and catch-and-release of amines
Typical Scavenging Conditions: Approx. 2–3 equivalents of resin relative to amine, 0.5–1 h, 20 °C
Resin Swelling: DCM, (2.7 mL/g), THF (3.0 mL/g), DMF (3.0 mL/g), MeOH (2.8 mL/g)

MP-TsOH(65) resin is similar to the MP-TsOH resin, except that the bead size is smaller and the capacity is somewhat lower. It is used for similar applications. Under some conditions, the reaction kinetics using MP-TsOH(65) may be faster than with MP-TsOH.

Ordering Information

Part Number	Quantity
800499	3 g
800478	10 g
800479	25 g
800480	100 g
800481	1000 g

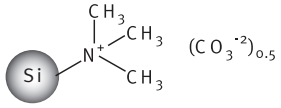
SPE Column Format

Part Number	Mass/Reservoir Volume
800477-0025-C	250 mg / 6 mL
800477-0100-D	1 g / 15 mL
800477-0250-E	2.5 g / 25 mL
800477-0010-BG	100 mg / 3 mL (tab-less)
800477-0025-CG	250 mg / 6 mL (tab-less)
800477-0050-CG	500 mg / 6 mL (tab-less)

Si-Carbonate (Si-TMA-Co3)

Si-Carbonate (Si-TMA-CO_3)

Scavenger/Base



Chemical Name: Silica Trimethylammonium Carbonate, (Si-Carbonate; Si-TMA(CO_3^{2-})$_{0.5}$; Si-CO_3)
Solid-Support Type: Silica
Typical Capacity: 0.6 mmol/g; 0.2 mmol/g (exchange capacity)
Size: 64 µm
Appearance: Free flowing off-white powder
Application: (1) Quaternary anion-exchanger for quenching, neutralizing, and desalting organic mixtures (2) Scavenger of organic acids such as carboxylic acids, boronic acids, 1-hydroxybenzotriazoles, N-hydroxysuccinimide, imidazoles, and phenols (3) Base in promoting reactions (e.g., Suzuki reaction.)
Compatible Solvents: Methanol (MeOH), Ethanol (EtOH), Dichloromethane (DCM), Dichloroethane (DCE)
Storage: Cool (4 °C), dry location

ISOLUTE® Si-Carbonate [Si-TMA(CO_3^{2-})0.5] is a bound equivalent of tetramethylammonium carbonate, which has traditionally been used as a quaternary anion-exchanger for quenching, neutralizing, and desalting organic mixtures. Recently more versatile applications have been reported such as organic acid scavenging for fast purification of amide and biaryl libraries and as a base in promoting Suzuki reaction.

ISOLUTE Si-Carbonate as an Organic Acid Scavenger

ISOLUTE Si-Carbonate scavenges acidic groups such as carboxylic acids, boronic acids, 1-hydroxybenzotriazole, N-hydroxysuccinimide and even imidazoles and phenols (pKa range 9.0- 0.4) from reaction mixtures. Optimal scavenging is achieved when the organic acid is flowed through columns packed with ISOLUTE Si-Carbonate as compared to batch processing. This can be explained by higher number of plate counts available in flow format rather than the single plate count of batch mode.

Applications

ISOLUTE Si-Carbonate was used to rapidly purify amide libraries. In the example shown in Figure 1[1] and 2[1], the excess HOBT/HATU[2] and carboxylic acid remaining in the amide library, prepared via microwave assisted solution phase synthesis (using PS-Carbodiimide[3] or PS-DIEA[4]), were completely scavenged by filtering the reaction mixture through a column packed with ISOLUTE Si-Carbonate.

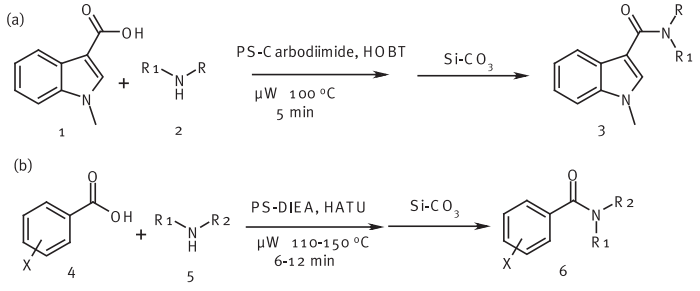


Figure 1. Work-up/purification of microwave-assisted amide coupling (PS-Carbodiimide or PS-DIEA) reaction mixture with ISOLUTE Si-Carbonate for scavenging of excess carboxylic acid and HOBt.

In the event of incomplete conversion, as in the case of N-methyl aniline and benzyl aniline, the unreacted anilines were removed by filtering the reaction mixture through a short column of ISOLUTE Si-Ethylphenylsulfonic Acid (SCX-3[5]). The resulting amides 6a-f (Table 1) were used directly (without further purification) in the next step involving a Suzuki reaction (Figure 2)[2].

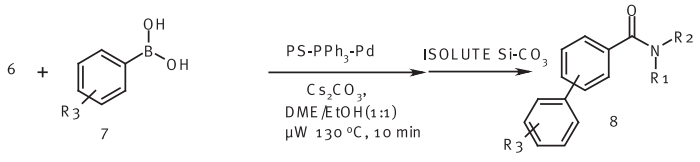


Figure 2. Work-up/purification of microwave-assisted Suzuki coupling (PS-PPh_3-Pd) reaction mixture with ISOLUTE Si-Carbonate for scavenging of excess/un-reacted boronic acid.

Si-Carbonate (Si-TMA-Co3)

Summary

Excellent yield and purity of product was obtained from Suzuki reactions using PS-PPh_3-Pd / Cs_2CO_3 in EtOH/DME (1:1) at 130 °C for 10 minutes. ISOLUTE Si-Carbonate was used for post-reaction scavenging of the excess boronic acids as shown in Figure 2 (page 186).

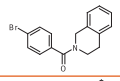
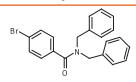
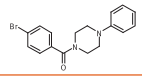
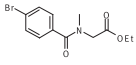
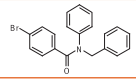
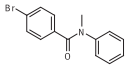
Product	Structure	Conditions	% Yield[a]	MS (M+1)[b]
6 a		110 ºC, 6 min	99	316
6 b		110 ºC, 6 min	91	379.9
6 c		110 ºC, 6 min	97	344.9
6 d		110 ºC, 6 min	90	299.9
6 e		150 ºC, 12 min	57	365.8
6 f		150 ºC, 12 min	59	289.9

Table 1. Reactions were performed in the Biotage Emrys™ Liberator microwave system in 2-5 mL reaction vials at 110-150 °C.

[a]Yield and purity determined by LC/MS with UV(220 and 254 nm). [b]LC/MS was carried out on an XTerra® MS C18 3x50 mm, 3.5 µm, Mobile phase: A: 0.5 mM CH_3COONH_4 in 5% MeCN, B: 0.5mM CH_3COONH_4 in MeCN, Gradient: 10 to 100 B in 5 min. Micromass® ZQ (Waters).

Ordering Information

Part Number	Quantity
9510-0010	10 g
9510-0025	25 g
9510-0100	100 g
9510-0500	500 g
9510-1000	1000 g

SPE Column format:

Part Number	Mass/Reservoir Vol.
510-0050-B	500 mg/3mL
510-0100-C	1 g/6 mL
510-0200-C	2 g/6 mL
510-0050-BG	500 mg/3 mL (tab-less)
510-0100-CG	1 g/6 mL (tab-less)
510-0200-CG	2 g/6 mL (tab-less)

References

1 N, N-(diisopropyl)aminomethylpolystyrene (PS-DIEA) in acetonitrile and excess of carboxylic acid (4-bromobenzoic acid) were reacted with hindered amides and anilines using microwave heating. The combination of MS with HATU/PS-DIEA resulted in higher purity and yield of these amides compared to the combination of PS-Carbodiimide/HOBT or HATU/DIEA.

2 Carpino, L.A.; El-Faham, A.; *J. Am. Chem. Soc.*; **1995**, 117(19), 5401-5402

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

4 PS-DIEA: Part Numbers 800494 (3g); 800279 (10g); 800280 (25g); 800281 (100g); 800312 (1000g)

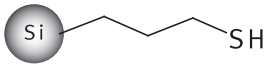
5 ISOLUTE Si-TsOH acid (SCX-3): Part Numbers 9533-0010 (10g); 9533-0025 (25g); 9533-0100 (100g); 9533-0500 (500g); 9533-1000 (1000g); 533-0050-B (SPE, 500mg/3mL); 533-0100-C (SPE, 1g/6mL)

6 PS-PPh3-Pd: Part Numbers 800473 (1g); 800474 (10g); 800475 (25g); 800476 (100g)

Si-Thiol

Si-Thiol

Metal Scavenger/Reagent



Chemical Name: Silica 1-propanethiol;
3-Mercaptopropyl silica gel (Si-Thiol; Si-SH)
Solid-Support Type: Silica
Typical Capacity: 1.3 mmol/g
Size: 63 µm
Appearance: Free flowing off-white powder
Application: Metal scavenger (e.g. Pd, Pt, Cu, Hg, Ag and Pb); electrophile scavenger (e.g. alkyl-, benzyl- and allyl- halides, acid chlorides, isocyanates)
Typical Conditions: Add 2-6 equiv to crude reaction mixture, stir for 1-12h, and then filter.
Storage: Cool (4 °C), dry location

ISOLUTE® Si-Thiol is the silica-supported equivalent of 1-propanethiol, which is useful for covalent scavenging of electrophiles. Its main application is in scavenging metals[1,2] used in organic chemistry including Pd, Pt, Cu, Hg, Ag and Pb. More recently, these types of materials have also been investigated in the removal of colored impurities from APIs.[3]

Stability

ISOLUTE® Si-Thiol has been manufactured using ultrapure bio-analytical grade silica backbone and has been shown to be chemically stable over a 12-month period with no significant evidence of aerial oxidation.

Non-specific interactions

There is no evidence of non-specific binding following exposure of Si-Thiol to basic amines (e.g. benzylamine), which suggests a lower risk of loss of API than, for example, using other basic metal scavengers.

Application

Palladium scavenger

The palladium scavenging efficiency was investigated using Dichlorobis(tetraphenylphosphine)Palladium II as the test analyte. UV activity was measured followng 16h of exposure to various concentrations of Si-Thiol. Results are shown in Figure 1.

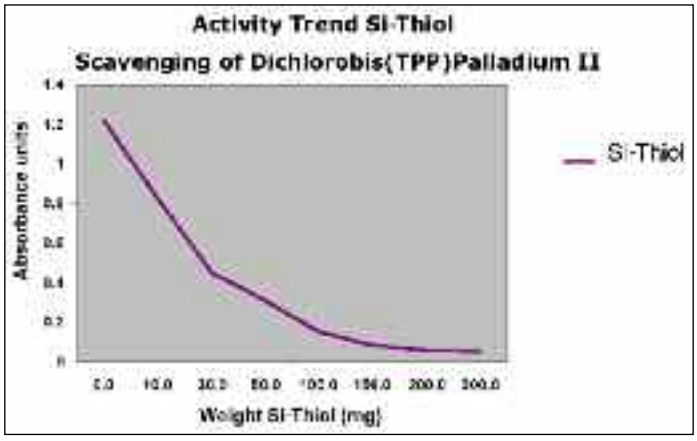


Figure 1. Chart showing scavenging trends from 3M solution of Dichlorobis(TPP)Palladium II (3 mL) in 1:1 DMF:THF over 16h.

Typical scavenging procedure

ISOLUTE Si-Thiol (2-6 equiv) was added to the crude reaction mixture. The mixture was allowed to stir at room temperature for 1-12 hours. The silica-based material was then removed by filtration and rinsed with the reaction solvent and/or THF.

References

1 Crudden, C.M.; Sateesh, M; Lewis, R.; *J. Am.* Chem. Soc. **2005**, 127 (28), 10045-10050.
2 Welsh, C.J.; Albaneze-Walker, J.; Leonard, W.R.; Biba, M.; Da Silva, J.; Henderson, D.; Laing, B.; Mathre, D.J.; Spencer, S.; Bu, X.; Wang, T. Org. Process Res. Dev. **2005**, 9, 198-205.
3 Welch, C.J; Leonard, W.R.; Henderson, D.W.; Dorner, B.; Glaser Childers, K.; Chung, J.Y.L.; Hartner, F.W.; Albaneze-Walker, J.; Sajonz, P. Org. Process Res. Dev. **2008**, 12, 81-87.

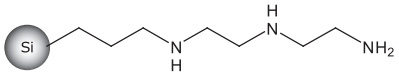
Ordering Information

Part Number	Quantity
9180-0010	10 g
9180-0025	25 g
9180-0100	100 g
9180-0500	500 g
9180-1000	1000 g

Si-Triamine

Si-Triamine

Scavenger/Reagent



Chemical Name: 3-(Diethylenetriamino) propyl silica (Si-Triamine)
Solid-Support Type: Silica
Typical Capacity: 2.4 mmol/g; 2.2 mmol/g (Benzoyl chloride scavenging)
Size: 65 µm
Appearance: Free flowing off-white powder
Application: Electrophile scavenger (for aldehydes, acid chlorides, sulfonyl chlorides, and isothiocyanates), Scavenger of heavy metal ions such as Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Pb^{2+}, Ru^{2+}, and Zn^{2+}
Typical Conditions: 3 equiv ISOLUTE Si-Triamine relative to acid chloride, 30 min, room temperature
Compatible Solvents: Dichloromethane (DCM), Acetonitrile (MeCN), N,N-Dimethylformamide (DMF), Dimethylsulfoxide (DMSO)
Storage: Cool (4 °C), dry location

ISOLUTE® Si-Triamine has versatile applications in today's modern organic synthesis, since it can be used either as a scavenger in a purification step or as an organic base in a reaction.

Application

A: ISOLUTE Si-Triamine as an Electrophile Scavenger

ISOLUTE Si-Triamine has been used to scavenge a variety of electrophiles, including aldehyde[1], acid chloride[2], sulfonyl chloride isocyanate as well as isothiocyanate and heavy metal ions such as Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Pb^{2+}, Ru^{2+} and Zn^{2+} via covalent bonding and chelation[3,4], respectively (Figure 1).

Sulfonyl chloride 1[5] and acid chloride 2 were completely scavenged by stirring with 3 equivalents of ISOLUTE Si-Triamine in DCM for 30 min at room temperature.

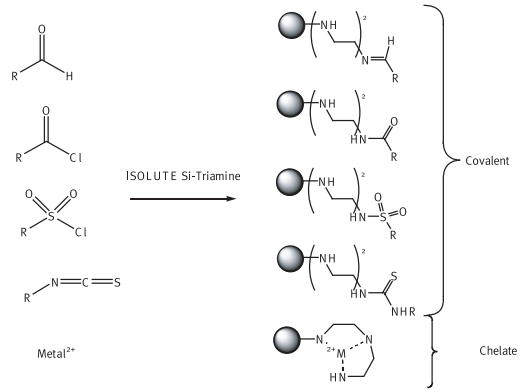
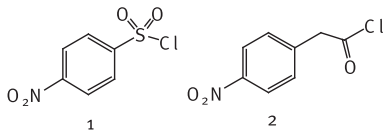
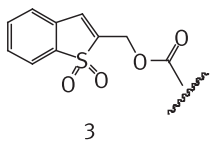


Figure 1. Scavenging of electrophiles and metal ions by ISOLUTE Si-Triamine

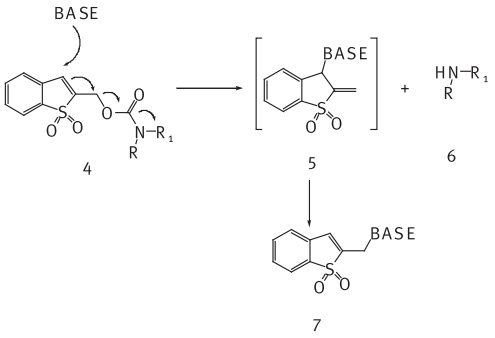


B: ISOLUTE Si-Triamine as a Reagent Base

ISOLUTE Si-Triamine has been used in the simultaneous de-blocking and scavenging of 1,1-dioxobenzo[b]thiophene-2-ylmethyloxycarbonyl (Bsmoc) **3**, which is a base sensitive amine protecting group commonly used in rapid solution phase peptide synthesis.



Michael-like addition of the base to the Bsmoc thiophene ring **4** results in cleavage of the Bsmoc-urethane bond, releasing the free amine **6** and a reactive intermediate[5] which rearranges to the stable by-product **7**.



Traditionally, the Bsmoc-urethane bond is cleaved upon stirring the Bsmoc-amine with tris (2-aminoethyl) amine (20 equiv) at room temperature for 15 minutes followed by reaction workup, which involves several extractions with saturated NaCl. The use of ISOLUTE Si-Triamine for Bsmoc-removal eliminates the aqueous extraction steps required for workup. The cleavage of Bsmoc amine protecting groups using ISOLUTE Si-Triamine can be significantly accelerated using microwave heating.[7]

General Procedure

A general procedure for microwave-assisted Bsmoc-urethane bond cleavage involves microwave heating the Bsmoc-amine in DCM in the presence of ISOLUTE Si-Triamine (10 equiv) at 90 ºC for 6 minutes. This reaction was repeated using different solvents such as DMSO, DMF and CH_3CN. Although the rate of reaction is faster in DMSO and DMF (90 ºC, 3 min), the lower boiling DCM and MeCN were used for ease of workup, an important factor in multi-step synthesis.

Ordering Information

Part Number	Quantity
9491-0010	10 g
9491-0025	25 g
9491-0100	100 g
9491-0500	500 g
9491-1000	1000 g

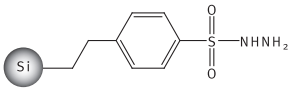
References

1 Flynn, D. L.; Crich, J. Z.; Devraj, R.V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem Soc*., **1997**, 119 (21), 4874-4881
2 Booth, J.; Hodges, J. *A. Chem. Res*. **1999**, 32, 18-26
3 Püpcüklü, S.; Yildiz, B.; Taralp, A. ACS, **2003**, New Orleans, Poster
4 El-Ashgar, N. M.; El-Nahhal, I. M.; Chehimi, M. M.; Babonneau, F.; Livage, J. *Reactive and Functional Polymers*, **2005**, 63, 199-213
5 Nicewonger, R.; Ditto, L.; Varady, L. *Tetrahedron Lett*. **2000**, 41, 2323-2326
6 Carpino, L.A.; Ismail, M.; Truran, G. A.; Mansour, E. M. E.; Iguchi, S.; Ionescu, D.; El-Faham, A.; Riemer, C.; Warrass R. *J. Org. Chem*. **1999**, 64, 4324-4338
7 To 35 mg of Bsmoc-PCA in 2 mL of DCM was added 0.9 g of ISOLUTE Si-Triamine. This mixture was heated at 90 ºC for 5 minutes in a microwave system (Emrys™ Liberator). The reaction mixture was filtered and the Si-Triamine washed with 7 mL of MeOH. PCA was collected in 95% yield

Si-Tosyl Hydrazide

Si-Tosyl Hydrazide (Si-TsNHNH$_2$)

Scavenger/Reagent



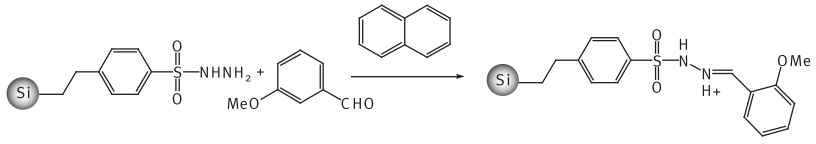
Chemical Name: Silica Ethylbenzenesulfonyl hydrazide (Si-TsNHNH$_2$)
Solid-Support Type: Silica
Typical Capacity: 0.8 mmol/g
Size: 60 µm
Appearance: Free flowing off-white powder
Application: Scavenger of carbonyl compounds
Typical Conditions: Stir crude reaction mixture with 2-4 equivalents for 1 h and filter.
Compatible Solvents: Dichloromethane (DCM), Acetonitrile (MeCN), Acetone, Tetrahydrofuran (THF), and other aprotic non-carbonyl containing solvents
Storage: Cool (4 °C), dry location

ISOLUTE® Si-Tosyl Hydrazide is a silica supported equivalent of p-toluenesulfonyl hydrazide. This bound reagent is an excellent scavenger for aldehydes and ketones.

Applications

General Procedure for Scavenging Aldehydes

ISOLUTE Si-Tosyl Hydrazide (0.6 g) was added to a mixture of 3-methoxybenzylaldehyde (20 µL, 1.5 mmol) and naphthalene (15 mg; internal standard) in THF (2 mL) (Scheme 1). This mixture was stirred for 30 min, then filtered and the Si-TsNHNH$_2$ was washed with MeOH (8 mL). The filtrate was concentrated and analyzed by RC-HPLC, which showed 82% of aldehyde as being scavenged.



Addition of 5% acetic acid in THF increased rate of scavenging to 90%. Microwave irradiation of this mixture at 100 ºC for 5 minutes further improved the rate of scavenging to 98% (Table 1, Figure 1).

Solvent	THF	THF + 5% HOAc	THF + 5% HOAc
Conditions	R.T. / 30 min.	R.T. / 30 min	µW: 100 ºC / 5 min
% Scavenged	82 %	90 %	98 %

Table 1. Aldehyde scavenging with ISOLUTE Si-Tosyl Hydrazide

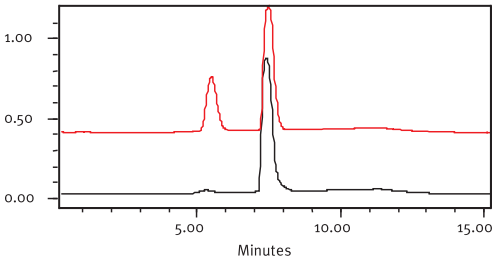
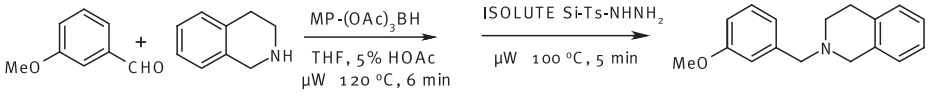


Figure 1. Overlay of starting mixture (red) with resultant mixture (black) after treating with ISOLUTE Si-Tosyl Hydrazide. The first peak is 3-methoxy benzaldehyde; the second is Naphthalene (internal standard)

Si-Tosyl Hydrazide

Reductive Amination

These conditions were applied for rapid clean up of tertiary amines prepared through reductive amination using MP-Triacetoxyborohydride and microwave irradiation (Scheme 2).



Scheme 2. One pot microwave-assisted reductive amination reaction followed by aldehyde scavenging via ISOLUTE Si-Tosyl Hydrazide

To a solution of the amine (0.5 mmol) and 3-methoxybenzaldehyde (0.7 mmol) in a solution of THF and 5 % acetic acid (2 ml) in a 5 mL Emrys™ process vial was added MP-Triacetoxyborohydride (523 mg, 2.39 mmol/g, 1.25 mmol). The vial was capped and heated to 120 ºC for 6 min, after which it was de-capped and ISOLUTE Si-Tosyl Hydrazide (0.6 g) added. The vial was then re-capped and heated to 100 ºC for 5 min, after which the reaction mixture was filtered. The solid was washed with a 1:1 solution of THF/MeOH (10 mL) and the filtrate was concentrated to afford the product in 86% yield (85% purity by LC-MS).

Ordering Information

Part Number	Quantity
9535-0010	10 g
9535-0025	25 g
9535-0100	100 g
9535-0500	500 g
9535-1000	1000 g

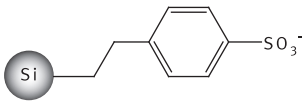
References

MP-Triacetoxyborohydride: Part Numbers: 800517 (3gm); 800417 (10g); 800414 (25g); 800415 (100g); 800416 (1000g)

Si-TsOH (SCX-3)

Si-TsOH (SCX-3)

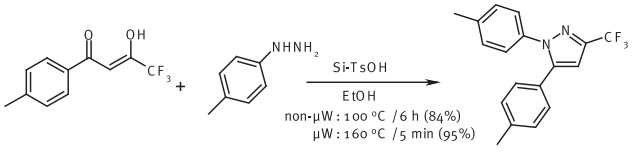
Scavenger/Reagent



Chemical Name: Silica Ethylbenzene sulfonic acid (Si-TsOH; Si-Tosic acid; SCX-3)
Solid-Support Type: Silica
Typical Capacity: 0.6 mmol/g
Size: 60 µm
Appearance: Free flowing off-white powder
Application: Scavenger of amine, Catch & Release, Acid catalyst/reagent, Metal scavenger (e.g., Ni and Ag)
Typical Conditions: Stir crude reaction mixture with 2-4 equivalents for 1 h and filter.
Compatible Solvents: Methanol (MeOH), Dichloromethane (DCM), Acetonitrile (MeCN), Acetone, Ethyl Acetate (EtOAc), N,N-Dimethylformamide (DMF), Dimethylsulfoxide (DMSO)
Storage: Cool (4 °C), dry location

ISOLUTE® Si-TsOH (SCX-3) is the bound equivalent of p-toluene sulfonic acid with a pKa <1. Similar to ISOLUTE propylsulfonic acid (SCX-2)[1], it can be used to (a) scavenge amines and other bases such as anilines and borohydrides (b) as an acid catalyst in reactions or (c) as a replacement for aqueous or organic acids in quenching reactions.

ISOLUTE Si-TsOH is stable to microwave heating and has been reported[2] as an excellent replacement to p-TsOH in both thermal and microwave assisted acid catalyzed reactions (Scheme 1).



Scheme 1. Synthesis of 1,5-diarylpyrazoles using Si-TsOH as an acidic reagent.

The advantage of using Si-TsOH was that no work-up was necessary. The crude reaction mixture was evaporated to dryness and the resulting free flowing solid was purified directly by flash column chromatography. The advantage of using Si-TsOH was that no work-up was necessary.

Applications

Catch & Release Purification of Amines

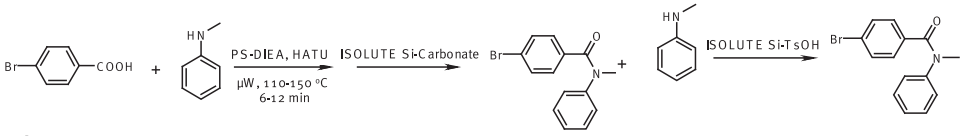
ISOLUTE Si-TsOH is a strong cation exchanger (SCX) for the "Catch & Release" purification of amines. When a solution containing an amine is passed through a Si-TsOH (SCX-3) column the amine is retained or "caught" by the SCX-3. Non-basic impurities are not retained and are further removed by washing the column with an organic solvent, such as methanol, acetonitrile, or THF. The product is subsequently "released" from the column by elution with a solution of ammonia in methanol. Amine salts of weak conjugate acids (e.g. acetate and trifluoroacetate) are exchanged onto the silica and are released as the free amine during the ammonia/methanol wash.

SCX-3 columns can be used successfully to isolate amines from solutions of DMF. After complete removal of the DMF using DCM or methanol, the retained amine is eluted with an ammonia/methanol solution. The amine is then isolated by removal of the volatile ammonia/methanol solution by evaporation. The slower sample flow rate exhibited by certain viscous solvents including DMF and DMSO can be improved by increasing the vacuum, applying positive pressure to the column, or diluting with a less viscous solvent.

Si-TsOH (SCX-3)

Application in Amidation Reactions

ISOLUTE Si-TsOH columns can be used to simplify the purification process following amide coupling reactions. In the event of incomplete conversion the unreacted amines can be removed by filtering the reaction mixture through a short column of ISOLUTE Si-TsOH. An example of this approach is provided in Scheme 1.[3] Amide coupling of p-bromobenzoic acid with N-methyl aniline was carried out with PS-DIEA[4] and HATU in acetonitrile. On completion, the reaction mixture was filtered and the filtrate passed through a conditioned ISOLUTE Si-Carbonate column[5] to remove the unreacted acid and HATU. The resulting filtrate, consisting of the amide product and unreacted amine, was passed through a column of ISOLUTE Si-TsOH. Unreacted aniline was retained on the column providing pure product in the filtrate.



Scheme 1.

Scavenging of Basic Impurities

ISOLUTE Si-TsOH columns, similar to MP-TsOH[6], can also be used to scavenge basic impurities and thereby purify reaction mixtures. Passing a reaction mixture through an ISOLUTE Si-TsOH column will result in removal of all basic components in the mixture. If additional selectivity is required, the use of a more selective scavenger resin is recommended, for example, PS-Isocyanate[7] (for removal of primary and secondary amines), or PS-Benzaldehyde[8] (for selective removal of primary amines). An alternative approach to selectivity enhancement is the use of derivatization purification techniques in conjunction with silica based strong cation exchange columns ISOLUTE SCX-2.

Ordering Information

Part Number	Quantity
9537-0010	10 g
9537-0025	25 g
9537-0100	100 g
9537-0500	500 g
9537-1000	1000 g

Also available in SPE Column and Array plate formats.

References

1 ISOLUTE Si-Propylsulfonic acid (SCX-2): Part Numbers 9532-0010 (10g); 9532-0025 (25g); 9532-0100 (100g); 9532-0500 (500g); 9532-1000 (1000g)

2 Humphries, P. S. and Finefield, J. M. *Tetrahedron Lett*. **2006**, 47, 2443–2446

3 Ghassemi, S. MEDI 46, ORGN 302, ACS Atlanta **2006**

4 PS-DIEA: Part Numbers 800494 (3g); 800279 (10g), 800280 (2 g), 800281 (100g); 800312 (1000g)

5 ISOLUTE Si-Carbonate: Part Numbers 9510-0010 (10g), 9510-0025 (25g), 9510-0100 (100g), 9510-0500 (500g), 9510-1000 (1000g); 510-0050-B (SPE; 500mg/3mL); 510-0100-C (SPE;1g/6 mL); 510-0200-C (2g/6 mL); 510-0050-BG (SPE tab-less; 500mg/3mL); 510-0100-CG (SPE tab-less;1g/6mL); 510-0200-CG (SPE tab-less; 2g/6mL)

6 MP-TsOH(65): Part Numbers 800477-0010-BG (SPE tab-less, 100mg/3 mL); 800477-0025-CG (SPE tab-less; 250mg/6mL); 800477-0050-CG (SPE tab-less; 500mg/6mL)

7 PS-Isocyanate: Part Numbers 800495 (3g); 800260 (10g), 800261 (25g), 800262 (100g); 800311 (1000g)

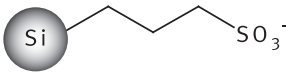
8 PS-Benzaldehyde: Part Numbers 800502 (3g); 800360 (10g), 800361 (25g), 800362 (100g); 800363 (1000g)

9 Request Technical Note TN128 Increasing the Selectivity of Silica Based Cation Exchange Sorbents for the Purification of Reaction Mixtures Using Derivatization Purification Techniques.

Si-Propylsulfonic Acid

Si-Propylsulfonic Acid (SCX-2)

Scavenger/Reagent



Chemical Name: Silica Propylsulfonic Acid (Si-propylsulfonic acid; SCX-2)
Solid-Support Type: Silica
Typical Capacity: 0.7 mmol/g
Size: 52 µm
Appearance: Free flowing off-white powder
Application: Scavenger of amine, Catch-and-Release, Acid catalyst
Typical Conditions: Stir crude reaction mixture with 2-4 equivalents for 1 h and filter.
Compatible Solvents: Methanol (MeOH), Dichloromethane (DCM), Acetonitrile (MeCN), Acetone, Ethyl Acetate (EtOAc), N,N-Dimethylformamide (DMF), Dimethylsulfoxide (DMSO)
Storage: Cool (4 °C), dry location

ISOLUTE® Si-Propylsulfonic acid (SCX-2) belongs to the class of strong acids. Similar to ISOLUTE Si-TsOH (SCX-3)[1], it can be used to (a) scavenge amines and other bases such as anilines and borohydrides (b) as an acid catalyst in reactions or (c) as a replacement for aqueous or organic acids in quenching reactions. The advantage of using SCX-2 as a bound acid reagent is that it eliminates work-up. The crude reaction mixture can be evaporated to dryness and the resulting free flowing solid can be purified directly by flash column chromatography.

Applications

Catch and Release Purification of Amines

ISOLUTE Si-Propylsulfonic Acid is a strong cation exchanger (SCX) for the Catch-and-Release purification of amines. When a solution containing an amine is passed through a Si-propylsulfonic acid (SCX-2) column the amine is retained or caught by the SCX-2. Non-basic impurities are not retained and are further removed by washing the column with an organic solvent, such as methanol, acetonitrile or THF. The product is subsequently released from the column by elution with a solution of ammonia in methanol. Amine salts of weak conjugate acids (e.g. acetate and trifluoroacetate) are exchanged onto the silica and are released as the free amine during the ammonia/methanol wash.

SCX-2 columns can be used successfully to isolate amines from solutions in DMF. After complete removal of the DMF using DCM or methanol, the retained amine is eluted with an ammonia/methanol solution. The amine is then isolated by removal of the volatile ammonia/methanol solution by evaporation. The slower sample flow rate exhibited by certain viscous solvents including DMF and DMSO can be improved by applying the vacuum, applying positive pressure to the column, or diluting with a less viscous solvent.

Scavenging of Basic Impurities

ISOLUTE Si-Propylsulfonic acid (SCX-2) columns, similar to ISOLUTE Si-TsOH (SCX-3)[1] and MP-TsOH[2], can also be used to scavenge basic impurities and thereby purify reaction mixtures. Passing a reaction mixture through an SCX-2 column will result in removal of all basic components in the mixture. If additional selectivity is required, the use of a more selective scavenger resin is recommended, for example, PS-Isocyanate[3] (for removal of primary and secondary amines), or PS-Benzaldehyde[4] (for selective removal of primary amines). An alternative approach to selectivity enhancement is the use of derivatization purification techniques.

Si-Propylsulfonic Acid

Other Applications

In Mitsunobu, Suzuki and Heck reactions, it is often challenging to isolate pure products from mixtures containing triphenylphosphine oxide and palladium. SCX-2 columns can be used to purify these products when they contain a basic functional group. The reaction mixture is applied to the column and the product is retained by SCX-2. The by-products can be easily removed with a methanol or DCM wash step. The product can then be released by eluting with 2 M ammonia in methanol.

Ordering Information

Part Number	Quantity
9536-0010	10 g
9536-0025	25 g
9536-0100	100 g
9536-0500	500 g
9536-1000	1000 g

Also available in SPE Column and Array plate formats.

References

1 ISOLUTE Si-TsOH acid (SCX-3): Part Numbers 9533-0010 (10g); 9533-0025 (25g); 9533-0100 (100g); 9533-0500 (500g); 9533-1000 (1000g); 533-0050-B (SPE, 500mg/3mL); 533-0100-C (SPE, 1g/6mL)
2 MP-TsOH(65): Part Numbers 800477-0010-BG (SPE tab-less, 100mg/3mL); 800477-0025-CG (SPE tab-less; 250mg/6mL); 800477-0050-CG (SPE tab-less; 500mg/6mL)
3 PS-Isocyanate: Part Numbers 800495 (3g); 800260 (10g), 800261 (25g), 800262 (100g); 800311 (1000g)
4 PS-Benzaldehyde: Part Numbers 800502 (3g); 800360 (10g), 800361 (25g), 800362 (100g); 800363 (1000g)

ISOLUTE® Columns and 96-well Plates

Column Configurations

ISOLUTE® products for reaction work-up are available in a choice of column and reservoir sizes. To assist in ordering, the last character of the ISOLUTE product part number identifies the column reservoir size. For example, ISOLUTE SCX-2 1 g/6 mL columns, part number 532-0100-C, uses column type C. Nominal volume listed for each column indicates the empty reservoir volume.

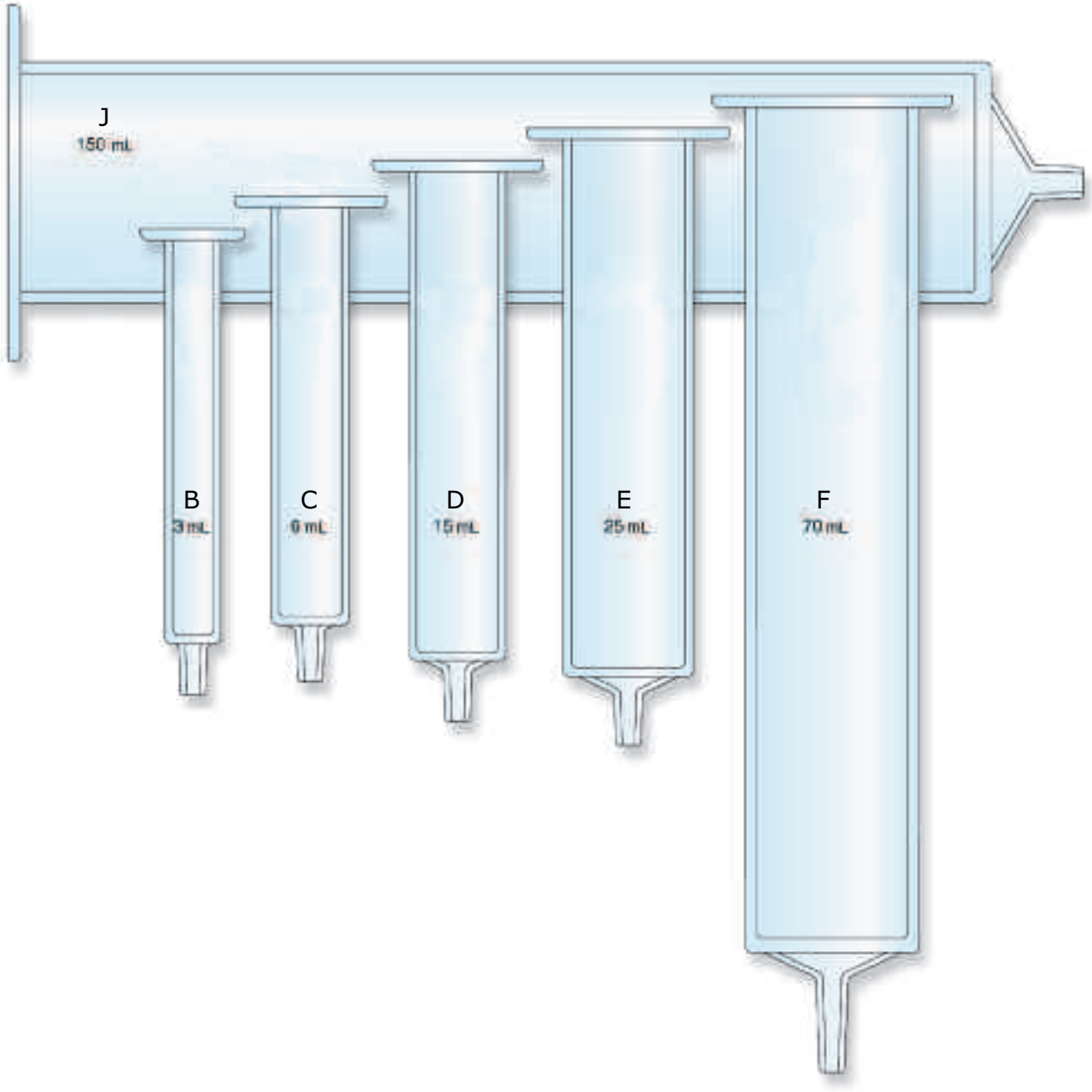
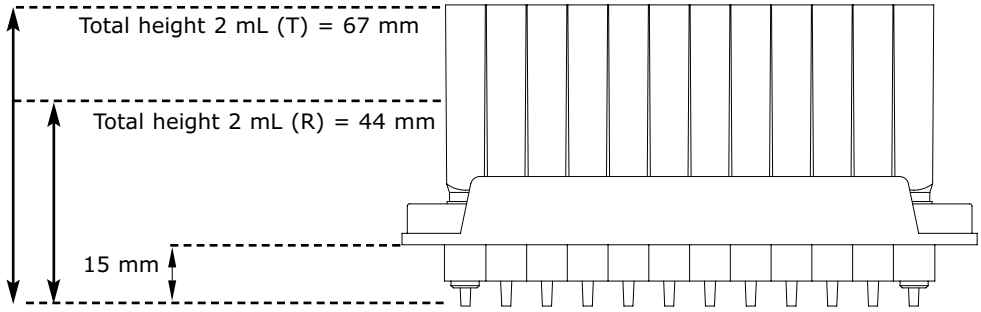
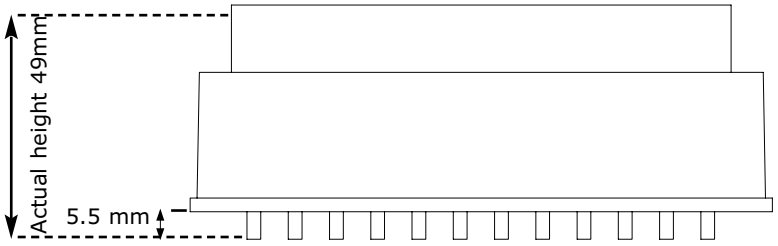


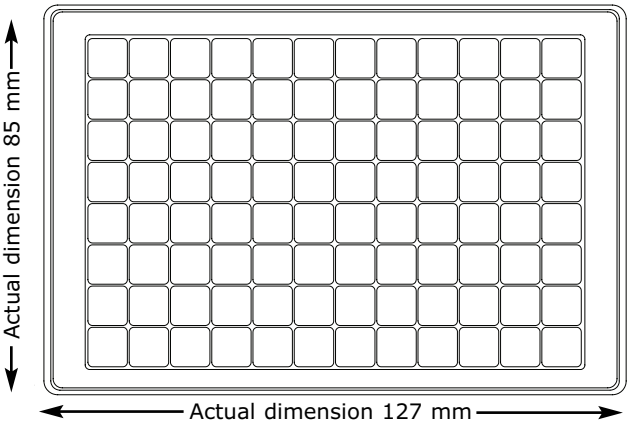
Plate Configurations

Biotage supplies two 96-well plate formats, the fixed-well plate, and the modular Array format. As with individual columns, the last character(s) of the part number identifies the format/column type. The suffix for fixed-well plates is -P01, while the suffices for ISOLUTE Array wells are -R (1 mL) and -T (2 mL). Prepacked ISOLUTE Array plates have the suffices -RP or –TP, respectively.

Scale diagrams (60% of actual size) of the fixed-well and pre-assembled Array plate are shown below. Note the "skirt" heights (distance from well outlet to sealing edge) of the two plates are different. To eliminate cross talk when processing plates, well outlets should penetrate the collection plate correctly. To accommodate this skirt height difference, the VacMaster™-96 is supplied complete with a spacer for use with the Array format. This spacer is not required for processing the fixed-well format.



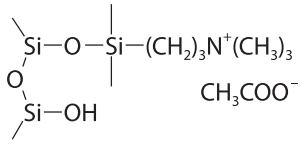




ISOLUTE PE-AX

ISOLUTE PE-AX

Catch & Release and Scavenging SPE of Acidic Compounds



Chemical structure of the PE-AX silane covalently bonded to the surface of a silica particle

ISOLUTE PE-AX is a silica-based sorbent with a chemically bonded quaternary amine functional group. It is used for the isolation of a wide range of acidic compounds using both Catch & Release and scavenging SPE protocols. ISOLUTE PE-AX is available packed into SPE columns or 96-well plates and in bulk for flow-through or batch applications. Using the Catch & Release SPE approach, acidic target compounds can be isolated from a range of reaction mixtures. ISOLUTE PE-AX columns and 96-well plates can be used in a scavenging SPE mode to remove excess acidic reagents, allowing neutral or basic compounds to pass straight through to the collection vessel.

Chemical Data

Base Material: Silica, 50 µm
Functional Group: Quaternary Amine
Capacity: 0.6 meq/g
Counter Ion: Acetate

Ordering Information

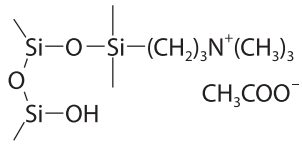
Description	Part Number	Quantity
ISOLUTE Columns		
ISOLUTE PE-AX 500 mg/3 mL	503-0050-B	50
ISOLUTE PE-AX 1 g/3 mL	503-0100-B	50
ISOLUTE PE-AX 500 mg/6 mL	503-0050-C	30
ISOLUTE PE-AX 1 g/6 mL	503-0100-C	30
ISOLUTE PE-AX 2 g/15 mL	503-0200-D	20
ISOLUTE PE-AX 5 g/25 mL	503-0500-E	20
ISOLUTE PE-AX 10 g/70 mL	503-1000-F	16
ISOLUTE PE-AX 20 g/70 mL	503-2000-F	16
ISOLUTE Tab-less Columns for High Throughput Work-up		
ISOLUTE PE-AX 500 mg/3 mL, tab-less	503-0050-BG[1]	50
ISOLUTE PE-AX 1 g/3 mL, tab-less	503-0100-BG[1]	50
ISOLUTE PE-AX 500 mg/6 mL, tab-less	503-0050-CG[2]	30
ISOLUTE PE-AX 1 g/6 mL, tab-less	503-0100-CG[2]	30
ISOLUTE-96 PE-AX Fixed-Well Plate		
ISOLUTE-96 PE-AX 100 mg	503-0100-P01	1
ISOLUTE-96 PE-AX 500 mg	503-0500-P01	1
ISOLUTE Array PE-AX 96-Well		
ISOLUTE Array PE-AX 100 mg/2 mL	503-0100-T[3]	100

[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see pg 221).
[3] ISOLUTE Array base plate and accessories can be found on pg 221.

- The principles of scavenging SPE can be found on pages 141-145.
- ISOLUTE PE-AX columns are processed using the FlashVac Sample Processing Manifold (see pg 222).
- Biotage's 96-well products are processed using the VacMaster-96 Sample Processing Manifold (see pg 220).

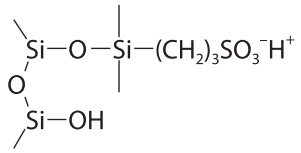
ISOLUTE PE-AX/SCX-2

Simultaneous Scavenging SPE of Basic and Acidic Compounds



Chemical structure of the PE-AX silane covalently bonded to the surface of a silica particle

ISOLUTE PE-AX/SCX-2 is a silica-based sorbent with chemically bonded propylsulfonic acid and quaternary amine functional groups. The sorbent is used for the isolation of a wide range of neutral compounds using a scavenging SPE protocol. ISOLUTE PE-AX/SCX-2 is available packed into SPE columns or 96-well plates and in bulk for flow-through or batch applications. Using the scavenging SPE approach, neutral target compounds can be purified from a range of reaction mixtures.



Chemical structure of the SCX-2 silane covalently bonded to the surface of a silica particle

Chemical Data

Quaternary Amine
Base Material: Silica, 50 µm
Functional Group: Quaternary amine
Capacity: 0.6 meg/g
Counter Ion: Acetate

Propylsulfonic Acid
Base Material: Silica, 50 µm
Functional Group: Propylsulfonic acid
Capacity: 0.5 meg/g
Counter Ion: Proton

Ordering Information

Description	Part Number	Quantity
ISOLUTE Columns		
ISOLUTE PE-AX/SCX-2 500 mg/3 mL	988-0050-B	50
ISOLUTE PE-AX/SCX-2 1 g/3 mL	988-0100-B	50
ISOLUTE PE-AX/SCX-2 500 mg/6 mL	988-0050-C	30
ISOLUTE PE-AX/SCX-2 1 g/6 mL	988-0100-C	30
ISOLUTE PE-AX/SCX-2 2 g/15 mL	988-0200-D	20
ISOLUTE PE-AX/SCX-2 5 g/25 mL	988-0500-E	20
ISOLUTE PE-AX/SCX-2 10 g/70 mL	988-1000-F	16
ISOLUTE PE-AX/SCX-2 20 g/70 mL	988-2000-F	16
ISOLUTE Tab-less Columns for High Throughput Work-up		
ISOLUTE PE-AX/SCX-2 500 mg/3 mL, tab-less	988-0050-BG[1]	50
ISOLUTE PE-AX/SCX-2 1 g/3 mL, tab-less	988-0100-BG[1]	50
ISOLUTE PE-AX/SCX-2 500 mg/6 mL, tab-less	988-0050-CG[2]	30
ISOLUTE PE-AX/SCX-2 1 g/6 mL, tab-less	988-0100-CG[2]	30
ISOLUTE-96 Fixed-Well Plates		
ISOLUTE-96 PE-AX/SCX-2 100 mg	988-0100-P01	1
ISOLUTE-96 PE-AX/SCX-2 500 mg	988-0500-P01	1
ISOLUTE Array PE-AX/SCX-2 96-well		
ISOLUTE Array PE-AX/SCX-2 100 mg/2 mL	988-0100-T[3]	100

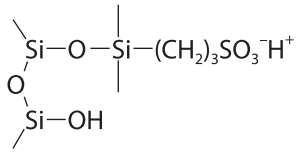
[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see pg 221).
[3] ISOLUTE Array base plate and accessories can be found on page 221.

- The principles of scavenging SPE can be found on pages 141-145.
- ISOLUTE PE-AX/SCX-2 columns are processed using the FlashVac Sample Processing Manifold (see page 222).
- Biotage's 96-well products are processed using the VacMaster-96 Sample Processing Manifold (see page 220).

ISOLUTE SCX-2

ISOLUTE SCX-2

Catch & Release and Scavenging SPE of Basic Compounds



Chemical structure of the SCX-2 silane covalently bonded to the surface of a silica particle

ISOLUTE SCX-2 is a silica-based sorbent with a chemically bonded propylsulfonic acid functional group. The sorbent is used for the isolation of a wide range of basic compounds using both Catch & Release and scavenging SPE protocols. ISOLUTE SCX-2 is available packed into SPE columns or 96-well plates and in bulk for flow-through or batch applications. Using the Catch & Release SPE approach, basic target compounds can be isolated from a range of reaction mixtures. ISOLUTE SCX-2 columns and 96-well plates can be used in a scavenging SPE mode to remove excess basic reagents, allowing neutral or acidic compounds to pass straight through to the collection vessel.

Chemical Data

Base Material: Silica, 50 µm
Functional Group: Propylsulfonic acid
Capacity: 0.6 meq/g
Counter Ion: Proton

Ordering Information

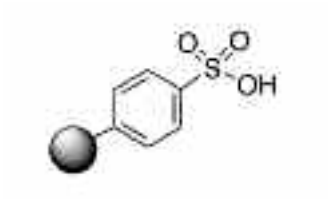
Description	Part Number	Quantity
ISOLUTE SCX-2 Columns		
ISOLUTE SCX-2 500 mg/3 mL	532-0050-B	50
ISOLUTE SCX-2 1 g/3 mL	532-0100-B	50
ISOLUTE SCX-2 500 mg/6 mL	532-0050-C	30
ISOLUTE SCX-2 1 g/6 mL	532-0100-C	30
ISOLUTE SCX-2 2 g/15 mL	456-0200-D	20
ISOLUTE SCX-2 5 g/25 mL	456-0500-E	20
ISOLUTE SCX-2 10 g/70 mL	456-1000-F	16
ISOLUTE SCX-2 20 g/70 mL	456-2000-F	16
ISOLUTE SCX-2 50 g/150 mL	456-5000-J	8
ISOLUTE SCX-2 70 g/150 mL	456-7000-J	8
ISOLUTE Tab-less Columns for High Throughput Work-up		
ISOLUTE SCX-2 500 mg/3 mL, tab-less	532-0050-BG[1]	50
ISOLUTE SCX-2 1 g/3 mL, tab-less	532-0100-BG[1]	50
ISOLUTE SCX-2 500 mg/6 mL, tab-less	532-0050-CG[2]	30
ISOLUTE SCX-2 1 g/6 mL, tab-less	532-0100-CG[2]	30
ISOLUTE-96 SCX-2 Fixed-Well Plate		
ISOLUTE-96 SCX-2 100 mg	532-0100-P01	1
ISOLUTE-96 SCX-2 500 mg	532-0500-P01	1
ISOLUTE Array SCX-2 96-Well		
ISOLUTE Array SCX-2 100 mg/2 mL	532-0100-T[3]	100

[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see pg 221).
[3] ISOLUTE Array base plate and accessories can be found on pg 221.

- The principles of Catch & Release and scavenging SPE can be found on pages 141-145.
- ISOLUTE SCX-2 columns are processed using the FlashVac Sample Processing Manifold (see pg 222).
- Biotage's 96-well products are processed using the VacMaster-96 Sample Processing Manifold (see pg 220).

MP-TsOH

Catch & Release and Scavenging SPE of Basic Compounds



Chemical structure of tosic acid functional group covalently bonded to a macroporous poly(styrene-co-divinylbenzene polymer

MP-TsOH is a macroporous polystyrene resin with a chemically bonded p-toluenesulfonic acid functional group. It is used for the isolation of a wide range of aliphatic, aromatic, and heterocyclic amines using both catch & release and scavenging SPE protocols. MP-TsOH is available packed into SPE columns and in bulk for flow-through or batch applications. Using the Catch & Release SPE approach, target compounds can be isolated from a range of reaction mixtures. MP-TsOH columns can be used in a scavenging SPE mode to remove excess basic reagents, allowing neutral or acidic compounds to pass straight through to the collection vessel.

MP-TsOH columns can be used to form free amines during Catch & Release SPE protocols. Amine salts of weak conjugate acids (e.g. acetate, trifluoroacetate, etc.) are exchanged onto MP-TsOH columns and then released as the free amine.

Chemical Data

Base Material: Macroporous poly (styrene-co-divinylbenzene), 50–100 µm
Functional Group: p-toluenesulfonic acid
Capacity: 2.5 mmol/g
Counter Ion: Proton

Ordering Information

Description	Part Number	Quantity
MP-TsOH Columns		
MP-TsOH 100 mg/3 mL	800477-0010-B	50
MP-TsOH 250 mg/6 mL	800477-0025-C	30
MP-TsOH 500 mg/6 mL	800477-0050-C	30
MP-TsOH 1 g/15 mL	800477-0100-D	20
MP-TsOH 2.5 g/25 mL	800477-0250-E	20
MP-TsOH Tab-less Columns for High Throughput Work-up		
MP-TsOH 100 mg/3 mL, tab-less	800477-0010-BG[1]	50
MP-TsOH 250 mg/6 mL, tab-less	800477-0025-CG[2]	30
MP-TsOH 500 mg/6 mL, tab-less	800477-0050-CG[2]	30

[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see page 221).

- ISOLUTE MP-TsOH columns are processed using the FlashVac Sample Processing Manifold (see page 222).
- The principles of Catch & Release and scavenging SPE can be found on pages 141-145.

ISOLUTE AL-N, ISOLUTE FL, ISOLUTE Si II

Clean-up Columns

ISOLUTE Clean-up Columns are used as a first pass work-up tool following organic synthesis. Reaction mixtures are typically applied directly to the appropriate size column. Impurities are removed and the crudely purified mixture collected for further purification. The approach is often referred to as "plug chromatography." Clean-up columns are available packed with a range of sorbents: alumina (neutral), Florisil,® and silica.

ISOLUTE Al-N is an aluminum oxide that uses both polar and acid-base interactions during the cleanup process. Unlike silica gel, neutral alumina can be used for compounds with acid sensitive functional groups such as acetals and ketals.

ISOLUTE FL is a magnesium oxide silica gel (Florisil), adsorbing compounds through polar interactions. It is useful for purification of highly polar compounds such as amines, amides, and heterocycles. These compounds adsorb less strongly on ISOLUTE FL compared with ISOLUTE Si II and can be eluted with less polar solvents.

ISOLUTE Si II columns are useful for removing highly polar impurities from crude reaction products. ISOLUTE Si II is used where ISOLUTE FL offers insufficient adsorption or capacity.

These columns are an easy-to-use alternative to adding media to filtration devices that then require washing before future use. ISOLUTE Clean-up Columns are processed using the FlashVac Sample Processing Manifold.

Chemical Data

ISOLUTE Al-N
Base Material: aluminum oxide
Particle Size: 50–200 µm

ISOLUTE FL
Base Material: Magnesium oxide silica gel
Particle Size: 150–250 µm

ISOLUTE Si II
Base Material: Silica gel
Particle Size: 50 µm

- The principles of using cleanup columns can be found on pages 146-147.
- The principles of catch and release scavenging SPE can be found on pages 141-145.
- ISOLUTE cleanup columns are processed using the FlashVac Sample Processing Manifold (see pg 222).

Ordering Information

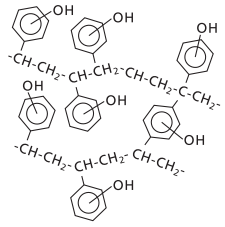
Description	Part Number	Quantity
ISOLUTE Al-N Columns		
ISOLUTE AL-N 200 mg/3 mL	714-0020-B	50
ISOLUTE AL-N 500 mg/3 mL	714-0050-B	50
ISOLUTE AL-N 500 mg/6 mL	714-0050-C	30
ISOLUTE AL-N 1 g/6 mL	714-0100-C	30
ISOLUTE AL-N 2 g/6 mL	714-0200-C	30
ISOLUTE AL-N Tab-less Columns for High Throughput Applications		
ISOLUTE AL-N 200 mg/3 mL, tab-less	714-0020-BG[1]	50
ISOLUTE AL-N 500 mg/3 mL, tab-less	714-0050-BG[1]	50
ISOLUTE AL-N 500 mg/6 mL, tab-less	714-0050-CG[2]	30
ISOLUTE AL-N 1 g/6 mL, tab-less	714-0100-CG[2]	30
ISOLUTE AL-N 2 g/6 mL, tab-less	714-0200-CG[2]	30
ISOLUTE FL Columns		
ISOLUTE FL 200 mg/3 mL	712-0020-B	50
ISOLUTE FL 500 mg/3 mL	712-0050-B	50
ISOLUTE FL 500 mg/6 mL	712-0050-C	30
ISOLUTE FL 1 g/6 mL	712-0100-C	30
ISOLUTE FL 2 g/6 mL	712-0200-C	30
ISOLUTE FL Tab-less Columns for High Throughput Applications		
ISOLUTE FL 200 mg/3 mL, tab-less	712-0020-BG[1]	50
ISOLUTE FL 500 mg/3 mL, tab-less	712-0050-BG[1]	50
ISOLUTE FL 500 mg/6 mL, tab-less	712-0050-CG[2]	30
ISOLUTE FL 1 g/6 mL, tab-less	712-0100-CG[2]	30
ISOLUTE FL 2 g/6 mL, tab-less	712-0200-CG[2]	30
ISOLUTE Si II Columns		
ISOLUTE Si II 200 mg/3 mL	440-0020-B	50
ISOLUTE Si II 500 mg/3 mL	440-0050-B	50
ISOLUTE Si II 500 mg/6 mL	440-0050-C	30
ISOLUTE Si II 1 g/6 mL	440-0100-C	30
ISOLUTE Si II 2 g/6 mL	440-0200-C	30
ISOLUTE Si II Tab-less Columns for High Throughput Applications		
ISOLUTE Si II 200 mg/3 mL, tab-less	440-0020-BG[1]	50
ISOLUTE Si II 500 mg/3 mL, tab-less	440-0050-BG[1]	50
ISOLUTE Si II 500 mg/6 mL, tab-less	440-0050-CG[2]	30
ISOLUTE Si II 1 g/6 mL, tab-less	440-0100-CG[2]	30
ISOLUTE Si II 2 g/6 mL, tab-less	440-0200-CG[2]	30

[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see page 221).

- ISOLUTE Array base plate and accessories can be found on pg 221.

ISOLUTE 103

Concentration of Prep-LC Fractions using Catch & Release SPE



Chemical structure of the ISOLUTE 103, a hydroxylated polystyrene divinylbenzene co-polymer

ISOLUTE 103 is a hydroxylated polystyrene divinylbenzene co-polymer. The resin is used for the isolation of a wide range of compounds from prep LC fractions using a Catch & Release SPE protocol. The approach replaces the need for time-consuming evaporation of aqueous based fractions.

Chemical Data

Base Material: Hydroxylated Polystyrene Divinylbenzene Co-polymer
Functional Group: N/A
Capacity: Up to 45% by weight (from 100% aqueous)
Counter Ion: N/A

Ordering Information

Description	Part Number	Quantity
ISOLUTE Columns		
ISOLUTE 103 200 mg/6 mL	103-0020-C	30
ISOLUTE 103 500 mg/6 mL	103-0050-C	30
ISOLUTE Tab-less Columns for High Throughput Work-up		
ISOLUTE 103 200 mg/6 mL, tab-less	103-0020-CG[1]	30
ISOLUTE 103 500 mg/6 mL, tab-less	103-0050-CG[1]	30

[1] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see pg 221).

- The principles of catch and release scavenging SPE can be found on pgs 141-145.
- ISOLUTE 103 columns are processed using the FlashVac Sample Processing Manifold (see pg 222).
- ISOLUTE Array base plate and accessories can be found on pg 221.

ISOLUTE Phase Separators

ISOLUTE Phase Separators

ISOLUTE Phase Separator columns are used to fractionate aqueous and chlorinated solvents following liquid-liquid extraction. The proprietary filtration device allows the flow of the organic solvent but holds up the aqueous layer (for up to 24 hours).

Ordering Information

Description	Part Number	Quantity
ISOLUTE Columns		
ISOLUTE Phase Separators, 3 mL	120-1903-B	100
ISOLUTE Phase Separators, 6 mL	120-1905-C	100
ISOLUTE Phase Separators, 15 mL	120-1906-D	100
ISOLUTE Phase Separators, 25 mL	120-1907-E	100
ISOLUTE Phase Separators, 70 mL	120-1908-F	50
ISOLUTE Phase Separators, 150 mL	120-1909-J	25
ISOLUTE Tab-less Columns for High Throughput Applications		
ISOLUTE Phase Separators, 3 mL, tab-less	120-1903-BG[1]	100
ISOLUTE Phase Separators, 6 mL, tab-less	120-1905-CG[2]	100
ISOLUTE Phase Separator Fixed-Well Plate		
ISOLUTE Phase Separator, fixed-well plate	120-1910-P01	1
ISOLUTE Array Phase Separator Wells		
ISOLUTE Array Phase Separators, 2 mL	120-1920-T[3]	100

[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see page 221).
[3] ISOLUTE Array base plate and accessories can be found on pg 221.

- See pg 151 for the principles of using ISOLUTE Phase Separators.
- ISOLUTE Phase Separators are processed using either the FlashVac Sample Processing Manifold (see pg 222) or IST Gravity Rack (see pg 224).
- Biotage's 96-well products are processed using the VacMaster-96 Sample Processing Manifold (see pg 220).

ISOLUTE HM-N

Rapid Aqueous Work-up and Removal of Water Soluble Impurities from Reaction Mixtures

ISOLUTE HM-N columns

ISOLUTE HM-N is a modified form of diatomaceous earth. The support has many uses in reaction work-up, including:

- Removal of water-soluble impurities from reaction mixtures
- Removal of water from water-immiscible organic solvents
- Liquid-liquid extraction on a support
- Phase exchange

The use of a support eliminates emulsion formation at the interface of the two liquids. All protocols using ISOLUTE HM-N are processed using gravity flow.

When removing polar compounds or salts from reaction mixtures, an aqueous solution is initially immobilized on the ISOLUTE HM-N support. As the reaction mixture is applied to the column, water soluble impurities transfer to the aqueous phase with the target compound remaining in the water-immiscible organic solvent.

ISOLUTE HM-N removes trace amounts of water from water-immiscible organic solvents. The maximum amount of water that can be adsorbed is 750 µL per g of ISOLUTE HM-N. This capacity may vary depending on the solvent used.

ISOLUTE HM-N

Ordering Information

Description	Part Number	Quantity
ISOLUTE Columns		
ISOLUTE HM-N, 0.3 mL	800-0040-BM	100
ISOLUTE HM-N, 1 mL	800-0100-CM	100
ISOLUTE HM-N, 3 mL	800-0220-DM	100
ISOLUTE HM-N, 5 mL	800-0350-EM	100
ISOLUTE HM-N, 10 mL	800-0700-FM	50
ISOLUTE HM-N, 20 mL	800-1300-FM	50
ISOLUTE Tab-less Columns for High Throughput Work-up		
ISOLUTE HM-N, 0.3 mL, tab-less	800-0040-BMG[1]	100
ISOLUTE HM-N, 1 mL, tab-less	800-0100-CMG[2]	100
ISOLUTE Bulk		
ISOLUTE HM-N, Bulk	9800-1000	1 Kg
ISOLUTE HM-N, Bulk	9800-5000	3 Kg

[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see page 221).

ISOLUTE HM-N columns are available to extract sample volumes from 400 µL to 20 mL

- The principles of supported liquid extraction can be found on pg 149.
- ISOLUTE HM-N columns are processed using the IST Gravity Rack (see pg 224).

ISOLUTE Sodium Sulfate

ISOLUTE Sodium Sulfate Drying Cartridges

In-line Water Removal

ISOLUTE Sodium Sulfate Drying Cartridge

Sodium sulfate is commonly used for drying water-immiscible organic solvents. ISOLUTE Sodium Sulfate Drying Cartridges are a convenient alternative to using the bulk material. The male/female Luer design allows the cartridge to be placed in-line after the main work-up column. Alternatively, connect to an empty reservoir and load larger volumes of solvent.

The cartridge contains 2.5 g sodium sulfate and can remove up to 3.5 mL water.

Ordering Information

Description	Part Number	Quantity
ISOLUTE Sodium Sulfate Drying Cartridge	802-0250-M	50

- ISOLUTE Sodium Sulfate Drying Cartridges are compatible with the FlashVac Sample Processing Manifold (see pg 222).

ISOLUTE Empty Reservoirs

ISOLUTE Empty Reservoirs

ISOLUTE Empty Reservoirs extend the volume of all ISOLUTE Catch & Release and scavenging SPE, filtration, and supported liquid extraction columns. The empty reservoirs are attached to the main work-up column using an ISOLUTE Column Adaptor (see pg 217). True-to-scale drawings of the complete range of empty reservoirs can be found on pg 200.

The reservoirs are manufactured from polypropylene and are stable to all common reaction and work-up solvents. They can be used for room-temperature reactions, when used in conjunction with ISOLUTE Column Caps and the Luer Tip Cap (see pg 217).

Ordering Information

Description	Part Number	Quantity
ISOLUTE SG Empty Reservoir, 3 mL	120-1102-B	100
ISOLUTE SG Empty Reservoir, 6 mL	120-1103-C	100
ISOLUTE SG Empty Reservoir, 15 mL	120-1106-D	100
ISOLUTE SG Empty Reservoir, 25 mL	120-1107-E	100
ISOLUTE SG Empty Reservoir, 70 mL	120-1109-F	50
ISOLUTE SG Empty Reservoir, 150 mL	120-1110-J	25

- ISOLUTE Empty Reservoirs are compatible with the FlashVac Sample Processing Manifold (see pg 222).

ISOLUTE Filtration Columns

ISOLUTE Filtration Columns

ISOLUTE Filtration Columns

ISOLUTE Filtration Columns are used to perform a range of filtration operations during reaction work-up. The columns contain a single 20 µm polyethylene (PE) frit and are a convenient cost-effective alternative to traditional filtration devices that require washing and drying prior to further use.

Used in conjunction with Biotage's Resins, ISOLUTE Filtration Columns provide an easy-to-use filtration device for quick and easy removal of the resin. Where the target compound is bound to the resin, wash steps are used to remove all impurities and by-products, before the compound is released from the resin using the appropriate conditions. Should the target compound be in solution, the reaction mixture is applied to the filtration column; the resin is filtered off, with the filtrate containing the required compound.

Catch & Release and scavenging SPE columns perform more reproducibly if the applied reaction mixture is particulate or precipitate free. ISOLUTE Filtration Columns can be attached to the main purification column by means of an ISOLUTE Column Adaptor (see pg 217). The filtration columns remove the particulates, allowing the reaction mixture to flow freely through the work-up column. Also available is the 50 mL ISOLUTE Wide Mouth Filtration Reservoir, where the filtered material is required after filtration. The 37 mm-diameter reservoir allows rapid filtration and easy access for removal using a spatula.

Ordering Information

Description	Part Number	Quantity
ISOLUTE Filtration Columns		
ISOLUTE SG Single Fritted Reservoir—20 µm PE, 3 mL	120-1112-B	100
ISOLUTE SG Single Fritted Reservoir—20 µm PE, 6 mL	120-1113-C	100
ISOLUTE SG Single Fritted Reservoir—20 µm PE, 15 mL	120-1115-D	100
ISOLUTE SG Single Fritted Reservoir—20 µm PE 25 mL	120-1116-E	100
ISOLUTE SG Single Fritted Reservoir—20 µm PE, 70 mL	120-1118-F	50
ISOLUTE SG Single Fritted Reservoir—20 µm PE, 150 mL	120-1119-J	25
ISOLUTE Wide Mouth Filtration Columns		
ISOLUTE SG Wide Mouth Single Fritted Reservoir—20 µm PE, 50 mL	120-1120-K	25
ISOLUTE Tab-less Columns for High Throughput Work-up		
ISOLUTE SG Single Fritted Reservoir—20 µm PE, tab-less, 3 mL	120-1112-BG[1]	100
ISOLUTE SG Single Fritted Empty Reservoir—20 µm PE, tab-less, 6 m	120-1113-CG[2]	100
ISOLUTE Fixed-Well Filtration Plate		
ISOLUTE fixed-well single fritted plate—20 µm	120-1022-P01	1
ISOLUTE Array Wells		
ISOLUTE Array single fritted well, 1 mL–20 µm	120-1010-R[3]	100
ISOLUTE Array single fritted well, 2 mL–20 µm	120-1010-T[2]	100
ISOLUTE Array 96-Well Populated Plates		
ISOLUTE Array single fritted plate, 1 mL–20 µm	120-1010-RP[3]	1
ISOLUTE Array single fritted plate, 2 mL–20 µm	120-1010-TP[3]	1

[1] ISOLUTE tab-less 3 mL columns are compatible with the Mettler Toledo Miniblock® System.
[2] ISOLUTE tab-less 6 mL columns are compatible with the ISOLUTE Array-24 System (see pg 221).
[3] ISOLUTE Array base plate and accessories can be found on pg 221.

- ISOLUTE Filtration Columns are processed using the FlashVac Sample Processing Manifold (see pg 222).
- Biotage's 96-well products are processed using the VacMaster-96 Sample Processing Manifold (see pg 220).

Celite® Columns:

"Tar" and Catalyst Removal During First-stage Reaction Work-up

Celite® columns are used as a filtration device for removal of "tar" and particulate materials (e.g. catalysts, as first- stage work-up following organic synthesis).

The columns contain an inert Celite material, a modified diatomaceous earth, with an optimized particle-size distribution for flow-through processing. The column holds up catalysts including Pt (IV) oxide and Pd/C, providing filtrates for subsequent work-up. The retention of the catalyst in a column format minimizes safety issues, a common problem when the catalyst is captured in an open filtration device such as a sintered funnel.

Ordering Information

Description	Part Number	Quantity
Celite Columns		
Celite column, 2.5 g/25 mL	810-0250-E	20
Celite column, 10 g/150 mL	810-1000-J	8
Celite 96-well Plates		
Celite 45 mg, fixed-well plate	810-0045-P01	1

- Celite Columns are processed using the FlashVac Sample Processing Manifold (see p 222) or the IST Gravity Rack (see p 224).

ISOLUTE Accessories

Biotage offers a range of accessories for use with ISOLUTE products for reaction work-up and purification. These accessories include column caps for all column sizes, Luer tip caps, column adaptors, and polyethylene and PTFE frits.

The accessories are used for room-temperature reactions, reaction work-up, and purification procedures, including solid sample loading onto ISOLUTE flash chromatography columns and flow control through individual columns.

ISOLUTE Column Adaptors

ISOLUTE Column Adaptors allow empty reservoirs and filtration columns to be attached to the main column. This increases the volume that can be added to the column in a single step or prevents particulate matter blocking the top frit of the column. The adaptors are made of polyethylene or PTFE and are available for all ISOLUTE column sizes.

ISOLUTE Column Caps

ISOLUTE Column Caps are used to seal either the column inlet (all column sizes) or the Luer outlet. The caps allow ISOLUTE columns to be transported from one location to another or for room-temperature reactions to be performed in either the empty reservoirs or filtration columns.

ISOLUTE Polyethylene and PTFE Frits

Biotage's products are based on fritted systems consisting of sintered particles (polyethylene [PE] or PTFE) which are compressed to produce a porous material. The nominal porosity of the frit is the average or mean size (e.g. 20 µm). The frits are relatively thick, which means the pores run through the material in a multidirectional channel system, allowing the frit to behave as a filter.

Biotage offers two materials, polyethylene (10 and 20 µm) and PTFE (20 µm) as standard. Other porosities are available through our Custom Manufacturing Service.

The frits are used as part of the solid sample loading technique prior to flash chromatography and in the construction of Catch & Release, and scavenging SPE and filtration devices.

Ordering Information

Description	Part Number	Quantity
ISOLUTE Column Adaptors		
Column Adaptor, PTFE (1, 3 & 6 mL columns)	120-1100	10
Column Adaptor, PE (1, 3 & 6 mL columns)	120-1101	10
Column Adaptor, PE (15 & 25 mL columns)	120-1102	10
Column Adaptor, PE (70 mL columns)	120-1103	10
Column Adaptor, PE (150 mL columns)	120-1106	5
ISOLUTE Column Caps		
Luer tip cap (fits all columns)	1201-0120	100
Top Cap, 3 mL column	1201-0122-B	100
Top Cap, 6 mL column	1201-0123-C	100
Top Cap, 15 mL column	1201-0126-D	100
Top Cap, 25 mL column	1201-0127-E	100
Top Cap, 70 mL column	1201-0128-F	100
Top Cap, 150 mL column	1201-0129-J	50
ISOLUTE polyethylene and PTFE frits		
ISOLUTE 20 µm PE Frits, 9 mm, 3 mL	120-1033-B	100
ISOLUTE 20 µm PE Frits, 13 mm, 6 mL	120-1035-C	100
ISOLUTE 20 µm PE Frits, 16 mm, 15 mL	120-1036-D	100
ISOLUTE 20 µm PE Frits, 20 mm, 25 mL	120-1037-E	100
ISOLUTE 20 µm PE Frits, 27 mm, 70 mL	120-1038-F	100
ISOLUTE 20 µm PE Frits, 37 mm, 150 mL	120-1039-J	50
ISOLUTE 10 µm PE Frits, 9 mm, 3 mL	120-1062-B	100
ISOLUTE 10 µm PE Frits, 13 mm, 6 mL	120-1063-C	100
ISOLUTE 10 µm PE Frits, 16 mm, 15 mL	120-1065-D	100
ISOLUTE 10 µm PE Frits, 20 mm, 25 mL	120-1066-E	100
ISOLUTE 10 µm PE Frits, 27 mm, 70 mL	120-1067-F	100
ISOLUTE 10 µm PE Frits, 37 mm, 150 mL	120-1068-J	50
ISOLUTE 20 µm PTFE Frits, 9 mm, 3 mL	120-1072-B	100
ISOLUTE 20 µm PTFE Frits, 13 mm, 6 mL	120-1073-C	100
ISOLUTE 20 µm PTFE Frits, 16 mm, 15 mL	120-1075-D	100
ISOLUTE 20 µm PTFE Frits, 20 mm, 25 mL	120-1076-E	100
ISOLUTE 20 µm PTFE Frits, 27 mm, 70 mL	120-1077-F	100


SPE Dry 96 Dual

Work-up Equipment

VacMaster™-96
FlashVac™
SPE Dry®
IST Gravity Rack

VacMaster™-96

The VacMaster™-96 Sample Processing Manifold is used for reaction work-up in a microplate format. The manifold can process 96- and 24-well plates from Biotage and is compatible with a wide range of commercially available shallow and deep-well collection plates.

The VacMaster-96 manifold is constructed from lightweight polypropylene and is compatible with all common reaction and work-up solvents. The vacuum control unit is independent of the manifold, preventing solvent corrosion and allowing the manifold to be used with automation devices that have their own vacuum control.

Features and Benefits

- Process ISOLUTE-96 fixed-well plate and modular ISOLUTE Array and Array-24 plate formats
- Independent vacuum control for manual use and automation compatibility
- Small footprint
- Lightweight, solvent-resistant construction
- Sloping manifold base for efficient solvent drainage

Ordering information

Item	Description	Part Number
System		
VacMaster-96 Sample Processing Manifold	Without vacuum control unit	121-9600
VacMaster-96 Vacuum Control Options		
Control Unit	VacMaster-96 Sample Processing Manifold vacuum control unit, VCU-1	121-9601
Control Unit with vacuum generator	VacMaster-96 Sample Processing Manifold vacuum control unit with integral vacuum generator, VCU-2	121-9602
Accessories		
Replacement gasket 1		121-9612
Replacement O-ring 2		121-9613
Collection plate spacer 3	(2 mm) for deep-well format	121-9614
ISOLUTE Array plate insert 4	(6 mm) for VacMaster-96 (Acetal) [1]	121-9610
ISOLUTE Array plate insert	(6 mm) for VacMaster-96 (PVDF) [2]	
Collection plate spacer 5	(29 mm) for shallow-well format	121-9615
ISOLUTE Array plate insert 6	(12 mm) for 3M/Qiagen/Ansys plates	121-9611
IST Trap Kit		121-2095
96-well collection plates	Collection plate, 2 mL	121-5203

[1] Supplied as standard with VacMaster-96 manifold

[2] For use with aggressive solvents

ISOLUTE Array

The ISOLUTE Array-96 and Array-24 systems offer work-up solutions in a microplate format suitable for Catch & Release, scavenging SPE, filtration and phase separation applications. This modular design allows for partial population of the plate with virtually any phase, employing re-usable caps or plugs for any unused wells and increasing cost effectiveness. The ISOLUTE Array-96 accommodates up to 96, 1 or 2ml columns and the Array-24 accommodates up to 24, 6ml columns. Both configurations are resistant to commonly used organic solvents and are compatible with the VacMaster-96 Sample Processing Manifold, allowing direct elution into the appropriate collection plate. The ISOLUTE Array-24 is also compatible with commonly used synthesis and work-up instruments (e.g. Mettler Toledo MiniBlock® System).

Features and Benefits

- Catch & Release and scavenging SPE, filtration, and phase separation applications
- Simultaneous processing of up to twenty four or ninety six samples in a microplate format
- Solvent resistant polypropylene construction
- Fully compatible with the VacMaster-96 Sample Processing Manifold

Ordering information

Item	Part Number	Quantity
ISOLUTE Array-96 Accessories		
ISOLUTE Array base plate	120-1000-P01	1
Base plate sealing strips (strip of 8)	120-1200	50
Adaptors (to fit a standard vacuum manifold)	120-1201	25
Well removing tool	120-1202	1

See individual product ordering pages for information on ISOLUTE Array wells compatible with the ISOLUTE Array system.

ISOLUTE Array-24 Accessories		
ISOLUTE Array-24 base plate	121-9650	1
ISOLUTE Array-24 sealing caps	121-9660	50

See individual product ordering pages for information on ISOLUTE tab-less 6 mL columns compatible with the ISOLUTE Array-24 system.

- For further information on plate formats compatible with the VacMaster-96 manifold, see pg 220.

FlashVac™

FlashVac™-10 Sample Processing Manifold

FlashVac Sample Processing Manifolds are used to process the complete range of ISOLUTE work-up columns. The manifolds can be used for Catch & Release and scavenging SPE, filtration, and off-line sample loading prior to flash chromatography. The FlashVac-10 manifold can process up to ten 150 mL columns simultaneously, and the FlashVac-20 manifold up to twenty 25 mL columns. The FlashVac-20 manifold can also process ten 70 or 150 mL columns in a staggered setup. Both units can accommodate 19 and 25 mm collection vessels, up to 150 mm in length.

The FlashVac manifolds are manufactured from glass and high density polyethylene and are inert to commonly used synthesis and reaction work-up solvents. The vacuum control is positioned remotely from all solvent flow and collection. This prevents corrosion so flow rate control is not compromised.

The vacuum control allows flow rates to be set for processing the required number of columns. If additional or individual flow rate control is required, the FlashVac-10 and -20 manifolds can be fitted with PTFE stopcocks or stopcock/needle units (see page 224). The FlashVac manifolds are fitted with stainless steel needles as standard.

Each FlashVac manifold is fully tested during manufacturing and fitted with a vacuum relief valve. This ensures the system does not exceed -20” Hg during routine operation.

Features and Benefits

- Inert glass and polyethylene system prevents corrosion from solvents, strong acids, and bases
- PTFE stopcocks and stopcock/needle units for individual flow control
- All operations visible in glass tank
- Tall glass tank accommodates collection tubes up to 50 mL volume and 150 mm length
- Vacuum controls isolated from solvents and solvent vapors
- Collection rack handle for easy removal and transport of collected solvent fractions
- Racks accommodate collection tubes up to 25 mm diameter

IST Trap Kit

Composed of solvent-resistant materials, this vacuum-safe solvent trap can be installed between the FlashVac-10 or -20 manifold and vacuum source to collect all solvents aspirated through the SPE or filtration column during reaction workup.

Ordering Information

Item	Description	Part Number
Systems		
FlashVac-10 Sample Processing Manifold	19 mm collection tube rack	122-1019
FlashVac-10 Sample Processing Manifold	25 mm collection tube rack	122-1025
FlashVac-20 Sample Processing Manifold	19 mm collection tube rack	122-2019
FlashVac-20 Sample Processing Manifold	25 mm collection tube rack[a]	122-2025

[a] *The 25 mm positions in the FlashVac-20 manifold are staggered in order to accommodate ten 150 mL columns*

Accessories

Item	Part Number	Quantity
IST Trap Kit	121-2095	1
FlashVac-10 Complete lid	122-0047	1
FlashVac-10 19 mm collection rack	122-1030	1
FlashVac-10 25 mm collection rack	122-1034	1
FlashVac-10 and -20 replacement tank with vacuum connector	122-0049	1
FlashVac-10 and -20 replacement silicone gasket (pk/5)	122-0030	1
FlashVac-20 complete lid	122-0048	1
FlashVac-20 19 mm collection rack	122-2061	1
FlashVac-20 25 mm collection rack	122-2062	1
Universal PTFE stopcock 1	121-0009	10
PTFE stopcock/needle unit 2	121-0001	10
PTFE needle unit 3	121-0002	10
Stainless steel needle 4	121-0003	20
Stainless steel needle retainer	121-0004	10

Gravity Rack

The IST Gravity Rack is a freestanding system for processing work-up tools that require gravity flow. The system is ideal for processing ISOLUTE HM-N Supported Liquid Extraction Columns and ISOLUTE Phase Separators.

The system is constructed from polyethylene and is compatible with all ISOLUTE column configurations, 3 to 70 mL. The Gravity Rack can process 20 columns up to and including the 25 mL format simultaneously; the system can process ten 70 mL columns at any one time. The unique two-part design ensures no cross contamination issues and easy access to collected fractions. The Gravity Rack will accommodate 16 and 19 mm collection tubes and is compatible with the range of PTFE stopcock and stopcock needle options, see below. The system is supplied with stainless steel needles as standard.

Features and Benefits

- Twenty-port system for processing work-up products that require gravity flow
- Manufactured from solvent-resistant polyethylene
- Compatible with 16 and 19 mm collection tubes
- Unique design prevents sample contamination issues

Ordering Information

Item	Description	Part Number
IST Gravity Rack	16 mm collection tube rack	123-2016
IST Gravity Rack	19 mm collection tube rack	123-2019

Accessories

Item	Part Number	Quantity
Universal PTFE stopcock	121-0009	10
PTFE stopcock/needle unit	121-0001	10
PTFE needle unit	121-0002	10
Stainless steel needle	121-0003	20
Stainless steel needle retainer	121-0004	10

SPE Dry™ 96

The SPE Dry™ 96 and SPE Dry 96 Dual Sample Concentrator Systems rapidly evaporate solvents following work-up. Heated gas flow from above and below the collection plate ensures efficient solvent evaporation.

An easy-to-use front panel display allows accurate temperature programming and gas flow control.

The systems are supplied as standard with stainless steel needles and are also available with PTFE-coated needles for applications using aggressive solvents, acids, and bases.

Features and Benefits

- Solvent evaporation following work-up with Catch & Release, scavenging SPE, phase separation, or filtration
- Compatible with 24-, 48-, 96- and 384-well collection plates
- Single and two-plate systems
- Compact footprint to minimize use of fume hood workspace
- Comes standard with stainless steel needles. PTFE-coated needles available for use with aggressive solvents

Ordering Information

Item	Description	Part Number
SPE Dry 96	110 V, USA	SD-9600-DHS-NA
SPE Dry 96	240 V, UK	SD-9600-DHS-UK
SPE Dry 96	240 V, Europe	SD-9600-DHS-EU
SPE Dry 96	110 V, Japan	SD-9600-DHS-JP
SPE Dry 96	Dual, 110 V, USA	SD2-9600-DHS-NA
SPE Dry 96	Dual, 240 V, UK	SD2-9600-DHS-UK
SPE Dry 96	Dual, 240 V, Europe	SD2-9600-DHS-EU
SPE Dry 96	Dual, 110 V, Japan	SD2-9600-DHS-JP

For further information, request Technical Note PS418 SPE Dry 96 and SPE Dry 96 Dual Sample Concentrator Systems.

Flash Purification Solutions and Optimization

Purification Solutions

Integrated Flash Purification Solutions

From synthesis to purification, Biotage delivers innovative solutions to streamline your work process, enabling you to reach your purification goals faster and easier.

Sample Work-up and Purification Cartridges

Post-synthesis sample work is a routine part of the purification process and typically includes scavenging excess reagents, using Catch & Release techniques to remove impurities, aqueous extraction, removing water and/or filtration. Once a sample has been cleaned up, it is typically purified by flash chromatography.

Biotage designs, develops, and manufactures products for both sample preparation and flash purification. For work-up, products include scavenging media and cartridges, Catch & Release media and cartridges, drying media and cartridges, phase separators, and filtration columns (see page 200 for more information). For purification, a wide variety of flash cartridges and TLC plates are available to use with Biotage and FlashMaster systems (see page 247 for more information).

Discovery-Scale Systems

New Isolera™ Automated FLASH Purification Systems

Isolera™, a new more compact flash purification system with intelligent features, enables chemists to easily achieve better separations. The advanced TLC-to-gradient feature automatically creates elution gradients and suggests cartridge and sample size. Collect fractions using two wavelengths, adjust the flow rate from 1 to 200 mL/min as needed and use up to four solvents in a single gradient, for maximum purity and yield. Isolera is available in a single cartridge base model, the Isolera One, and a 4-cartridge configuration, the Isolera Four, which is ideal for multi-user or high-throughput laboratories. (see page 268 for more information).

FLASH 12+™, 25+™, and 40+™ Reservoir-based FLASH Purification Systems

Simplify and accelerate the isolation of your discovery-scale compounds with our cost-effective FLASH 12+, 25+, and 40+ reservoir-based FLASH purification systems. These systems require no electricity to operate, just compressed air, and can be used to purify up to five grams of crude sample in a single run (see page 286-293 for more information).

FlashMaster™ Personal and FlashMaster Personal Plus™ Pump-based FLASH Purification Systems

These entry-level flash systems use electric pumps to deliver solvent. The FlashMaster Personal is a single-cartridge system capable of purifying upwards of 5 grams of sample per run (see page 294 for more information). The FlashMaster Personal Plus is a two-cartridge system capable of using two cartridges in series to purify difficult samples. The second cartridge can also be used to load sample to the primary purification cartridge (see page 294 for more information).

Development-Scale Systems

FLASH 75i™ and 150i™ Systems

Save hours, even days, purifying multigram quantities of synthetic compounds with the FLASH 75i and FLASH 150 systems compared to glass column purification (see page 298 for more information). FLASH 75 and FLASH 150 purification methods can be developed directly from TLC (see page 242 for more information).

FLASH-AC™

Upgrade product quality by removing reaction by-products, color and other contaminants using activated-carbon (see page 258-264 for more information).

Optimizing FLASH Chromatography: Method Development Tips for Better Purification Results

This flash chromatography method development guide covers three specific types of flash purification methods—normal-phase isocratic, normal-phase gradient, and reversed-phase. These guidelines address important issues related to successful flash purification:

Normal-phase:

- Converting TLC (thin-layer chromatography) Rf (retention factors) to CV (column volumes)
- Determining the best solvent selectivity using TLC
- Determining the best solvent strength using TLC
- Determining the optimum cartridge size and sample load based on TLC data

Reversed-phase:

- Converting HPLC (high-performance liquid chromatography) retention times and gradient methods to CV
- Determining the optimum cartridge size and sample load based on TLC data

Normal-Phase Isocratic FLASH

1. Predicting compound retention and resolution using TLC

For successful FLASH purification, Biotage recommends method development using Biotage TLC plates. Component retention on TLC plates is measured in terms of Rf (retention factor). In FLASH purification, retention is usually measured in CV (column volumes). Methods developed using TLC are generally transferable to FLASH chromatography because the relationship between Rf and CV is reciprocal, CV=1/Rf (Figure 1).

Rf	CV
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

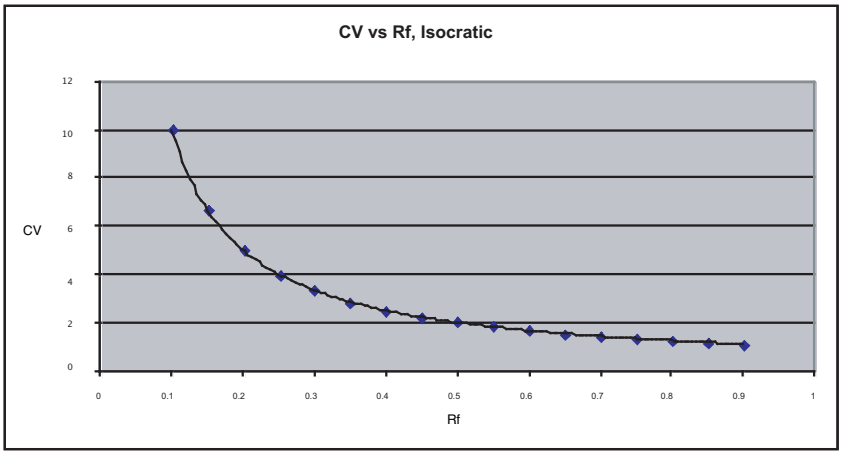


Figure 1. Rf to CV correlation, isocratic elution.

FLASH OPTIMIZATION

When scouting TLC solvent systems, it is important to realize a low Rf (0.15 – 0.35) is preferred because a lower Rf means a greater CV. Large CVs indicate increased compound-silica contact time, improving the chances of component resolution. Since CV is a measure of compound retention, then ΔCV is the measure of compound resolution, (see Figure 2). In FLASH purification, ΔCV dictates the sample load range possible for any given cartridge size, (see Table 1). For two adjacent components, a large ΔCV is desirable.

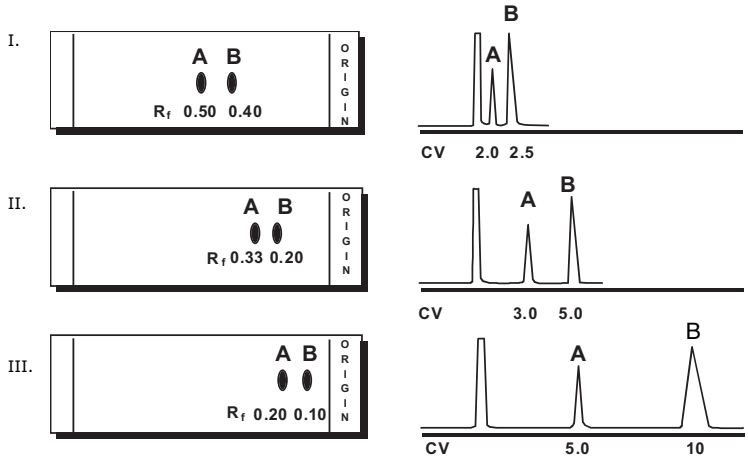


Figure 2. The Rf–CV relationship is illustrated in this graphic. (I) Although compounds A and B are well resolved on TLC with Rf of 0.5 and 0.4, respectively, FLASH purification with the same solvent conditions provides low retention and low resolution (ΔCV = 0.5) for A and B, respectively. (II) Lowering the Rf (A = 0.33, B = 0.20) provides increased retention and resolution (ΔCV = 2). (III) Extremely high resolution (ΔCV = 5) is obtained by further reducing the compounds' Rf.

Cartridge	Dimensions (mm x cm)	Typical Flow Rates (mL/min)	Column Volume	Silica Weight	Difficult ΔCV = 1	Typical ΔCV = 2	Easy ΔCV = 6
FLASH 12+S	12 x 7.5	2.5 – 12	6mL	4.5g	4 - 20mg	20 - 100mg	100 - 200mg
FLASH 12+M	12 x 15	2.5 – 12	12mL	9g	8 - 40mg	40 - 200mg	200 - 400mg
FLASH 25+S	25 x 7.5	10 – 25	24mL	20g	15 - 80mg	80 - 400mg	400 - 800mg
FLASH 25+M	25 x 15	10 – 25	48mL	40g	30 - 160mg	160 - 800mg	800 - 1600mg
FLASH 40+S	40 x 7.5	25 – 50	66mL	50g	40 - 200mg	200 - 1000mg	1 - 2g
FLASH 40+M	40 x 15	25 – 50	132mL	100g	80 - 400mg	400 - 2000mg	2 - 5g
FLASH 65i	65 x 20	65 – 85	470mL	350g	300 - 1600mg	1.6 - 8g	8 - 20g
FLASH 75S	75 x 9	100 – 250	300mL	200g	160 - 800mg	0.8 - 4g	4 - 10g
FLASH 75M	75 x 15	100 – 250	500mL	400g	400 - 2000mg	2 - 10g	10 - 20g
FLASH 75L	75 x 30	100 – 250	1000mL	800g	800 - 4000mg	4 - 20g	20 - 40g
FLASH 150M	150 x 30	500 – 1000	4.3L	2.5kg	3 - 16g	16 - 80g	80 - 160g
FLASH 150L	150 x 60	500 – 1000	8.6L	5kg	6 - 32g	32 - 160g	160 - 320g
FLASH 400M	400 x 30	7000	38L	20kg	0.03 - 0.25kg	0.25 - 1.0kg	1 - 2kg
FLASH 400L	400 x 60	7000	76L	40kg	0.06 - 0.50kg	0.5 - 2.0kg	2 - 4kg
SNAP 10g	2.1 x 5.5	10 - 20	15mL	10g	8 - 40mg	40 - 200mg	200 - 400mg
SNAP 25g	3.0 x 7.2	20 – 40	33mL	25g	20 -100mg	100 -200mg	500 – 1000mg
SNAP 50g	3.9 x 8.1	30 - 50	66mL	50g	40 - 200mg	200 - 400mg	1 - 2g
SNAP 100g	39 x 15.7	31 - 50	132mL	100g	80 - 400mg	400 - 2000mg	2 - 5g
SNAP 340g	71 x 16.8	65 - 100	470mL	340g	300 - 1600mg	1.6 - 8g	8 - 20g

Table 1. Biotage cartridge loading table for isocratic purifications

2. Optimizing selectivity

The first step in successful FLASH purification is maximizing ΔCV. Accomplish this by evaluating various solvent mixtures by TLC. Look for a binary mixture that provides the largest ΔCV between the compound of interest and all the impurities.

All solvents fall into a selectivity group. Each group has a different impact on a sample component's relative retention to another compound (selectivity). In Table 2, the most frequently used flash solvents and their selectivity groups are shown.

When possible, selectivity optimization should include mixtures of hexane with ethyl acetate (VIa), methylene chloride (V), toluene (VII), tetrahydrofuran (III), and ether (I). For more polar compounds and amines, mixtures of methylene chloride (V) with methanol (II) or acetonitrile (VIb) should be evaluated. These solvent combinations provide a broad range of separation selectivity and will help define the correct solvents for a sample's purification (Figure 3). For more discussion regarding solvent selectivity in chromatography (see Introduction to Modern Chromatography by L.R. Snyder and J.J. Kirkland[1]).

Solvent	Selectivity Group
Ether	I
Methanol	II
Ethanol	II
Isopropanol	II
Tetrahydrofuran	III
Dichloromethane	V
Acetone	VIa
Ethyl acetate	VIa
Acetonitrile	VIb
Toluene	VII
Chloroform	VIII
Hexane	-----
Heptane	-----
Isooctane	-----

Table 2. Solvent selectivity chart[1]

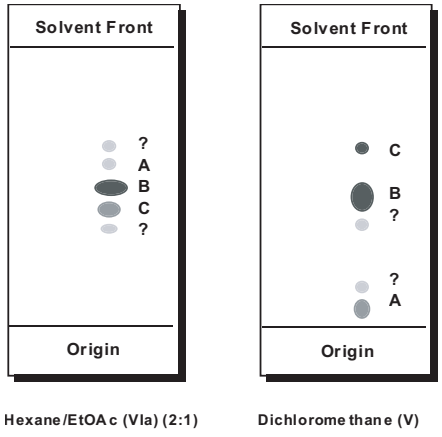


Figure 3. Impact of solvent selectivity on a chromatographic separation. In hexane/ethyl acetate the compound of interest (B) is poorly resolved from its major impurities (A and C). In dichloromethane, the retention of impurities A and C has been dramatically altered, providing a better purification of B.

3. Solvent strength optimization

When the correct solvents have been determined, the next step is to adjust the solvent composition (solvent strength) so the compound of interest elutes within the Rf range 0.15 – 0.35 (6.7 – 2.8 CV). By adjusting solvent strength to provide elution within this window, the chances for optimal purification are greatly enhanced.

As with selectivity, each solvent has its own polarity (Table 3). Each solvent mixture or mobile phase then has its own unique solvent strength. Calculation of a solvent mixture's strength is useful for comparison to other solvent mixtures. Solvent mixtures with the same strength but different selectivity can then be evaluated.

[1] L. R. Snyder and J. J. Kirkland, *Introduction to Modern Liquid Chromatography*, Wiley, 1979.

To bring the Rf of the compound of interest into the optimal range, reduce the amount of polar solvent in the mobile phase. As an example, in Figure 4, the results of a solvent selectivity study show a mobile phase of 50% hexane and 50% ethyl acetate (solvent strength = 0.30), providing adequate selectivity for a crude sample (Figure 4, top). The Rf for the compound of interest (B) is 0.4 (2.5 CV) and the Rf of the impurity (A) is 0.55 (1.8 CV), providing a ΔCV of 0.7. With a ΔCV this low, only a small sample amount can be FLASH purified before overload (resolution loss, low purity fractions) occurs. By weakening the solvent strength to 60% hexane and 40% ethyl acetate (solvent strength 0.24) (Figure 4, middle); the Rf of compound B falls to 0.2 (5 CV) and impurity A's Rf is lowered to 0.3 (3.3 CV) with a resulting ΔCV of 1.7, enabling a potential fivefold increase in sample load on a FLASH cartridge (Table 1).

Solvent	Strength
Methanol	0.95
Ethanol	0.88
Isopropanol	0.82
Acetonitrile	0.65
Ethyl acetate	0.58
Tetrahydrofuran	0.57
Acetone	0.56
Dichloromethane	0.42
Chloroform	0.40
Ether	0.38
Toluene	0.29
Hexane	0.01
Heptane	0.01
Isooctane	0.01

Table 3. A solvent mixture's strength is calculated using volume proportions and the individual solvent's strength.

In the example above, diluting a solvent mixture with a less polar solvent (hexane) from 50% to 60% reduces solvent strength, increasing compound retention and resolution (ΔCV). Also, solvent combinations of similar strength but different selectivity can also be compared. Both hexane/ethyl acetate (50:50) and hexane/dichloromethane (30:70) have solvent strength of 0.3, but ethyl acetate and dichloromethane provide different selectivity.

Formula:

$$\frac{(\text{Solvent A\% x solvent A strength})}{100} + \frac{(\text{Solvent B\% x solvent B strength})}{100}$$

Examples:

Hexane/ethyl acetate (50:50)
Solvent strength = (0.5 x 0.01) + (0.5 x 0.58) = 0.30

Hexane/ethyl acetate (60:40)
Solvent strength = (0.6 x 0.01) + (0.4 x 0.58) = 0.24

Hexane/dichloromethane (30:70)
Solvent strength = (0.3 x 0.01) + (0.7 x 0.42) = 0.30

If you find adequate component retention with a particular solvent mixture, you can prepare other solvent mixtures of similar strength but different selectivity for comparison (Figure 4, bottom).

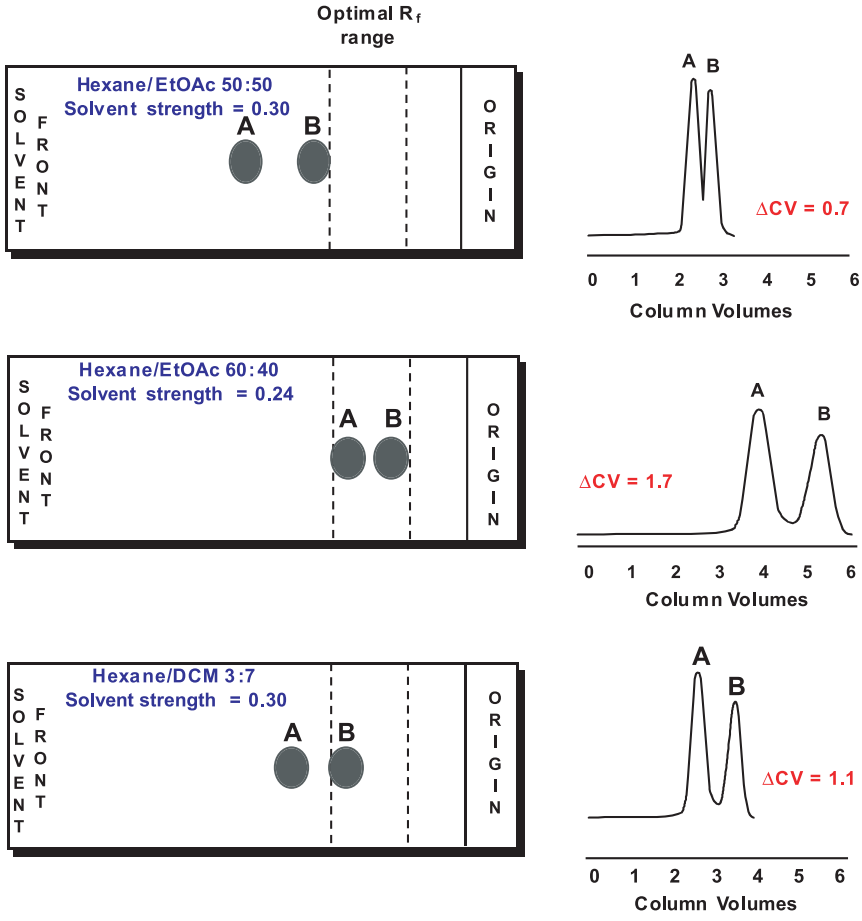


Figure 4. Examples of solvent strength on compound retention and resolution. The top TLC shows two sample components resolved with a 50:50 hexane/ethyl acetate solvent system (ΔCV = 0.7). Neither the component of interest (B) nor the impurity (A) has an Rf value within the optimal 0.15–0.35 range. This leads to poor flash purification (top chromatogram). After adjusting the solvent to 60% hexane/40% ethyl acetate, the Rf values for both A and B fall into the optimal zone (middle TLC). FLASH chromatography with these conditions (middle chromatogram) shows increased compound retention and greatly improved resolution (ΔCV = 1.7). Replacing 50:50 hexane/ethyl acetate with 30:70 hexane/dichloromethane (both 0.30 solvent strength) alters both selectivity and resolution (ΔCV = 1.1).

Once a solvent system has been selected, Rf values measured, and ΔCV values calculated, use Table 1 on page 230 to select the correct cartridge for your sample size and ΔCV. The data generated from your TLC method development efforts are applicable to any sized Biotage cartridge.

Normal-Phase Gradient Flash

Gradient elution enables chemists to speed purification, improve recovery and yield, and even increase fraction purity. In a gradient, the stronger eluting solvent concentration is increased over time, increasing the solubility of more highly retained components and causing them to elute sooner and in tighter bands compared to isocratic elution. Because solvent strength is increasing during the purification, the isocratic CV=1/Rf relationship does not hold. In a gradient, compounds elute with fewer column volumes than predicted by the isocratic relationship. The exact number of elution CV depends on the gradient slope.

Biotage chemists have developed an applicable algorithm to help chemists transfer TLC Rf to gradient CV. This algorithm* is incorporated into the SP1™ and SP4™ graphic user interface software (Touch Logic Control). If you are using a Biotage Horizon™ or original SP4, a generally applicable algorithm to use is:

Segment 1: 1/4 the TLC polar solvent concentration for 1 CV
Segment 2: Segment 1 to 2x TLC conditions over 10 CV
Segment 3: Hold segment 2 for 2 CV

These conditions work when your compound of interest has an Rf of ~0.4. For example, the TLC conditions are 8:2 hexane/ethyl acetate and the Rf is 0.4. Set the gradient as follows:

Segment 1: 5% ethyl acetate for 1 CV
Segment 2: 5% to 40% ethyl acetate over 10 CV
Segment 3: Hold 40% ethyl acetate for 2 CV

Using these conditions, a compound with an Rf of 0.4 elutes near the middle of the purification and is separated from other compounds within the Rf range of 0.1 to 0.9, if sample loading is correct (see Table 4).

* Patent pending

Cartridge	Dimensions (mm x mm)	ΔCV = 0.1-0.5 Load (g)	ΔCV = 0.6-1.0 Load (g)	ΔCV = 1.1-1.5 Load (g)	ΔCV = 1.6-2.0 Load (g)	ΔCV = 2.1-2.5 Load (g)	ΔCV = 2.6-3.0 Load (g)	ΔCV = 3.1 – 3.5 Load (g)	ΔCV = 3.6 – 4.0 Load (g)	ΔCV = 4.1 – 4.9 Load (g)	ΔCV > 5 Load (g)
FLASH 12+S	12 x 75	0.025	0.050	0.075	0.100	0.125	0.150	0.175	0.200	0.225	0.250
FLASH 12+M	12 x 150	0.050	0.100	0.150	0.200	0.250	0.300	0.350	0.400	0.450	0.500
FLASH 25+S	25 x 75	0.125	0.250	0.375	0.500	0.625	0.750	0.875	1.000	1.125	1.250
FLASH 25+M	25 x 150	0.250	0.500	0.750	1.000	1.250	1.500	1.750	2.000	2.250	2.500
FLASH 40+S	40 x 75	0.275	0.550	0.825	1.100	1.375	1.650	1.925	2.200	2.475	2.750
FLASH 40+M	40 x 150	0.50	1.10	1.65	2.20	2.75	3.30	3.85	4.40	4.95	5.50
FLASH 65i	65 x 200	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0	18.0	20.0
FLASH 75iS	75 x 90	1.2	2.4	3.5	4.7	5.9	7.0	8.2	9.4	10.6	11.8
FLASH 75iM	75 x 150	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0	18.0	20.0
FLASH 75iL	75 x 300	3.9	7.8	11.7	15.6	19.5	23.4	27.3	31.2	35.1	39.0
FLASH 150iM	150 x 300	15.6	31.2	46.9	62.5	78.1	93.8	109.4	125.0	140.6	156.2
FLASH 150iL	150 x 600	31.2	62.5	93.8	125	160	190	220	250	280	310
FLASH 400iM	400 x 300	110	220	330	440	550	670	780	890	1000	1110
FLASH 400iL	400 x 600	220	440	670	890	1110	1330	1550	1780	2000	2220
SNAP 10g	21 x 5.5	0.050	0.100	0.150	0.200	0.250	0.300	0.350	0.400	0.450	0.500
SNAP 25g	30 x 7.2	0.050	0.100	0.150	0.200	0.250	0.300	0.350	0.400	0.450	0.500
SNAP 50g	39 x 81	0.275	0.550	0.825	1.100	1.375	1.650	1.925	2.200	2.475	2.750
SNAP 100g	39 x 157	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
SNAP 340g	71 x 168	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0	18.0	20.0

Table 4. Gradient loading table

Reversed-Phase Flash

As a technique used for purification of water-soluble compounds, reversed-phase flash purification method development uses an approach different than normal-phase. The recommended approach for reversed-phase includes developing and optimizing the method using HPLC and a Biotage KP-C18 scaling column (4.6 x 250 mm). The scaling column is packed with the identical C18 phase as the KP-C18 FLASH cartridges. Begin by creating a gradient on the HPLC from 10–90% acetonitrile (or methanol) in water at 3 mL/min (1 CV/min) with this gradient.

Segment 1: 10% ACN (or MeOH) for 1 min
Segment 2: 10-90% ACN (MeOH) over 10 min
Segment 3: Hold 90% ACN for 2 min

Continue to modify this until the compound of interest is fully separated from its impurities and has a retention time of at least five minutes. On the HPLC, the optimal load can be determined by increasing the sample amount until resolution has been lost. To transfer the HPLC method to flash, convert compound retention time (Tr) to column volume using the following equation:

Compound CV = compound Tr/To, where To = the void time (about 1 min at 3 mL/min)

Use the same formula to convert the gradient program from time to CV:

Gradient segment length (time)/To = flash segment length (CV)

By using these formulas and the same solvents, reproducible reversed-phase flash gradients can be developed.

Flash Scale-up

Flash scale-up is based on equalizing solvent linear velocity and relative sample load for cartridges of different sizes or volumes. Flash purification performed on a small scale is easily scaled to larger cartridges using the scale-up factors based on media mass in Table 5, which take into account the cartridge differences.

To successfully scale a purification, find your current FLASH cartridge in the left column. Then read across that row until you find the number closest to the scale-up factor for your larger sample. Read up to find the appropriate FLASH cartridge for that scale factor. For example, if a 1-gram purification on FLASH 25+S requires scale-up to 30 g, the appropriate scale-up cartridge, according to the table below, is a FLASH 75L.

SCALE TO

SCALE FROM	4.6 x 250	Flash 12+S	Flash 12+M, SNAP 10g	Flash 25+S	Flash 25+M	Flash 40+S, SNAP 50g	Flash 40+M, SNAP 100g	Flash 65M, SNAP 340g	Flash 75S	Flash 75M	Flash 75L	Flash 150M	Flash 150L	Flash 400M	Flash 400L
4.6x250 mm	1	2	5	9	18	23	45	159	91	159	318	1273	2545	9091	18182
Flash 12+S		1	2	4	9	11	22	78	44	78	156	622	1244	4444	8889
Flash 12+M, SNAP 10g			1	2	4	5	10	35	20	35	70	280	560	2000	4000
Flash 25+S				1	2	3	5	18	10	18	35	140	280	1000	2000
Flash 25+M					1	1	3	9	5	9	18	70	140	500	1000
Flash 40+S, SNAP 50g						1	2	7	4	7	14	56	112	400	800
Flash 40+M, SNAP 100g							1	4	2	4	7	28	56	200	400
Flash 65M, SNAP 340g								1	0	1	2	8	16	57	114
Flash 75S									1	2	4	14	28	100	200
Flash 75M										1	2	4	16	57	114
Flash 75L											1	4	2	29	57
Flash 150M												1	2	7	14
Flash 150L													1	4	7
Flash 400M														1	2
Flash 400L															1

Table 5. Scale-up table for use with FLASH cartridges


Biotage® SNAP Cartridge
KP-NH™
110g

FLASH Purification Cartridges

Cartridges, Media, Samplet™ Cartridges, and Accessories

Cartridges

Flash Purification Cartridges

With the launch of SNAP cartridges in 2007, Biotage has increased the range and diversity of its flash purification cartridge line. Four distinct cartridge styles now enable the chemist to choose the cartridge which best suits the purification need and purification system:

- **SNAP Flash Cartridges**
- **Biotage FLASH+® HPFC™ cartridges**
- **Biotage ISOLUTE® FLASH cartridges**
- **Development - Scale flash cartridges**

See page 240 for more information on SNAP cartridges

All are designed to meet the high-performance requirements of Biotage HPFC (high-performance flash chromatography) systems—Isolera™ One, Isolera™ Four, SP1™, SP4™, and FlashMaster™ systems. Automated cartridge-packing systems efficiently pack Biotage FLASH cartridges to minimize performance variability. Inert polypropylene barrels (meeting extractables requirements of 21 CFR 177.1520) are packed with the highest quality silica, amino, and C18 materials available. Strict ISO quality controls and years of production experience ensure consistent performance cartridge to cartridge.

Biotage Packing Materials

KP-SIL™ Silica

The most frequently used silica for flash purification features high surface area (500 m2/g), moderate porosity (60 Å), a tight uniform particle distribution (40-63 µm), neutral pH, and low metals content. These factors combine to provide high loading capacity, efficiency, and reproducibility. ISOLUTE® silica II (Si II) is the same as KP-SIL.

KP-C18-HS™

For samples requiring water-based solvents and a lipophilic stationary phase, KP-C18-HS, a 400 m^2/g, 90 Å C18 bonded silica provides purification of polar and ionizable organic compounds. Tight, uniform particle distribution (35-70 µm) and an 18% carbon load (by weight) provide excellent efficiency, selectivity, and retention. To minimize secondary, non-specific adsorption, KP-C18-HS is end-capped with smaller organo-silanes designed to reduce the number of silanol sites remaining after bonding with C18.

ISOLUTE™ C18 (EC)

Similar to KP-C18-HS but bonded on a larger surface area silica (500 m^2/g) with a higher carbon content (20%).

KP-C18-WP™

For larger MW compounds (>5000 Da) a larger porosity stationary phase is required. The larger pores provide access for the higher MW samples, allowing them to partition and separate more effectively. KP-C18-WP is a 300 Å, 90 m^2/g C18 bonded phase with a tight, uniform particle distribution (40-63 µm) and a 3% carbon load (by weight), providing excellent efficiency, selectivity, and retention.

To minimize secondary, non-specific adsorption, KP-C18-WP is end-capped with smaller organo-silanes designed to reduce the number of silanol sites remaining after bonding with C18.

KP-C4-WP™

For larger MW compounds (>5000 Da) that are relatively hydrophobic, a less retentive version of KP-C18-WP is useful. Like KP-C18-WP, the larger pores provide access to the higher MW samples, allowing them to partition and separate more effectively; the C4 carbon chain is less hydrophobic and provides earlier elution than KP-C18-WP. KP-C4-WP is a 300 Å, 90 m2/g C4 bonded phase with a tight, uniform particle distribution (40-63 µm) and a 1.5% carbon load (by weight), providing excellent efficiency, selectivity, and retention.

To minimize secondary, non-specific adsorption, KP-C4-WP is end-capped with smaller organo-silanes designed to reduce the number of silanol sites remaining after bonding with C4.

KP-NH™

Developed for normal-phase purification of organic amines, this amine-functionalized silica provides high sample loads, excellent selectivity, and improved purity and recovery using non-chlorinated solvents. KP-NH has a surface area 230 m2/g, 100 Å pores and uniform particle distribution (40-75 µm). This unique media accepts high sample loads of polar, amine-containing samples and minimizes amine-silanol interaction.

ISOLUTE NH2™

This 1° amine-bonded silica works in a similar fashion to KP-NH, for normal-phase purification of organic amines, but also as an ion exchange media. ISOLUTE NH has a surface area 500 m^2/g, 60 Å pores and uniform particle distribution (40-63 µm). This media accepts high sample loads of polar, amine-containing samples and minimizes amine-silanol interaction and can be used to purify carbohydrate mixtures.

HP20™, HP20SS™

HP20 and HP20SS are styrene-divinyl benzene copolymers primarily used as traps for organic molecules from aqueous fermentation solutions. HP20 has a particle size of 250-600 µm, while HP20SS has a particle size of 75-150 µm. Each has a high 600 m2/g surface area, which allows a large concentration of organic materials to accumulate from aqueous solutions. HP20 and HP20SS are not available in the FLASH+ cartridge format.

Media Specifications

Packing	Chemistry	Particle Distribution (µm)	Surface Area (m^2/g)	Pore Volume (mL/g)	Pore Diameter (Å)
KP-SIL™	Silica	40-63	500	0.7	60
KP-C18-HS™	C18	37-70	400	0.95	90
KP-C18-WP™	C18	40-63	90	0.7	300
KP-C4-WP™	C4	40-63	90	0.7	300
ISOLUTE C18™(EC)	C18	40-63	500	0.7	60
KP-NH™	amine	40-75	230	0.6	100
ISOLUTE NH2™	1° amine	40-63	500	0.7	60
HP20™	S-DVB	250-600	600	1.3	300-600
HP20SS™	S-DVB	75-150	600	1.3	300-600

SNAP Cartridges

Biotage SNAP Cartridges

SNAP Cartridges

Biotage SNAP Cartridges are ready-to-use flash cartridges designed to withstand 100 psi* (7 bar) without the use of compression modules. Improved cartridge packing protocols deliver higher loading capacities with tighter elution bands resulting in higher purity fractions. They are available in five sizes (10 g, 25 g, 50 g, 100 g, 340 g) and packed with KP-SIL (silica), KP-C18-HS and KP-NH.

They are constructed with USP Class VI plastics (medical-grade) for lower extractables and cleaner fractions. SNAP enables seven types of loading techniques including three internal dry loading options. They are packed to provide the highest plate count of any 50µm particle cartridge on the market providing increased loading capacity and better separation between peaks.

SNAP® Cartridge Features and Benefits

- Luer-lock connections eliminate adapters simplifying attachment to any flash system
- "SNAP" cap eliminates use of compression module and is removable to allow dry loading
- 3000 N/M minimum performance provides narrower elution bands increasing sample load
- 100 psi pressure rating enables faster flow rates and use with viscous solvents
- Translucent barrel provides assurance that solvent is flowing and separation is occurring
- USP Class VI construction materials minimize extractables providing cleaner purified products
- Extra column head space allows samplet and bulk dry-loading to improve purification performance
- Three standard medias provide selectivity choices for optimal purification
- Pre-packed Samplet cartridges increases loading capacity and produces tighter elution bands by removing the injection solvent effect
- Self-packed Samplet™ cartridges provides other media options and pre-adsorbed sample dry loading

*SNAP 340g cartridge maximum pressure is 75psi

KP-SIL™ Silica

The most frequently used silica for flash purification features high surface area (500 m2/g), moderate porosity (60 Å), a tight uniform particle distribution (40-63 µm), neutral pH, and low metals content. These factors combine to provide high loading capacity, efficiency, and reproducibility.

KP-C18-HS™

Reversed-phase flash chromatography is a very effective purification technique. Its main application areas include polar, ionizable and highly lipophilic compounds which cannot easily be separated by normal-phase techniques.

Unlike normal-phase chromatography, reversed-phase uses a hydrophobic stationary phase (e.g. C18 or ODS) and hydrophilic mobile phases (methanol/water, acetonitrile/water). By converting silica's active, polar silanols sites to neutral, lipophilic sites, compounds that will either aggressively stick to silica or not stick at all can be retained, separated and eluted using water-based solvent systems.

KP-NH™

KP-NH chemistry shields synthetic organic amines from acidic silanols providing improved selectivity, peak shape, purity and yield. Unlike traditional silica and 1° amine (propyl amine) bonded silica, KP-NH does not require the use of chlorinated solvents or amine additives.

Biotage KP-NH flash cartridges and matching TLC plates separate 2°, 3°, and heterocyclic amines using non-chlorinated solvents. Biotage KP-NH TLC plates are made using the same chemistry as Biotage KP-NH flash cartridges. Methods developed using KP-NH TLC plates accurately transfer to KP-NH flash cartridges simplifying flash purification.

FLASH+™ Cartridges

Biotage Packed Cartridges

FLASH+™ Cartridges

FLASH+ cartridges are designed to provide maximum performance. They are available in three diameters (12 mm, 25 mm, 40 mm) and two lengths (75 mm and 150 mm) to accommodate a broad sample load range. FLASH+ cartridges are the only cartridges designed to allow five different sample loading techniques, including two liquid-load and three dry-load.

Dry loading of samples typically improves the purification because the dissolution solvent has been evaporated. FLASH+ cartridges provide the capability of not only an external dry load but also two internal dry load techniques—Samplet™ cartridges and direct, on-cartridge dry loading with sample-on-silica.

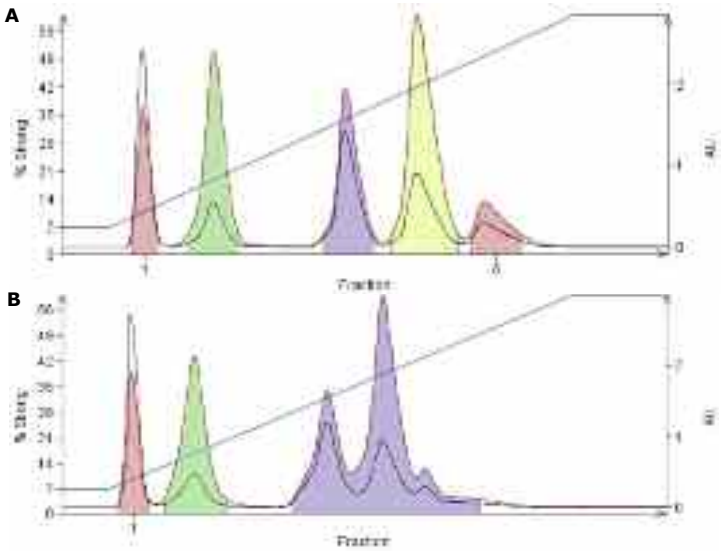
FLASH+™ Cartridge Features and Benefits

- High surface-area silica ensures high capacity and efficiency
- Uniform particle-size distribution generates narrow elution bands
- High-pressure (100 psig) capability allows faster flow rates and provides increased throughput
- Recessed inlet provides room for Biotage Samplet cartridge and axial compression for higher throughput and resolution
- Three diameters accommodate purification of milligram to multigram sample loads
- Two cartridge lengths provide options for separating simple or complex mixtures
- Scalable to larger development-scale cartridges
- Three standard medias provide selectivity choices for optimal purification
- FLASH silica available in TLC format improves optimization and analysis
- Polyethylene cartridge barrels reduce product cost and are disposable
- Cartridges meet 21 CFR 177.1520 regulations for extractables
- Prepacked cartridges eliminate hazards of loose silica and are safer than glass columns

Samplet™ cartridges

Samplet cartridges are small cartridges developed for quick and convenient sample introduction and act as sample pre-concentrators and as guard cartridges. After sample has been applied to the Samplet cartridge and the solvent evaporated, the Samplet is inserted into the cartridge, providing a dry, concentrated sample for purification, which enhances the separation and improves compound recovery, purity, and loading capacity (Figure 1)

Samplet cartridges are available for both SNAP and FLASH+ cartridges.



Conditions

System:	SP1
Solvents:	A) Hexane B) Ethyl acetate
Gradient:	7%B for 12 mL 7-60%B in 120 mL 60%B for 24 mL
Flow rate:	12 mL/min
Sample load:	150mg
Collection:	Threshold @ 0.25AU

Figure 1. Increased performance of a Samplet-loaded (A) sample compared to a liquid-loaded (B) sample purification. The dissolution solvent was methanol and the sample load was 300 mL of a 0.5 g/mL solution. By allowing the sample to dry in the Samplet cartridge, methanol's strong displacement effects are eliminated and full purification is achieved.

Development - scale FLASH

Development - Scale Cartridges

These original design flash cartridges provide excellent purification, are easy to use, and are available in 75 mm through 400 mm ID, providing a straightforward purification scale-up path. These cartridges are available packed with several different media including KP-SIL, KP-C18-HS, KP-C18-WP, KP-C4-WP, FLASH-AC, and Diaion HP20 and HP20SS.

Features and Benefits

- High surface-area media ensures high capacity and efficiency
- Uniform particle-size distribution generates narrow elution bands
- High-pressure (100 psig) capability allows faster flow rates and provides increased throughput
- Four diameters accommodate purification of milligram to kilogram sample loads
- Several cartridge lengths provide options for separating simple or complex mixtures
- Several media selections provide selectivity choices for optimal purification
- FLASH silica available in TLC format improves optimization and analysis
- Polyethylene cartridge barrels reduce product cost and are disposable
- Cartridges meet 21 CFR 177.1520 regulations for extractables
- Pre-packed cartridges eliminate hazards of loose silica and are safer than glass columns

ISOLUTE™ FLASH Cartridges

Based on a simple syringe-barrel design, ISOLUTE FLASH cartridges are utilized "on-line" with manual or automated FlashMaster™ systems or "off-line" with a FlashVac™ Sample Processing Station. ISOLUTE FLASH cartridges are available in several sizes and media quantities from 5 g to 100 g. Stationary phase availability includes KP-SIL, ISOLUTE C18 (EC), and ISOLUTE NH2.

On-line purification of synthetic sample mixtures is easy and direct using FlashMaster systems and cartridge adapters. Off-line applications include sample clean-up or sample work-up such as scavenging and Catch & Release.

Features and Benefits

- High surface-area media ensures high capacity and efficiency
- Uniform particle-size distribution generates narrow elution bands
- Nine size offerings accommodate purification of milligram to multigram sample loads
- Several media selections provide selectivity choices for optimal purification and clean-up
- FLASH silica available in TLC format improves optimization and analysis
- Polyethylene cartridge barrels reduce product cost and are disposable
- Cartridges meet 21 CFR 177.1520 regulations for extractables
- Pre-packed cartridges eliminate hazards of loose silica and are safer than glass columns

Ordering Information

SNAP Cartridge and Samplet Ordering Information

Cartridge	Size (mm)	Media Wt. (g)	Part Number	Qty/cs
Silica Cartridge (KP-SIL)				
SNAP 10g	21 x 55	10	FSK0-1107-0010	20
SNAP 25g	30 x 72	25	FSK0-1107-0025	20
SNAP 50g	39 x 81	50	FSK0-1107-0050	20
SNAP 100g	39 x 157	100	FSK0-1107-0100	20
SNAP 340g	71 x 168	340	FSK0-1107-0340	6
Silica Samplet (KP-SIL)				
SNAP 1g	19 x 6.5	1	SAS-1107-0010	20
SNAP 3g	29 x 9	2.5	SAS-1107-0025	20
SNAP 10g	37 x 17	10	SAS-1107-0100	20
SNAP 34g	69 x 18	34	SAS-1107-0340	6
KP-C18-HS Cartridge				
SNAP 12g	21 x 55	12	FSL0-1118-0012	2
SNAP 30g	30 x 72	30	FSL0-1118-0030	2
SNAP 60g	39 x 81	60	FSL0-1118-0060	2
SNAP 120g	39 x 157	120	FSL0-1118-0120	2
SNAP 400g	71 x 168	400	FSL0-1118-0400	1
KP-C18-HS Samplet				
SNAP 1g	19 x 6.5	1	SAS-1118-0012	20
SNAP 3g	29 x 9	3	SAS-1118-0030	20
SNAP 12g	37 x 17	12	SAS-1118-0120	20
SNAP 40g	69 x 18	40	SAS-1118-0400	6
KP-NH Cartridge				
SNAP 11g	21 x 55	11	FSN0-0909-0011	10
SNAP 28g	30 x 72	28	FSN0-0909-0028	10
SNAP 55g	39 x 81	55	FSN0-0909-0055	10
SNAP 110g	39 x 17	110	FSN0-0909-0110	10
SNAP 375g	71 x 168	375	FSN0-0909-0375	1
KP-NH Samplet				
SNAP 1g	19 x 6.5	1	SAS-0909-0011	20
SNAP 3g	29 x 9	3	SAS-0909-0028	20
SNAP 11g	37 x 17	11	SAS-0909-0110	20
SNAP 37g	69 x 18	37	SAS-0909-0375	6

SNAP Cartridge Accessories

Accessories	Description	Part Number	Qty/cs
Adapter kit, 10g	SNAP 10g cartridge adapter ring and connecting tubing for SP systems	410792	1
Adapter kit, 25g	SNAP 25g cartridge adapter ring and connecting tubing for SP systems	411824	1
Adapter kit, 50/100g	SNAP 50g/100g cartridge adapter ring and connecting tubing for SP systems	410797	1
Holder, 340g	SNAP 340g cartridge holder for SP systems	410800	1
Adapter kit, 340g	SNAP 340g cartridge adapter kit for non-Biotage SP systems	410805	1
Injection Valve Adapter	Adapter to attach a Biotage 3-way injection valve to a SNAP cartridge	411081	1
Empty Samplet kit, 1g	Empty Samplet kit for SNAP 1g Samplet	SES-0010	20
Empty Samplet kit, 3g	Empty Samplet kit for SNAP 3g Samplet	SES-0025	20
Empty Samplet kit, 10g	Empty Samplet kit for SNAP 10g Samplet	SES-0100	20
Empty Samplet kit, 34g	Empty Samplet kit for SNAP 34g Samplet	SES-0340	6

Ordering Information

Dry load frits, 10g	Dry load frits for 10g SNAP cartridges	SLF-0010	20
Dry load frits, 25g	Dry load frits for 25g SNAP cartridges	SLF-0025	20
Dry load frits, 50/100g	Dry load frits for 100g SNAP cartridges	SLF-0100	20
Dry load frits, 340g	Dry load frits for 340g SNAP cartridges	SLF-0340	6
Frit insertion tool, 1g empty Samplet	Frit insertion tool for 1g empty SNAP Samplet cartridges	SFS-0010	1
Frit insertion tool, 3g empty Samplet	Frit insertion tool for 3g empty SNAP Samplet cartridges	SFS-0025	1
Frit insertion tool, 10g empty Samplet	Frit insertion tool for 10g empty SNAP Samplet cartridges	SFS-0100	1
Frit insertion tool 34g empty Samplet	Frit insertion tool for 34g empty SNAP Samplet cartridges	SFS-0340	1
FlashMaster adapter	SNAP to FlashMaster II and Personal Plus adapter	411069	1

FLASH+™ Cartridge Ordering Information

Cartridge	Description (mm)	Media Wt. (g)	Column Vol. (mL)	Part Number	Qty/cs
Silica (KP-SIL)					
FLASH 12+™S	12 x 75	4.5	6	FPK0-1107-15026	20
FLASH 12+M	12 x 150	9	12	FPK0-1107-15046	20
FLASH 25+™S	25 x 75	20	24	FPK0-1107-16026	20
FLASH 25+M	25 x 150	40	48	FPK0-1107-16046	20
FLASH 40+™S	40 x 75	50	66	FPK0-1107-17026	20
FLASH 40+M	40 x 150	100	132	FPK0-1107-17046	20
C18-HS (KP-C18-HS)					
FLASH 12+S	12 x 75	5	6	FPL0-1118-15025	2
FLASH 12+M	12 x 150	10	12	FPL0-1118-15045	2
FLASH 25+S	25 x 75	22	24	FPL0-1118-16025	2
FLASH 25+M	25 x 150	44	48	FPL0-1118-16045	2
FLASH 40+S	40 x 75	55	66	FPL0-1118-17020	1
FLASH 40+M	40 x 150	110	132	FPL0-1118-17040	1
NH (Amine) (KP-NH)					
FLASH 12+S	12 x 75	5	6	FPNH-12S	20
FLASH 12+M	12 x 150	10	12	FPNH-12M	20
FLASH 25+S	25 x 75	22	24	FPNH-25S	10
FLASH 25+M	25 x 150	44	48	FPNH-25M	10
FLASH 40+S	40 x 75	55	66	FPNH-40S	5
FLASH 40+M	40 x 150	110	132	FPNH-40M	5
C18-WP (KP-C18-WP)					
FLASH 40+S	40 x 75	50	66	FPV1-0906-17020	1
FLASH 40+M	40 x 150	100	132	FPV1-0906-17040	1
C4-WP (KP-C4-WP)					
FLASH 40+S	40 x 75	50	66	FPV1-1104-17020	1
FLASH 40+M	40 x 150	100	132	FPV1-1104-17040	1

FLASH+ Samplet Cartridge Ordering Information

Cartridge	Description (mm)	Media Wt. (g)	Column Vol. (mL)	Part Number	Qty/cs
Silica (KP-SIL)					
FLASH 12+	12 Samplet	0.9	1.1	SAM-1107-1421J	48
FLASH 25+	25 Samplet	3.9	4.8	SAM-1107-16016	20
FLASH 40+	40 Samplet	9.9	12	SAM-1107-17016	20

Continued on page 248

Ordering Information

C18-HS (KP-C18-HS)					
FLASH 12+	12 Samplet	1.0	1.1	SAM-1118-1421J	48
FLASH 25+	25 Samplet	4.7	4.8	SAM-1118-16016	20
FLASH 40+	40 Samplet	11	12	SAM-1118-17016	20
NH (Amine) (KP-NH)					
FLASH 12+	12 Samplet	1.0	1.1	SAM-NH12	48
FLASH 25+	25 Samplet	4.7	4.8	SAM-NH25	20
FLASH 40+	40 Samplet	11	12	SAM-NH40	20
C18-WP (KP-C18-WP)					
FLASH 40+	40 Samplet	9.9	12	SAM-0906-17016	20
C4-WP (KP-C4-WP)					
FLASH 40+	40 Samplet	9.9	12	SAM-1104-17016	20

FLASH 75i™ and 150i™ Cartridge Ordering Information

Cartridge	Description (mm)	Media Wt. (g)	Column Vol. (mL)	Part Number	Qty/ Case
Silica (KP-SIL)					
FLASH 75S	75 x 90	200	300	FK0-1107-19165	2
FLASH 75M	75 x 150	400	500	FK0-1107-19045	2
FLASH 75L	75 x 300	800	1000	FK0-1107-19075	2
FLASH 75S (Jumbo)	75 x 90	200	300	FK0-1107-19163	10
FLASH 75M (Jumbo)	75 x 150	400	500	FK0-1107-19043	10
FLASH 75L (Jumbo)	75 x 300	800	1000	FK0-1107-19073	10
FLASH 150M	150 x 300	2500	4300	FK0-1107-25075	2
FLASH 150L	150 x 600	5000	8600	FK0-1107-25155	2
C18-HS (KP-C18-HS)					
FLASH 75S	75 x 90	250	300	FL0-1118-19160	1
FLASH 75M	75 x 150	415	500	FL0-1118-19040	1
FLASH 75L	75 x 300	830	1000	FL0-1118-19070	1
FLASH 150M	150 x 300	3585	4300	FL0-1118-25070	1
Diaion HP20					
FLASH 75S	75 x 90	270	300	FT6-2030-19165	2
FLASH 75M	75 x 150	450	500	FT6-2030-19045	2
FLASH 75L	75 x 300	900	1000	FT6-2030-19075	2
FLASH 75S (Jumbo)	75 x 90	270	300	FT6-2030-19163	10
FLASH 75M (Jumbo)	75 x 150	450	500	FT6-2030-19043	10
FLASH 75L (Jumbo)	75 x 300	900	1000	FT6-2030-19073	10
FLASH 150M	150 x 300	3600	4300	FT6-2030-25075	2
FLASH 150L	150 x 600	7200	8600	FT6-2030-25155	2
Diaion HP20SS					
FLASH 75S	75 x 90	270	300	FT6-2530-19160	1
FLASH 75M	75 x 150	450	500	FT6-2530-19040	1
FLASH 75L	75 x 300	900	1000	FT6-2530-19070	1
FLASH 150M	150 x 300	3600	4300	FT6-2530-25070	1
FLASH 150L	150 x 600	7200	8600	FT6-2530-25150	1
C18-WP (KP-C18-WP)					
FLASH 75S	75 x 90	240	300	FV1-0906-19160	1
FLASH 750M	75 x 150	400	500	FV1-0906-19040	1
FLASH 75L	75 x 300	795	1000	FV1-0906-19070	1
FLASH 150M	150 x 300	3200	8600	FV1-0906-25070	1
C4-WP (KP-C18-WP)					
FLASH 75S	75 x 90	240	300	FV1-1104-19160	1
FLASH 75M	75 x 150	400	500	FV1-1104-19040	1
FLASH 75L	75 x 300	795	1000	FV1-1104-19070	1
FLASH 150M	150 x 300	3200	8600	FV1-1104-25070	1

Ordering Information

ISOLUTE Cartridge Ordering Information

Cartridge	Description	Media Wt. (g)	Column Vol. (mL)	Part Number	Qty/ Case
Silica					
ISOLUTE 5g	Silica II, 25 5g/25ml	5	7	440-0500-E	20
ISOLUTE 10g	Silica II, 70 10g/70mL	10	14	440-1000-F	16
ISOLUTE 20g	Silica II, 70 20g/70mL	20	27	440-2000-F	16
ISOLUTE 25g	Silica II, 150 25g/150mL	25	32	440-2500-J	8
ISOLUTE 50g	Silica II, 150 50g/150mL	50	65	440-5000-J	8
ISOLUTE 70g	Silica II, 150 70g/150mL	70	83	440-7000-J	8
ISOLUTE 100g	Silica II, 22 100g/22cm	100	129	440-100G-X	12
C18					
ISOLUTE 5g	C18, 25 5g/25ml	5	7	451-0500-E	20
ISOLUTE 10g	C18, 70 10g/70mL	10	14	451-1000-F	16
ISOLUTE 20g	C18, 70 20g/70mL	20	27	451-2000-F	16
ISOLUTE 25g	C18, 150 25g/150mL	25	32	451-2500-J	8
ISOLUTE 50g	C18, 150 50g/150mL	50	65	451-5000-J	8
ISOLUTE 70g	C18, 150 70g/150mL	70	83	451-7000-J	8
NH					
ISOLUTE 5g	NH, 25 5g/25ml	5	7	454-0500-E	20
ISOLUTE 10g	NH, 70 10g/70mL	10	14	454-1000-F	16
ISOLUTE 20g	NH, 70 20g/70mL	20	27	454-2000-F	16
ISOLUTE 25g	NH, 150 25g/150mL	25	32	454-2500-J	8
ISOLUTE 50g	NH, 150 50g/150mL	50	65	454-5000-J	8
ISOLUTE 70g	NH, 150 70g/150mL	70	83	454-7000-J	8

Method Development Tools

KP-SIL and KP-NH TLC Plates

To ensure optimal compound purity, Biotage offers KP-SIL and KP-NH on TLC (thin-layer chromatography) plates to assist in FLASH optimization and post-chromatographic analysis. The TLC plate has the exact chemistry and physical specifications as the FLASH grade silica and KP-NH but with a smaller particle size ensuring that methods developed on Biotage TLC plates directly scale to Biotage FLASH cartridges.

Scaling Columns

Another useful method development tool is the scaling column. Used with an HPLC, these HPLC columns are used to optimize elution conditions and perform loading studies. It is the best reversed-phase flash method development technique. Methods developed on scaling columns are directly transferable to flash because the same flash media is used to pack the scaling column so no compensation for particle size is required. Once a method has been developed on a scaling column, flash purification uses the same elution conditions (run time and solvent ratio) but requires only an increase in flow rate and sample size.

Scale to

Scale from	Media mass (g)	4.6 x 250	Flash 12+S	Flash 12+M, SNAP 10g	Flash 25+S	SNAP 25g	Flash 25+M	Flash 40+S, SNAP 50g	Flash 40+M, SNAP 100g
4.6 x 250	2	1	2	4	10	13	20	25	50
Flash 12+S	4.5		1	2	4	6	9	11	22
Flash 12+M, SNAP 10g	9			1	2	3	4	6	11
Flash 25+S	20				1	1	2	3	5
SNAP 25g	25					1	2	2	4
Flash 25+M	40						1	1	3
Flash 40+S, SNAP 50g	50							1	2
Flash 40+M, SNAP 100g	100								1

Scale to

Scale from	Media mass (g)	Flash 65i, SNAP 340g	Flash 75S	Flash 75M	Flash 75L	Flash 150M	Flash 150L	Flash 400M	Flash 400L
4.6 x 250	2	175	100	200	400	1,250	2,500	10,000	20,000
Flash 12+S	4.5	78	44	89	178	556	1,112	4,449	8,898
Flash 12+M, SNAP 10g	9	39	22	44	89	278	556	2,224	4,449
Flash 25+S	20	18	10	20	40	125	250	1,000	2,000
SNAP 25g	25	14	8	16	32	100	200	800	1,600
Flash 25+M	40	9	5	10	20	63	125	500	1,000
Flash 40+S, SNAP 50g	50	7	4	8	16	50	100	400	800
Flash 40+M, SNAP 100g	100	4	2	4	8	25	50	200	400
Flash 65i, SNAP 340g	350	1	1	1	2	7	14	57	114
Flash 75S	200		1	2	4	13	25	100	200
Flash 75M	400			1	2	6	13	50	100
Flash 75L	800				1	3	6	25	50
Flash 150M	2,500					1	2	8	16
Flash 150L	5,000						1	4	8
Flash 400M	20,000							1	2
Flash 400L	40,000								1

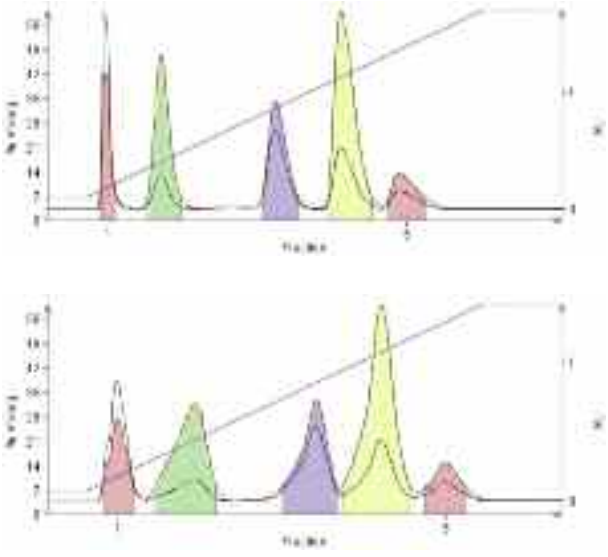
Ordering Information

Description	Media	Part Number	Qty/Case
TLC plates			
2.75 cm x 7.5 cm, glass	KP-SIL	TLC-2575-FI	100
5 cm x 10 cm, glass	KP-SIL	TLC-0510-FI	50
10 cm x 10 cm, glass	KP-SIL	TLC-1010-FI	25
10 cm x 10 cm, pre-scored	KP-NH	TLC-KPNH-2510-F1	25
Scaling columns			
KP-SIL Silica	4.6 mm x 250 mm	S1K0-1107-93050	1
KP-SIL Silica	10 mm x 250 mm	S1K0-1107-95050	1
KP-C18-HS	4.6 mm x 250 mm	S1L0-1118-93050	1
KP-C18-HS	10 mm x 250 mm	S1L0-1118-95050	1
Diaion HP20	4.6 mm x 250 mm	SFT6-2030-93050	1
Diaion HP20	10 mm x 250 mm	SFT6-2030-95050	1
Diaion HP20SS	4.6 mm x 250 mm	SFT6-2530-93050	1
Diaion HP20SS	10 mm x 250 mm	SFT6-2530-95050	1

FLASH Accessories

Compression Modules

Compression modules ensure cartridge stability under pressure (up to 100 psi or 7 bar) and actually improve cartridge performance by compressing the media bed, minimizing excess interstitial volume that causes band-broadening. Biotage FLASH+ cartridges require the use of compression modules to ensure quality performance and are available for 12+S, 12+M, 25+S, 25+M, 40+S, and 40+M cartridges. A FLASHPac+ kit is available which incorporates all three head assemblies and all six barrel sizes.



Conditions

System: SP1
Cartridges: A) Biotage 12+M (9 g) w/ compression module
B) Competitive cartridge (12 g) w/o compression module
Solvents: A) Hexane
B) Ethyl acetate
Gradient: 7% B for 12 mL
7-60% B in 120 mL
60% B for 24 mL
Flow rate: 12 mL/min
Sample load: 150mg in 300 mL of acetone

Figure 2. By axially compressing the packed bed, interstitial volume is minimized, helping to ensure maximum bed density and available surface area. This is seen in the comparison of a Biotage FLASH 12+M cartridge (A) containing 9 grams of silica and a competitive cartridge (B) with 12 grams of silica that does not require a compression module. Not only is the peak shape improved but 33% more sample load per gram of silica is possible.

FLASH+ Compression Modules

FLASH+ compression modules' patented ZIF™ design incorporates performance-enhancing features which provide axial compression to improve separation and sample load, the ability to use on-cartridge, internal dry sample loading with a Samplet cartridge or loose adsorbent, and leak-free operation to 100 psi (Figure 2). The fluid path is made from stainless steel and fluoropolymers, ensuring compatibility with most sample types and solvents.

Ordering Information

Development-Scale Compression Modules

Compression modules for development-scale cartridges perform either axial compression (65i) or patented radial compression (75i, 150i, 400i) to improve cartridge peformance. FLASH 75i and 150i compression modules use a patented knife-edge to seal the system to 100 psi pressure.

Features and Benefits

- Compression modules exert either axial compression or radial compression to maximize sample contact with silica (higher sample load) and separation performance (greater purity, recovery)
- FLASH+ compression modules built with stainless steel and fluoropolymers for maximum durability and effectiveness
- FLASH+ compression modules available for either Samplet cartridges or on-cartridge dry load
- Compression modules seal up to 100 psi, ensuring leak-free operation even with high flow rates and reversed-phase solvents
- Knife-edge sealing mechanism in the FLASH 75 and FLASH 150 compression modules seals to 100 psi without o-rings

Ordering Information

Cartridge	Dimensions	Description	Part Number
FLASH+ Compression Modules			
12+S	12 x 75 mm	FLASH 12+S comp. mod., Samplet	07857
12+M	12 x 150 mm	FLASH 12+M comp. mod., Samplet	07858
12+S	12 x 75 mm	FLASH 12+S comp. mod., dry load	09553
12+M	12 x 150 mm	FLASH 12+M comp. mod., dry load	09554
25+S	25 x 75 mm	FLASH 25+S comp. mod., Samplet	FC-022-16024
25+M	25 x 150 mm	FLASH 25+M comp. mod., Samplet	FC-022-16044
25+S	25 x 75 mm	FLASH 25+S comp. mod., dry load	09555
25+M	25 x 150 mm	FLASH 25+M comp. mod., dry load	09556
40+S	40 x 75 mm	FLASH 40+S comp. mod., Samplet	07975
40+M	40 x 150 mm	FLASH 40+M comp. mod., Samplet	07976
40+S	40 x 75 mm	FLASH 40+S comp. mod., dry load	09551
40+M	40 x 150 mm	FLASH 40+M comp. mod., dry load	09552
FLASH+ (all)		12+S through 40+M comp. mod., dry load	08615
FLASH Development-Scale Compression Modules			
65iM	65 x 200 mm	FLASH 65iM comp. mod.	07868
75iS	75 x 90 mm	FLASH 75iS comp. mod.	FC-022-19161
75iM	75 x 150 mm	FLASH 75iM comp. mod.	FC-022-19041
75iL	75 x 300 mm	FLASH 75iL comp. mod.	FC-022-19071
75iS (AutoFlash)	75 x 90 mm	FLASH 75iS module, AutoFlash, gauge & valve	AF-005-19160
75iM (AutoFlash)	75 x 150 mm	FLASH 75iM module, AutoFlash, gauge & valve	AF-005-19040
75iL (AutoFlash)	75 x 300 mm	FLASH 75iL module, AutoFlash, gauge & valve	AF-005-19070
150iM	150 x 300 mm	FLASH 150iM comp. mod.	FC-022-25071
150iL	150 x 600 mm	FLASH 150iL comp. mod.	FC-022-25151

FLASH Accessories

FlashPack™ Modules and Plungers

The ISOLUTE syringe barrel cartridge format utilizes a simple, effective plunger to attach to FlashPack cartridge modules and FlashMaster flash purification systems.

FlashPack cartridge modules are available for single cartridges or for multiple cartridge use (5- and 8-position), can be attached to most commercially available flash systems, and can be used with any ISOLUTE cartridge size. The 5- and 8-position modules provide the ability to attach cartridges of different sizes on the same module. FlashPack modules are spring-tensioned to ensure a positive seal at the cartridge outlet.

Made from PEEK and fluoropolymers, the FlashPack plungers are inert, seal to 50 psi, and use a standard 1/4-28 union on the inlet. FlashPack plungers are available for all ISOLUTE flash cartridges from 5g to 100g.

FlashPack Module and Plunger Features and Benefits

- FlashPack modules available in single, 5- or 8-position formats for maximum throughput
- Can be used with most flash systems and all ISOLUTE flash cartridges
- Positive spring-tension ensures pressure stability to 50 psi (3.5 bar)
- FlashPack plungers enhance ISOLUTE cartridge use with FlashPack modules and FlashMaster systems

Ordering Information

Module	Description	Part Number
Single	FlashPack single cartridge module without plunger	01-999-000
5-position	FlashPack 5-cartridge module without plungers	05-999-000
8-position	FlashPack 8-cartridge module without plungers	08-999-000

ZIF-SIM™

SIM™ and ZIF-SIM™ External Dry Loading Systems

Sample dry loading is a technique that allows chemists to purify samples which either require a large dissolution volume or require very strong dissolution solvents; both negatively impact the purification results. In dry loading, an adsorbent (e.g., KP-SIL silica or HM-N diatomaceous earth) is added to the dissolved reaction mixture in a ratio of 3 parts sorbent to 1 part sample mass, mixed and then evaporated until a dry powder forms. The dry powder is packed into a SIM module or ZIF-SIM (zero insertion force) cartridge and installed in the flash purification system between the pump and the main purification cartridge.

Biotage manufactures SIMs and ZIF-SIMs, which are available for uses with all cartridge sizes. ZIF-SIMs are available in three sizes (10 mL, 35 mL, and 60 mL) for use with FLASH+, Flash 65 and all SNAP cartridges. A ZIF-SIM kit comes with a reusable sealing head, 20 disposable cartridges, 20 frits, a frit insertion tool, and connecting tubing for FLASH+ or FLASH 65 compression modules. ZIF-SIMs attach directly to SNAP cartridge through their Luer connectors.

SIM modules are used with FLASH 65 and larger flash cartridges and consist of a reusable stainless steel reservoir, sealing rings, frits, frit insertion tool, connecting tubing, and external filter housing. SIM modules are available in 100 mL, 500 mL, 1000 mL, 2000 mL, and 10,000 mL volumes. SIM modules can also be used to inject large-volume sample solutions where a syringe is not appropriate.

Features and Benefits

- Provide ability to easily dry load samples to improve purification performance
- Broad size range accommodates dry load needs at scales from mg to kilograms
- SIM modules provide dry loading and liquid loading option for large-volume samples
- Disposable ZIF-SIM cartridges are convenient and cost efficient

Liquid Injection Valve

Liquid Sample Injection Valve

For liquid samples, Biotage offers a three-way injection valve that attaches directly to Biotage compression modules. This stainless steel valve comes complete with fingertight fittings and a Luer adapter for syringe injection. The straight-through injection design contains only 180 µL to minimize wash volume and minimizes precipitation potential.

Features and Benefits

- Stainless steel construction for inertness and durability
- Straight-through design eliminates angles and minimizes unswept volume
- Compatible with all FLASH+ and development-scale compression modules

Ordering Information

Size	Description	Part Number
ZIF-SIM		
10 mL	ZIF-SIM head assembly, 10 mL, incl. 20 barrels and frits	FZIM-0010
35 mL	ZIF-SIM head assembly, 35 mL, incl. 20 barrels and 20 frits	FZIM-0035
60 mL	ZIF-SIM head assembly, 60 mL, incl. 20 barrels and 20 frits	FZIM-0060
ZIF-SIM barrels and frits		
10 mL	Replacement 10 mL barrels and frits, 20/pk	SBF-0010
35 mL	Replacement 35 mL barrels and frits, 20/pk	SBF-0035
60 mL	Replacement 60 mL barrels and frits, 20/pk	SBF-0060
Accessories		
3-way injection valve		FIV-VLV-1000

Samplet™ Heating Blocks

Samplet™ Heating Blocks

Samplet cartridge heating blocks are designed to enhance solvent evaporation from Samplet cartridges when used in a vacuum oven or hot plate by improving heat transfer to the cartridge, thereby decreasing solvent evaporation time.

These modular blocks are constructed of solid anodized aluminum for maximum heat retention and to provide uniform cartridge heating and are machined to standard microtiter plate dimensions for easy integration with an automated liquid handler. Each anodized block is Teflon® coated for added chemical resistance and contains one thermometer and one thermocouple well to ensure accurate temperature control and monitoring.

Features and Benefits

- Anodized and Teflon® coated solid aluminum blocks ensure uniform cartridge heating and chemical resistance
- Improved heat transfer to Samplet cartridges to decrease drying time
- Microtiter plate dimensions for easy integration with an automated liquid handler
- Available in 12, 25, and 40 sample-loading cartridges
- Protective sleeves available to minimize block contamination

Samplet Heating Blocks

Ordering Information

Item	Description	Part Number
12+ Samplet Heating Block	Solid aluminum block with Teflon® coating holds 24 12+ Samplet cartridges and sleeves	09644
12+ Sleeves	Straight-side polyethylene shell for use with 12+ Samplet cartridges and heating blocks, pack of 24	09641
25+ Samplet Heating Block	Solid aluminum block with Teflon® coating holds 8 25+ Samplet cartridges and sleeves	09645
25+ Sleeves	Straight-side polyethylene shell for use with 25+ Samplet cartridges and heating blocks, pack of 24	09642
40+ Samplet Heating Block	Solid aluminum block with Teflon® coating holds 4 40+ Samplet cartridges and sleeves	09646
40+ Sleeves	Straight-side polyethylene shell for use with 40+ Samplet cartridges and heating blocks, pack of 24	09643

FLASH-AC™

Activated-Carbon Prepacked Cartridges

Research, Development and Production-scale Purifications

FLASH-AC™ Activated-Carbon Cartridges

- High-performance, easy-to-use cartridges for the purification of pharmaceuticals and fine chemicals
- Available in 12-mm, 75-mm, 150-mm, and 400-mm cartridge diameters
- Provide a clean, efficient, and convenient process for carbon-adsorption in a cGMP (current Good Manufacturing Practices) environment
- Engineered for optimum adsorption kinetics and fluid hydraulics for simple and effective purifications
- Custom-packing services of specific carbon media available, please inquire.

Biotage FLASH-AC™ cartridges are well suited for the pre-treatment of compounds that will be crystallized for final purification. Pre-treatment with FLASH-AC can effectively remove contaminants that co-crystallize with the product. FLASH-AC cartridges are recommended for the following applications:

- Removal of reaction by-products, color, and other contaminants
- Removal of catalysts
- Removal of lipopolysaccharide (LPS) pyrogens
- Clean-up of degraded reagents
- Predictable scale-up from research through production

How It Works

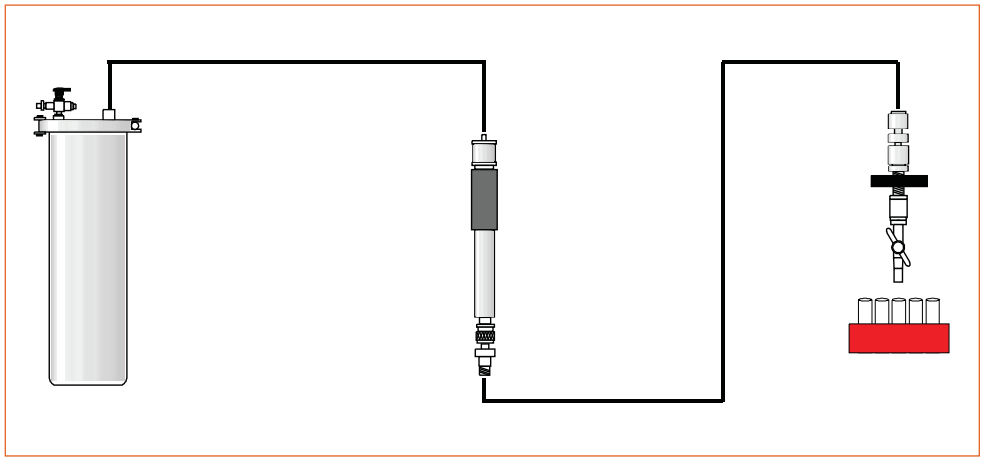


Figure 1. The FLASH-AC™ 12 cartridge (12-mm ID) fits into a standard FLASH purification system. See page 264 of this catalog for a complete description of FLASH 12 systems and options.

Batch vs. Cartridge Convenience

FLASH-AC Cartridges Easier to Use than Batch Processes

- Insert a pre-packed FLASH-AC cartridge into the compression module
- Fill the pressure reservoir with solution
- Apply gas pressure
- Collect purified solution

Clean-up is Even Easier

- Drain and blow down the system
- Remove the top from the compression module
- Remove the spent pre-packed cartridge, seal both ends, send out for disposal
- No reactors to clean
- No exposure to potentially hazardous materials

Batch vs. Cartridge Performance

The graph in Figure 2 clearly demonstrates that FLASH-AC cartridges are much more effective in removing impurities than a batch-mode process.

Even with a 24-hour contact time, the batch process removed only 18% of the contaminant. By contrast, the FLASH-AC cartridge removed 100% of the contaminant and did so in less than one-tenth the time. (For complete details about this test, please see Biotage Application Note 12 "Purifying Labile Reagents with FLASH-AC™ Cartridges" on our Web site, www.Biotage.com.)

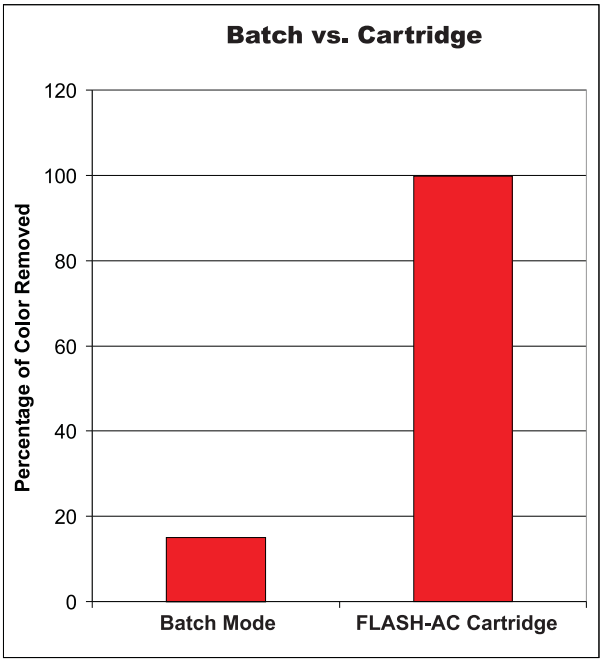


Figure 2. FLASH-AC Cartridges vs. batch-mode process for removing impurities

FLASH-AC™

Benefits of the FLASH-AC Cartridges

- Reduce process time up to 10X
- Eliminate loose carbon to reduce reactor and piping cleaning
- Eliminate the need for recrystallization and improve product yields, production rates, and solvent consumption
- Simplify operation: ready-to-use cartridge reduces set-up and clean-up times

Quality Assurance

- Manufactured in an ISO 9000-2001 certified facility
- Completely traceable materials
- Plastic components meet 21 CFR 177.1520 requirements for all components
- Certificate of compliance for activated-carbon media

Superior Packing Technology

Our proprietary packing technique is critical to the high performance of the FLASH-AC cartridges. The radial compression of the cartridge eliminates early breakthrough and provides predictable scale-up.

A poorly packed column allows solution to pass through only partially treated, leading to early contaminant breakthrough and poor carbon utilization. Biotage's high-performance FLASH-AC media provides the optimum balance between adsorption kinetics and hydraulic pressure-drop for maximum performance.

FLASH-AC Specifications

Cartridge	Dimensions (mm x cm)	Typical Load (L)	Flow Rate (mL/min)
FLASH AC™ 12S	12 x 7.5	0.1 - 5	20 - 15
FLASH AC 12M	12 x 15	0.1 - 5	20 - 15
FLASH AC™ 75S	75 x 9	50 - 300	50 - 600
FLASH AC 75M	75 x 15	50 - 300	50 - 600
FLASH AC 75L	75 x 30	100 - 600	50 - 600
FLASH AC™ 150M	150 x 30	300 - 1500	0.2 - 2.4 (L/min)
FLASH AC 150L	150 x 60	600 - 3000	0.2 - 2.4 (L/min)
FLASH AC™ 400M	400 x 30	2500 - 1000	2 - 15 (L/min)
FLASH AC 400L	400 x 60	2500 - 10000	2 - 15 (L/min)

FLASH-AC™ Cartridges Provide Predictable Scale-up

Testing has demonstrated an excellent correlation from a lab-scale FLASH-AC purification and the actual full-scale performance. Convert existing batch and deep-bed processes to FLASH-AC cartridges with a minimal amount of process development and validation.

Contact Biotage's 1-POINT SUPPORT team for assistance with scale-up matters:

US: 1 800 446 4752 EU: +46 18 56 59 11 JP: +81 422 28 1233

Production Scale FLASH-AC

FLASH-AC 150-mm and 400-mm cartridges are currently in use at major pharmaceutical companies around the world. Biotage products provide standard and custom approaches to activated-carbon purifications.

Ordering Information

FLASH-AC Ordering Information

Item	Description	Part Number	Qty/Case
Acid-Activated Carbon Cartridges			
FLASH-WAC-12S	12 mm x 7.5 cm	C1YR-4021-15026	20
FLASH-WAC-12M	12 mm x 15 cm	C1YR-4021-15046	20
FLASH-WAC-75S	75 mm x 9 cm	C1YR-4021-19163	10
FLASH-WAC-75M	75 mm x 15 cm	C1YR-4021-19043	10
FLASH-WAC-75L	75 mm x 30 cm	C1YR-4021-19073	10
FLASH-WAC-150M	150 mm x 30 cm	C1YR-4021-25075	2
FLASH-WAC-150L	150 mm x 60 cm	C1YR-4021-25155	2
FLASH-WAC-400M	400 mm x 30 cm	C1YR-4021-50075	2
FLASH-WAC-400L	400 mm x 60 cm	C1YR-4021-50155	2

The FLASH purification systems sold in this catalog readily accept FLASH-WAC acid-activated carbon cartridges, as indicated above.

FLASH-AC Systems Ordering Information

FLASH-AC Cartridge Model	Compatible FLASH Purification System	FLASH System Part Number
12S	FLASH 12i	SF-020-15024
12M	FLASH 12i	SF-022-15024
75S	FLASH 75S	SF-022-19161
75M	FLASH 75M	SF-022-19041
75L	FLASH 75L	SF-022-19071
75S	AUTOFLASH 75S	AF-005-19160
75M	AUTOFLASH 75M	AF-005-19040
75L	AUTOFLASH 75L	AF-005-19070
150M	FLASH 150M	SF-022-25071
150L	FLASH 150L	SF-022-25151
400M	FLASH 400M	SF-521-50070
400L	FLASH 400L	SF-521-50150

FLASH 12i: The Purification Setup
FLASH-AC-12 Cartridges

The FLASH 12i™ system includes one compression module (FLASH 12Si, 12 mm ID x 7.5 cm L), one FLASH 12M barrel (12 mm x 15 cm, interchangeable with the 12Si module), one injection valve, one solvent reservoir, one ZIF-SIM10™ sample-loading cartridge, one stand, a start-up kit, and a user's manual. This system is also available without the ZIF-SIM™. (For a description of ZIF-SIMs, see page 254 of this catalog.)

FLASH 12i Ordering information

Item	Description	Part Number
FLASH 12i with ZIF-SIM	Full system with ZIF-SIM	SF-022-15024
FLASH 12i	Full system, no ZIF-SIM	SF-020-15024

Diaion HP20 and HP20SS

Chemical adsorption (chemisorption) involves the formation of strong chemical interactions between adsorbate molecules and specific surface locations used to remove contamination or to concentrate compounds of interest. Organic resins (HP20, HP20SS) are used in fermentation synthesis to trap and enrich the organic compounds created.

FLASH 40i (i-style) Ordering Information

Cartridge	Description (mm)	Media Wt. (g)	Column Vol. (mL)	Qty/ Case	Part Number
Diaion HP20					
FLASH 40S	HP20, 40 x 70	58	75	12	FT6-2030-17024
FLASH 40M	HP20, 40 x 150	115	150	12	FT6-2030-17044
FLASH 75S	HP20, 75 x 90	230	90	2	FT6-2030-19165
FLASH 75S	HP20, 75 x 90	230	90	10	FT6-2030-19163
FLASH 75M	HP20, 75 x 150	460	150	2	FT6-2030-19045
FLASH 75M	HP20, 75 x 150	460	150	10	FT6-2030-19043
FLASH 75L	HP20, 75 x 300	920	300	2	FT6-2030-19075
FLASH 75L	HP20, 75 x 300	920	300	10	FT6-2030-19073
FLASH 150M	HP20, 150 x 300	2,875	300	2	FT6-2030-25075
FLASH 150L	HP20, 150 x 600	5,750	600	2	FT6-2030-25155
Diaion HP20SS					
FLASH 40S	HP20SS, 40 x 70	58	75	1	FT6-2530-17020
FLASH 40M	HP20SS, 40 x 150	115	150	1	FT6-2530-17040


Biolage

Isolera™ FLASH Purification Systems

Fast, Intuitive, Automated Flash Purification

Isolera FLASH Purification Systems

Isolera™, a new more compact flash purification system with intelligent features, enables chemists to easily achieve better separations. The advanced TLC-to-gradient feature automatically creates elution gradients and suggests cartridge and sample size. Collect fractions using two wavelengths, adjust the flow rate from 1 to 200 mL/min as needed and use up to four solvents in a single gradient, for maximum purity and yield.

Isolera is available in a single cartridge base model, the Isolera One, and a 4-cartridge configuration, the Isolera Four, which is ideal for multi-user or high-throughput laboratories.

Faster Flow Rates – increase productivity and save valuable time

With a flow range of 1 to 200 mL/min, Isolera dramatically shortens purification run-times. For example, a 10.5 g sample was purified at 200 mL/min on a 340 g Biotage SNAP cartridge in less than 19 minutes, see Figure 1. If this same separation had been performed using a typical flash system with a 100 mL/min flow rate limitation, the purification would have taken twice as long.

Largest integrated fraction capacity

Isolera offers an impressive 4.8 L fraction capacity that can rapidly be doubled to 9.6 L with the expanded fraction capacity option (EXP). This allows large cartridges or multiple samples to be purified on the system without the need for rack changes.

Collect on 2 separate wavelengths – Recover more compounds

Collect eluting compounds that don't absorb at the primary wavelength using the variable wavelength detector option. Instead of fractionating on a single wavelength while monitoring a second, Isolera can fractionate simultaneously on two unique, user-defined wavelengths. This capability enables chemists to recover more of the compounds and get cleaner fractions, as highlighted in Figure 2.

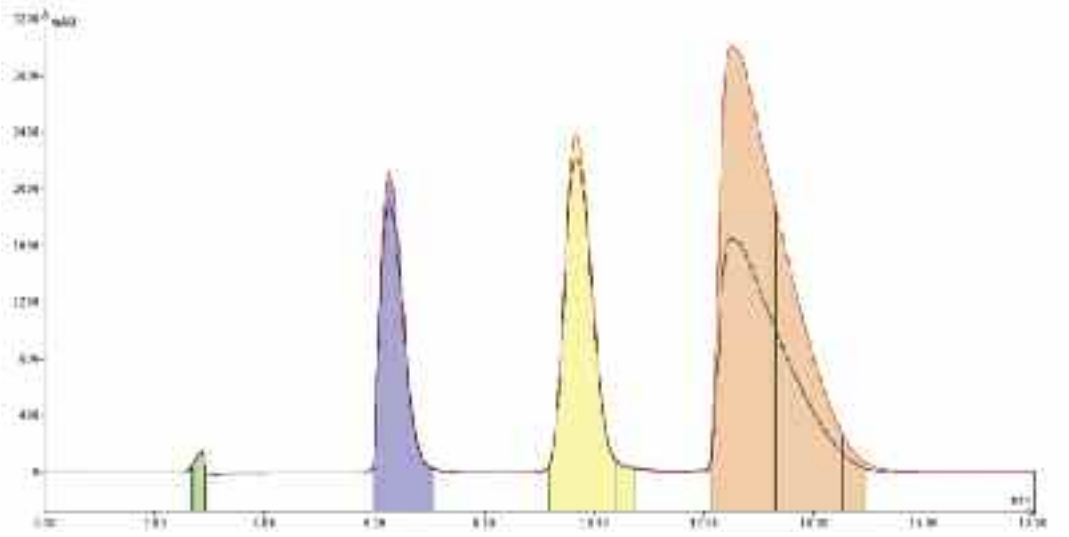


Figure 1. The value of fast flow rates can be seen in the 10.5 gram purification at 200 mL/min using a SNAP 340g KP-SIL cartridge on an Isolera One. The total run time is 18.8 minutes.

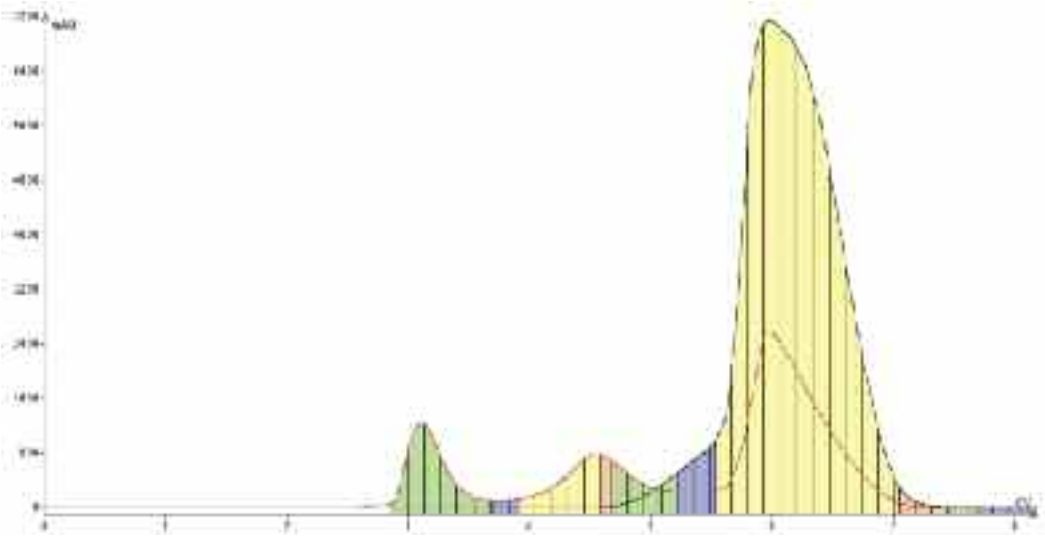


Figure 2. Fractionation using two wavelengths ensures collection of UV absorbing compounds at both wavelengths without sacrificing valuable fraction collection capacity in a "collect all" mode.

Quatro-binary Gradient – Use up to four solvents in a single gradient

Easily purify samples with diverse polarity using the quatro-binary gradient feature. A traditional binary gradient of hexane/ethyl acetate can graduate to a powerful quartro-binary gradient of hexane/ethyl acetate to ethyl acetate/methanol to methanol/water without fear of solvent immiscibility or emulsions. This gives chemists a simple way to purify poorly retained and highly retained compounds using a single gradient.

Isocratic co-solvent – Increase compound solubility and recovery

Precipitating compounds decrease recovery and can create system overpressure failures, often requiring a service call. Isolera systems alleviate this issue by offering the ability to isocratically pump a third co-solvent into the binary gradient helping to maintain compound solubility.

Default Methods – Simplify method creation

Isolera provides default methods built around both TLC conditions and SNAP cartridge sizes enabling chemists to quickly get you running and speed you to faster purification results.

On-the-fly editing – Modify purification runs in progress

Edit the gradient (click & drag points AND segments), the flow rate, collection volume, fraction wavelengths and modes, and even add more collection racks if you need to all while the run is in progress.

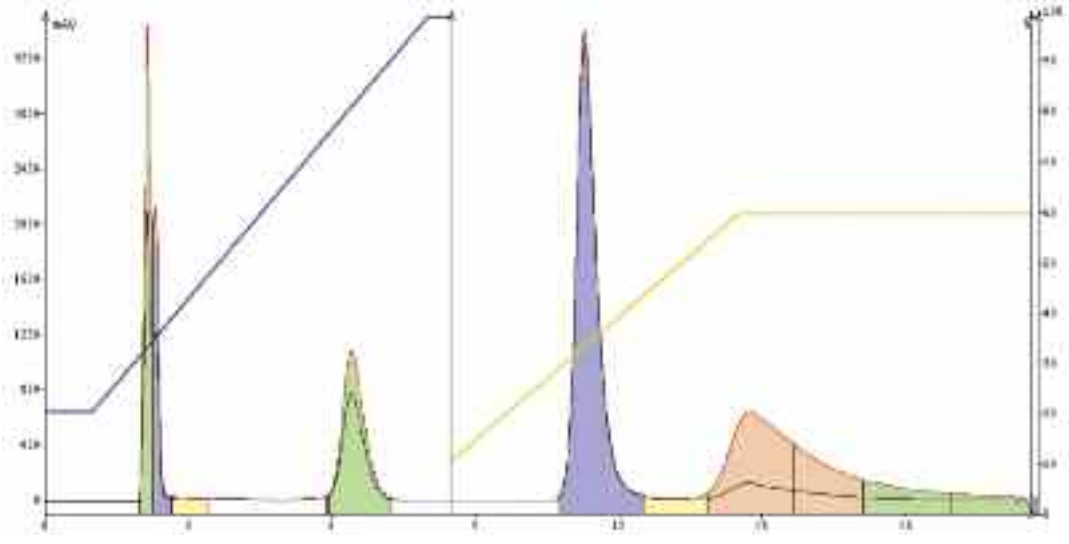
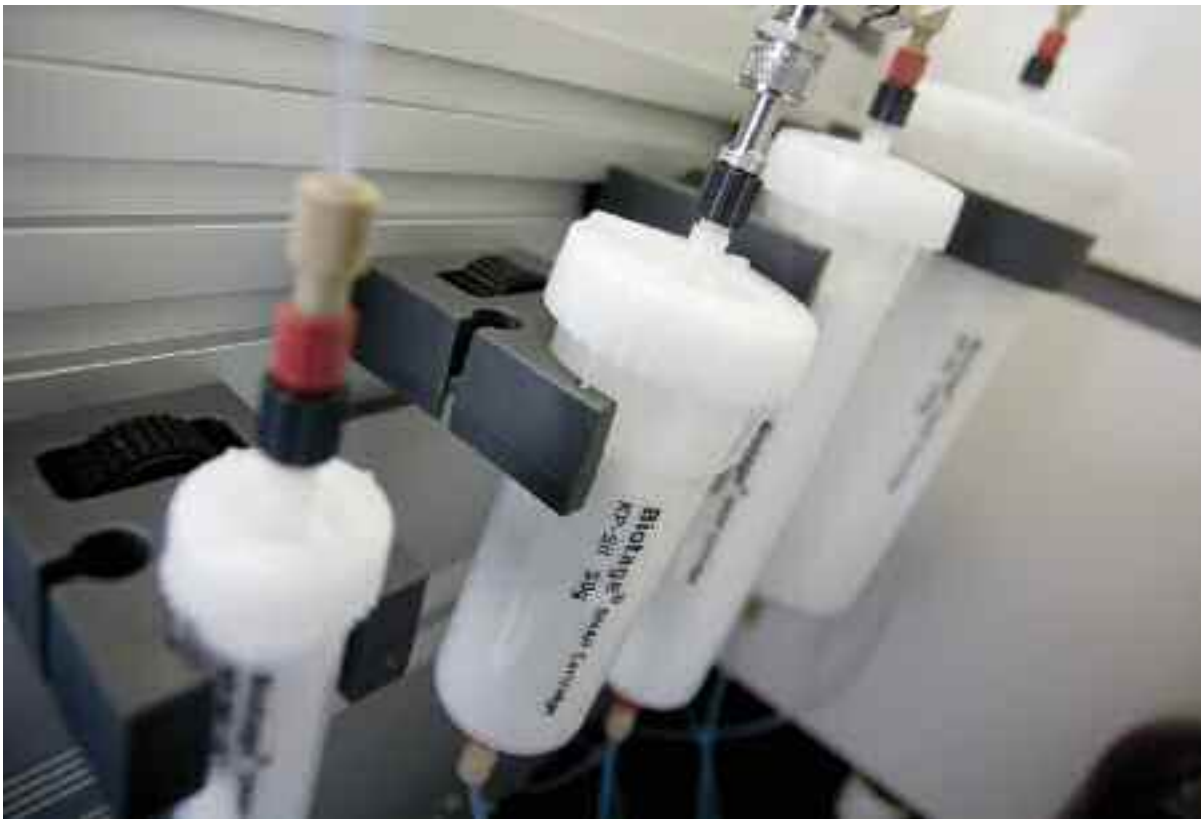


Figure 3. The synergy between Isolera flash systems and SNAP cartridges can be seen in the purification at 100 mL/min using a SNAP 50g KP-SIL cartridge on an Isolera One. The total run time at 100 mL/min is 8 minutes compared to a normal purification time of 20 minutes at the standard 40 mL/min flow rate for this cartridge.



SNAP cartridges – Increase loading capacity and improve compound separations.

The Isolera systems come complete with SNAP cartridges and everything needed to begin purifying samples. SNAP cartridges provide 20% more loading capacity, internal and external loading capabilities and operate at faster flow rates providing higher throughput, purity and yield, see Figure 3.

Add an auxiliary detector – Use other detectors

Purify samples with poor or no UV chromophore by connecting an external detector such as refractive index or ELSD. Isolera will fractionate compounds from using the auxiliary detector's signal while you can simultaneously monitor the Isolera UV signal.

Specifications

Solvent delivery	Two piston HPFC™ pump
Flow rate	1 – 200 mL/min
Pressure limit	145 psi (10 bar)
UV Detection	Choice of variable dual-wavelength (200 – 400 nm) or fixed (254 nm) detector
Flow cell path length	0.3 mm
UV collection modes	One wavelength Two wavelengths (variable UV only)
Fractionation modes	Volume, threshold, threshold with volume, low slope, medium slope, custom slope
Collection vessels	Test tubes (13, 16, 18, and 25 mm) and bottles (120 mL, 240 mL, and 480 mL)
Power	100 – 240 VAC, 50/60 Hz, 4.0 A
System control & data management	On-board computer with 10.4” diagonal touch-screen interface
Dimensions (W x H x D)	
Single bed	355 mm x 596 mm x 497 mm (14” x 23.5” x 19.6”)
Expanded bed	565 mm x 596 mm x 497 mm (22” x 23.5” x 19.6”)
Weight	30-35 kg (66-77 lb)
Certifications	CE, cTÜVus

Ordering Information

The Isolera One and Isolera Four systems are available in eight different configurations:

Systems

Part Number	Description
ISO-1SF	Isolera One with fixed 254 nm wavelength detector and single fraction collector bed
ISO-1SV	Isolera One with variable 200-400 nm wavelength detector and single fraction collector bed
ISO-1EF	Isolera One with fixed 254 nm wavelength detector and expanded fraction collector bed
ISO-1EV	Isolera One with variable 200-400 nm wavelength detector and expanded fraction collector bed
ISO-4SF	Isolera Four with fixed 254 nm wavelength detector and single fraction collector bed
ISO-4SV	Isolera Four with variable 200-400 nm wavelength detector and single fraction collector bed
ISO-4EF	Isolera Four with fixed 254 nm wavelength detector and expanded fraction collector bed
ISO-4EV	Isolera Four with variable 200-400 nm wavelength detector and expanded fraction collector bed

Accessories

Part number	Description
411789	Test tube rack, 13 x 100 mm, 4/pk
411790	Test tube rack, 16 x 100 mm, 4/pk
411791	Test tube rack, 16 x 150 mm, 4/pk
411792	Test tube rack, 18 x 150 mm, 4/pk
411793	Test tube rack, 25 x 150 mm, 4/pk
411794	Bottle rack, 120 mL, 4/pk
411934	Bottle rack, 240 mL, 1/pk
411929	Bottle rack, 480 mL, 1/pk
411926	Expanded bed upgrade
FIV-VLV-1000	Injection valve
411081	Injection valve to SNAP cartridge adapter

Evaporation Systems

Fast, Automated and Safe Drying

V-10 System

The Biotage V-10™ solvent evaporation system rapidly dries samples dissolved in both aqueous and organic solvents up to 20x faster than traditional rotary or centrifugal evaporators, leaving solvent-free product in the vial. This innovative vortex and vacuum evaporation technology was developed through collaboration with major pharmaceutical companies. The high performance vacuum capability of the V-10 allows low temperature evaporation of high boiling solvents. Optimized evaporation methods protect the sample against bumping and overheating. Versatility and scalability eliminate handling and reformatting issues.

Features and Benefits

Rapid Three-way Drying

Evaporate samples up to 20x faster than traditional rotary or centrifugal evaporators using a patented combination of drying techniques, including high-speed vial rotation, uniform IR controlled heating and vacuum drying. This unique system provides rapid and complete evaporation of solvents with boiling points from 30 to 205° C at atmospheric pressure. Samples dried on a V-10 have little or no solvent residue to interfere with downstream analysis such as NMR.

Evaporation of high boiling solvents

The V-10's high performance vacuum capability allows low temperature evaporation of high boiling solvents. Solvents include DMF, aqueous, aqueous/organic mixtures and even DMSO and NMP with the high vacuum pump option (see Table 1).

Solvent	BP (º C)	Biotage V-10 evaporation	Centrifugal evaporation	Blow-down evaporation
NMP	202	18 min	N/A	N/A
DMSO	180	15 min	180 min	N/A
DMF	150	4 min	90 min	N/A
Pyridine	115	5.5 min	70 min	N/A
Water	100	9 min	140 min	240 min
Methanol	65	3 min	70 min	40 min
Cychlohexane	81	2.5 min	40 min	20 min

Table 1. Time to evaporate 8-mL of solvent at 40º C using Hi Boil method

Versatility and Automation

V-10's versatility enables evaporation of single samples (up to 12 mL) or large pooled volumes using the V-10 syringe or peristaltic pumps. Adding the automated vial loading/changing carousel enables unattended evaporation of up to 16 samples. Integrate the system with a liquid handling robot using the V-10 Control Center software. Combine multiple fractions/samples from different test tube racks and dry them into a single vial in one operation.

Clean and safe evaporation

Bump-free vortex evaporation prevents sample loss while the system's precise temperature control eliminates sample overheating. Maximize sample recovery with the V-10's automatic, end-of-run detection.

V-10 System

Protect your Compound

Bump-free vortex evaporation prevents sample loss while the system's precise temperature control eliminates sample overheating. Maximize sample recovery with the V-10's automatic, end-of-run detection.

Green chemistry

This environmentally friendly system captures up to 98% of solvent vapors.

Simple operation

The system is operated via touchpad control or the via the Control Center software. On the base unit easy-to-use touchpad control directly provides pre-programmed and user-configurable methods for optimal drying conditions. The Control Center software provides simple simultaneous control of the V10 and the integrated liquid handler.

Compact footprint

Localized key pad operation along with built-in, solvent-resistant vacuum pump and refrigerated condenser save valuable bench space.

Eliminate Reformatting

Using the patented, three-way drying system, the V-10 dries your compound of interest directly into the vial of choice, leaving no residual solvent to interfere with NMR analysis.

Specifications

Sample delivery	5-mL syringe pump and/or peristaltic pump
Vial size compatibility	4mL (3 variants), 20 mL scintillation vial, 30 mL scintillation vial
Liquid Handling compatibility	Gilson 221 (use with peristaltic pump) Gilson 222, 215 or GX271 (use with dual pumps)
System Requirements	
Power	110 VAC (± 10%), 60 Hz, 15A (USA) 110 VAC (± 10%), 50/60 Hz, 15A (Japan) 230 VAC (± 10%), 50 Hz, 8A (EU/UK)
Gas and Pressure limit	Compressed Nitrogen regulated up to maximum of 2 bar
Dimensions (W x H x L)	40 cm x 53 cm x 48 cm (16" x 21" x 18.5") 49 cm x 53 cm x 54 cm (19.5" x 21" x 21.5")
Weight	45 kg (100 lb) 50 kg (111lb)
Certifications	CE
Interfaces	
Network connections	Rs232 or TCP/IP Switched I/O

Accessories

Part Number	Description
411181	20mL Vial Carousel Holder
411182	4mL 16.5mm Carousel Holder
411183	4mL 14.5mm Carousel Holder
411816	Gilson Liquid Handler GX271 for the V10

Ordering Information

Contact Biotage or your local representative for part numbers and pricing or to request a demonstration.


FlashMaster II
FlashPack

FlashMaster II Purification System

Fast, Automated Organic Compound Purification

FlashMaster II

A Cost-Effective Shared Resource for Fast, Automated Organic Compound Purification

The FlashMaster II system is a space-saving and cost-effective solution for groups of chemists with a high throughput profile that want to adopt automated purification methods in order to purify more compounds in less time. It is an instrument that is ideal for centralized purification facilities.

The FlashMaster II system automates gradient solvent mixing, flow control, peak detection, and fraction collection to increase laboratory workflow dramatically. Pre-packed, disposable cartridges eliminate hours of time required for cleaning, assembling, and packing non-disposable glass columns. FlashMaster II systems operate with both Isolute and SNAP cartridges.

Features and Benefits

Multi-user instrument

FlashMaster II is set up with four solvent inlets, independent waste lines, and separate collection blocks to support true multi-user capabilities. All purifications are set up with their own unique run parameters and individual user profiles for each chemist to facilitate fast access to methods and archived data.

10-column capacity

The system comes with 10 independently programmed column positions accessible in random order to support multiple methods and users. This automated multi-user resource saves time, money, and lab space.

Walk-away automation

Load your sample onto the cartridge, click it into any of the 10 positions, and add it to the run-list using its own parameter set using the set-up wizard without interrupting the current run. When the sample is completed, the FlashMaster II system sends e-mail notification to your inbox with attached purification data.

Full gradient flexibility

Program isocratic, linear, or multi-step elution using binary, ternary or quaternary gradients. Drag-and-drop gradient creation saves time and offers full purification method flexibility.

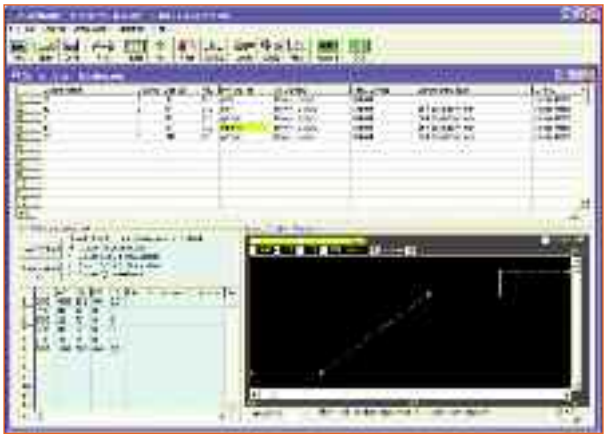
Unlimited detection

The system not only comes with a variable UV-V15 detector that presents the broadest wavelength selection on the market (190-720nm), it also allows the use of auxiliary detectors such as ELSD or CLD. Online detection and real-time visualization of separations speed up method development and allow interaction with active sample.

FlashMaster software

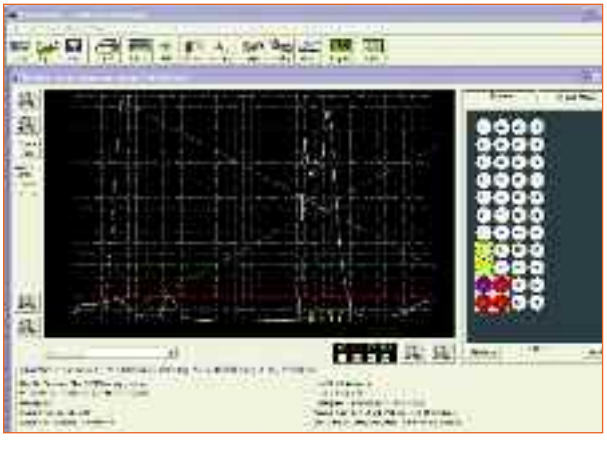
FlashMaster software combines the advanced feature set of sophisticated chemical separations analysis software with the ease of flash chromatography. Color-coded correlations between chromatogram peaks and individual collection tubes allow rapid fraction location. Safety and convenience features track available solvent volumes and flow rate changes, recover and restart after power interruptions, and respond to high and low pressure limits.

Method Creation
Methods are created and samples are loaded and run through one simple spreadsheet-type window.



Sample Wizard
Samples can also be added using the sample wizard.

Results
Results are clearly displayed. Color-coded correlations between chromatogram peaks and individual collection tubes allow rapid fraction location.



SPECIFICATIONS

Specifications

Purification Process	
Solvent delivery	High pressure HPLC pump
Solvent inlets	4 inlets, binary, ternary or quaternary gradient
Flow rate	1 – 40 mL/min
Pump pressure limit	300 psi (21 bar)
Column positions	10
Liquid sample loading	3-way liquid injection valve or directly on column
Solid sample loading	Dry-loading onto column, Samplet (SNAP cartridges)
Detector	UV-V15 (190-740 nm) detector with deuterium (standard) or halogen lamp Auxiliary detectors can be used
Fractionation modes	Time, UV threshold, UV slope
Collection vessels	Test tubes: 10-21 mm diameter tubes
Max number of fractions	432 (10 mm tubes)/fraction collector
Max volume per fraction	60 mL (21 x 180 tubes)
Max total volume	5.8 L/fraction collector
Max number of fraction collectors	4
System Requirements	
Power	110 – 240 VAC, 50/60 Hz
Dimensions,	
FM2 base system	28” x 20” x 24” W x D x H (71 cm x 51 cm x 62 cm)
Gilson 204	19” x 18” x 18” W x D x H (48 cm x 46 cm x 46 cm)
Certifications	CE, CSA certified
Interfaces	
System control and data management	Laptop or desktop computer control with Windows® XP or 2000

Ordering Information

Systems

Part Number: FMII – __ __ – __ __ __

Instructions: Simply choose one component from each column in the model code table. Choose as many options as you need, moving from left to right. See example below.

Model Code Table

Main Power Requirement	Country	Computer	Printer	Fraction Collector
1: 110V	U: USA	D: Desktop	0: None	0: None
2: 220V	E: UK	L: Laptop	1: 110V	3: Gilson 203
	K: Europe		2: 220V	4: Gilson 204
	J: Japan			
	A: Australia			
	C: China			

Examples:

Part Number: FMII – 1 U – L 1 4
FM II system with 110V mains for USA supplied with a laptop computer, 110V printer and a Gilson 204 fraction collector

Part Number: FMII – 2 K – D 0 3
FM II system with 220V mains for Europe supplied with a desktop computer and a Gilson 203 fraction collector, but without a printer

Accessories

Item	Description	Part number
Plungers	FlashPack Plunger Assembly, 12mm	109219
Plungers	FlashPack Plunger Assembly, 16mm	109220
Plungers	FlashPack Plunger Assembly, 20mm	109221
Plungers	FlashPack Plunger Assembly, 27mm	109222
Plungers	FlashPack Plunger Assembly, 37mm	109223
Plungers	FlashPack Plunger Assembly, 40mm	109224
Isolute cartridges	See page 249 for ordering information	

Discovery-Scale FLASH™ Chromatography Systems and Modules

For the Manual Purification of Organic Molecules

FLASH+™ Systems

FLASH+ Purification and FlashMaster Personal Systems: High-Yield, High-Performance, Milligram- to Gram-Scale Purifications

Simple, easy to use Biotage FLASH+ and FlashMaster Personal purification systems incorporate all the tools you need for efficient, effective isocratic FLASH purification. These low-cost systems are designed for purification of mg to grams of crude reaction mixtures.

FLASH+ Systems

FLASH+ systems simplify and accelerate the isolation of organic compounds. These manual systems require no electricity, only a compressed air source for operation. Providing flow rates up to 100 mL/min, purification can be very fast and effective using FLASH 12+, FLASH 25+, and FLASH 40+ cartridges. FLASH 65i cartridges can also be operated using FLASH+ systems when the optional 4-L solvent reservoir is used.

FLASH+ systems are shipped with all the components required for operation—a cartridge support stand, solvent reservoir with two-way valve, air and solvent tubing, compression module (of your choosing), and a ZIF-SIM™ of your choosing (patented, zero insertion force sample injection module), three-way injection valve and disposable syringes. Options include an air regulator (with filter) and extra compression module barrels.

Typical applications involve purification throughout multi-step solution-phase synthesis. The scale of purification ranges from milligrams to grams for simple and complex mixtures (see page 289 for more detailed application information).

For more information on compression modules and cartridge offering, please refer to the FLASH Purification Cartridges, Media, Samplet™ Cartridges, and Accessories section, page 238.

Features and Benefits

- Capable of purifying milligrams to grams of crude synthetic mixtures
- Can operate at flow rates to 100 mL/min at 100 psi pressure resistance
- Modularity provides flexibility in product selection
- Requires no electricity to operate

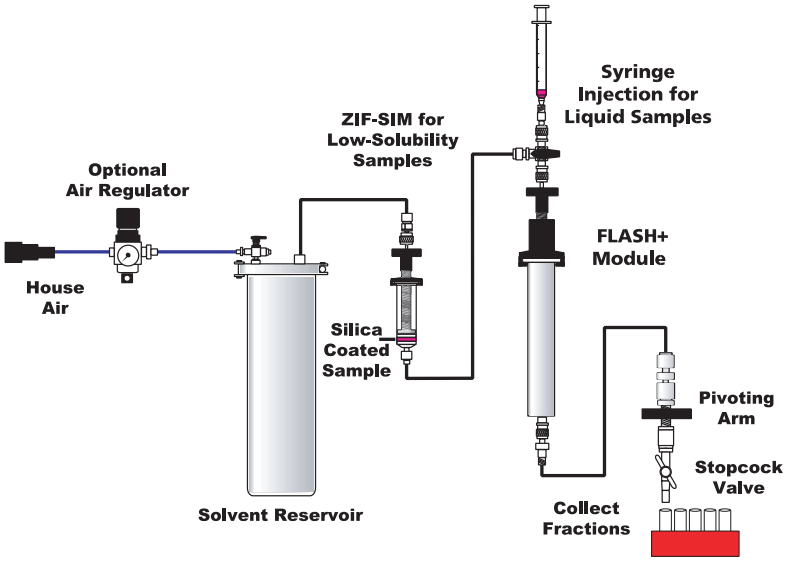


Figure 1. FLASH+ flow diagram.

FLASH+ Compression Modules Incorporate ZIF™ and Samplet™ Technologies

FLASH+ compression modules use Biotage-patented FLASH+ cartridges packed with a range of normal and reversed-phase media (see page 238-239 for more detailed packing-media information).

The FLASH+ compression modules are designed with patented ZIF (Zero Insertion Force) head technology that improves purification of synthetic and natural products by axially compressing the FLASH+ cartridge. Axial compression of the cartridge bed minimizes void space, which improves separation efficiency and loading capacity. For simplified sample handling, the FLASH+ compression modules accept Samplet sample-loading cartridges. For low-solubility samples that cannot be dissolved in an appropriate volume for Samplet loading, a ZIF-SIM™ adds additional purification capabilities.

ZIF head assembly, designed to distribute sample and solvent flow evenly through each cartridge

FLASH+™ Systems

The FLASH 12+™ Compression Module and 12-mm ID Pre-packed Cartridges

Designed for Milligram-scale FLASH Separations

FLASH 12+M System with ZIF-SIM10™, ZIF-SIM35™, and test-tube rack

FLASH 12+S and 12+M compression modules, head assemblies. FLASH 12+S and 12+M cartridges and Samplets

Flash 12+ Specifications

Cartridge	Dimensions (mm x mm)	Sample size (mg)	Flow rate (mL/min)	ZIF-SIM
FLASH 12+S	12 x 75	4-200	2.5-12	10
FLASH 12+M	12 x 150	8-400	2.5-12	10

Please refer to page 291 for all FLASH+ System ordering information.

The FLASH 25™+ Compression Module and 25-mm ID Pre-packed Cartridges

Designed for Milligram-to-Gram Scale FLASH Separations

FLASH 25+M System with ZIF-SIM10™, ZIF-SIM35™, and ZIF-SIM60™ and test-tube rack

FLASH 25+S and 25+M compression modules head assemblies. FLASH 25+S and 25+M cartridges and Samplets

Flash 25+ Specifications

Cartridge	Dimensions (mm x mm)	Sample size (mg)	Flow rate (mL/min)	ZIF-SIM
FLASH 25+S	25 x 75	15-800	10-25	35
FLASH 25+M	25 x 150	30-1600	10-25	35

Please refer to page 291 for all FLASH+ System ordering information.

The FLASH 40+™ Compression Module and 40-mm Pre-packed Cartridges

Designed for Gram-Scale FLASH Separations

FLASH 40+™M System with ZIF-SIM10™, ZIF-SIM35™, and ZIF-SIM60™ and test-tube rack

FLASH 40+S and 40+M compression modules, head assemblies. FLASH 40+S and 40+M cartridges and Samplets

Flash 40+ Specifications

Cartridge	Dimensions (mm x mm)	Sample size (mg)	Flow rate (mL/min)	ZIF-SIM
FLASH 40+S	40 x 75	40-2000	25-50	60
FLASH 40+M	40 x 150	80-5000	25-50	60

Please refer to page 291 for all FLASH+ System ordering information.

Ordering Information

FLASH+ systems are modular, providing the opportunity to select only the components needed. In the following table, select one item from each Component column and any options desired, filling in the spaces in the part number template. The template can only be used with FLASH 12+, 25+, and 40+ systems. Refer to the FLASH 65 system ordering information section for FLASH 65i system ordering information.

Part number template: FS1-R _ _ - _ _ _

Component 1	Component 2	Component 3	Options
FS1-R Any FLASH+ System and 1-Liter Reservoir	**A** FLASH 12+ S Compression Module	**0** No ZIF-SIM™	**-A** 12+S Barrel
	B FLASH 12+M Compression Module	**1** ZIF-SIM 10™	
	C FLASH 25+ S Compression Module		**-B** 25+S Barrel
	D FLASH 25+M Compression Module		
	E FLASH 40+ S Compression Module	**2** ZIF-SIM 35™	**-C** 40+S Barrel
	F FLASH 40+M Compression Module		
	G FLASH 12+S and 25+S Compression Modules	**3** ZIF-SIM 60™	**-D** 12+M Barrel
	H FLASH 12+M and 25+M Compression Modules	**4** ZIF-SIM 10 and 35	
	J FLASH 12+S and 40+S Compression Modules		**-E** 25+M Barrel
	K FLASH 12+M and 40+M Compression Modules	**5** ZIF-SIM 10 and 60	
	L FLASH 25+S and 40+S Compression Modules		**-F** 40+M Barrel
	M FLASH 25+M and 40+M Compression Modules	**6** ZIF-SIM 35 and 60	
	N FLASH 12, 25, 40+S Compression Modules		**-G** Air Regulator with filter
	P FLASH 12, 25, 40+M Compression Modules	**7** ZIF-SIM 10, 35, and 60	

Ordering Information

Item	Description	Part Number
Accessories		
Injection Valve	3-way vertical injection valve with Luer-Lok adapter for liquid injections	FIV-VLV-1000
1-Liter Solvent Reservoir	1-L stainless-steel solvent reservoir; for FLASH 12+ to 40+ systems	FN-001-41201
4-Liter Solvent Reservoir	4-L stainless-steel solvent reservoir; for FLASH 12+ to 40+ systems	FN-004-41201
Air Regulator	Regulates air pressure; for use with all air-operated Biotage systems (0-60 psig); contains particulate filter	09350
FLASH+ Start-Up Kit	Frame and tubing	07923
FLASH 12+S Compression Module	For use with FLASH 12+S and Samplet cartridges	07857
FLASH 12+M Compression Module	For use with FLASH 12+M and Samplet cartridges	07858
FLASH 12+S Barrel	For use with FLASH 12+S cartridges	07395
FLASH 12+M Barrel	For use with FLASH 12+M cartridges	07383
FLASH 25+S Compression Module	For use with FLASH 25+S and Samplet cartridges	FC-022-16024

Ordering Information

Item	Description	Part Number
Accessories		
FLASH 25+M Compression Module	For use with FLASH 25+M and Samplet cartridges	FC-022-16044
FLASH 25+S Barrel	For use with FLASH 25+S cartridges	FB-022-16024
FLASH 25+M Barrel	For use with FLASH 25+M cartridges	FB-022-16044
FLASH 40+S Compression Module	For use with FLASH 40+S and Samplet cartridges	07975
FLASH 40+M Compression Module	For use with FLASH 40+M and Samplet cartridges	07976
FLASH 40+S Barrel	For use with FLASH 40+S cartridges	07387
FLASH 40+M Barrel	For use with FLASH 40+M cartridges	07388
FLASH-Pac+	Set of 12+M, 25+M, 40+M compression modules and 12+S, 25+S, 40+S barrels	08615

FlashMaster™ Personal

The FlashMaster Personal is an easy-to-use, pump-driven, single-cartridge, manual flash purification system. With a flow rate range of 5 – 240 mL/min, purification can be done in a flash. Its small footprint design uses minimal bench space and allows direct attachment of ISOLUTE flash cartridges.

Features and Benefits

- Reproducible pump-driven solvent delivery and flow-rate control
- Easy-to-use, no programming needed to operate
- Compact size for efficient use of hood space
- Uses easy-to-install pre-packed ISOLUTE or SNAP flash cartridges

Specifications

Flow Rate (mL/min)	5-240
Pressure limit (PSI/bar)	80/5.5
Wetted parts	316 stainless steel, LCP, PTFE
Cartridge capacity	1
Dimensions (W x D x H)	7.5” x 7.5” x 18.1” (19 cm x 19 cm x 46 cm)
Weight (lbs/kg)	6.6/3
Power	110-120 V AC, 50-60 Hz
	220-240 V AC, 50-60 Hz

Ordering Information

Item	Part Number
FlashMaster Personal	
Single cartridge personal flash system with one plunger for North America	FMP-1N
Single cartridge personal flash system with one plunger for United Kingdom	FMP-1U
Single cartridge personal flash system with one plunger for Europe	FMP-1E
Single cartridge personal flash system with one plunger for Japan	FMP-1J

FlashMaster™ Personal Plus

The FlashMaster Personal Plus is an upgraded FlashMaster Personal that provides the addition of a second cartridge position for large dry load purification or serial purification for difficult-to-resolve sample mixtures, or as a guard column to protect the purification column from contaminants in the reaction mixture, or for on-line sample preparation (scavenging or catch and release) using a pre-packed functionalized-media ISOLUTE SPE column.

Switching from one- to two-column operation is easily accomplished using the column selection valve on the front panel of the system and does not require breaking any solvent connections. The FlashMaster Personal Plus maintains the small footprint design of the FlashMaster Personal system and uses ISOLUTE or SNAP flash cartridges.

Features and Benefits

- Reproducible pump driven solvent delivery and flow rate control for reproducible purifications
- Easy-to-use, no programming needed to operate
- Compact size for efficient use of hood space
- Uses easy-to-install pre-packed ISOLUTE or SNAP cartridges
- A second column to accommodate an extended range of applications (two-column model)
- Valve for selecting one- or two-column operation
- Valve for on-line loading of liquid samples

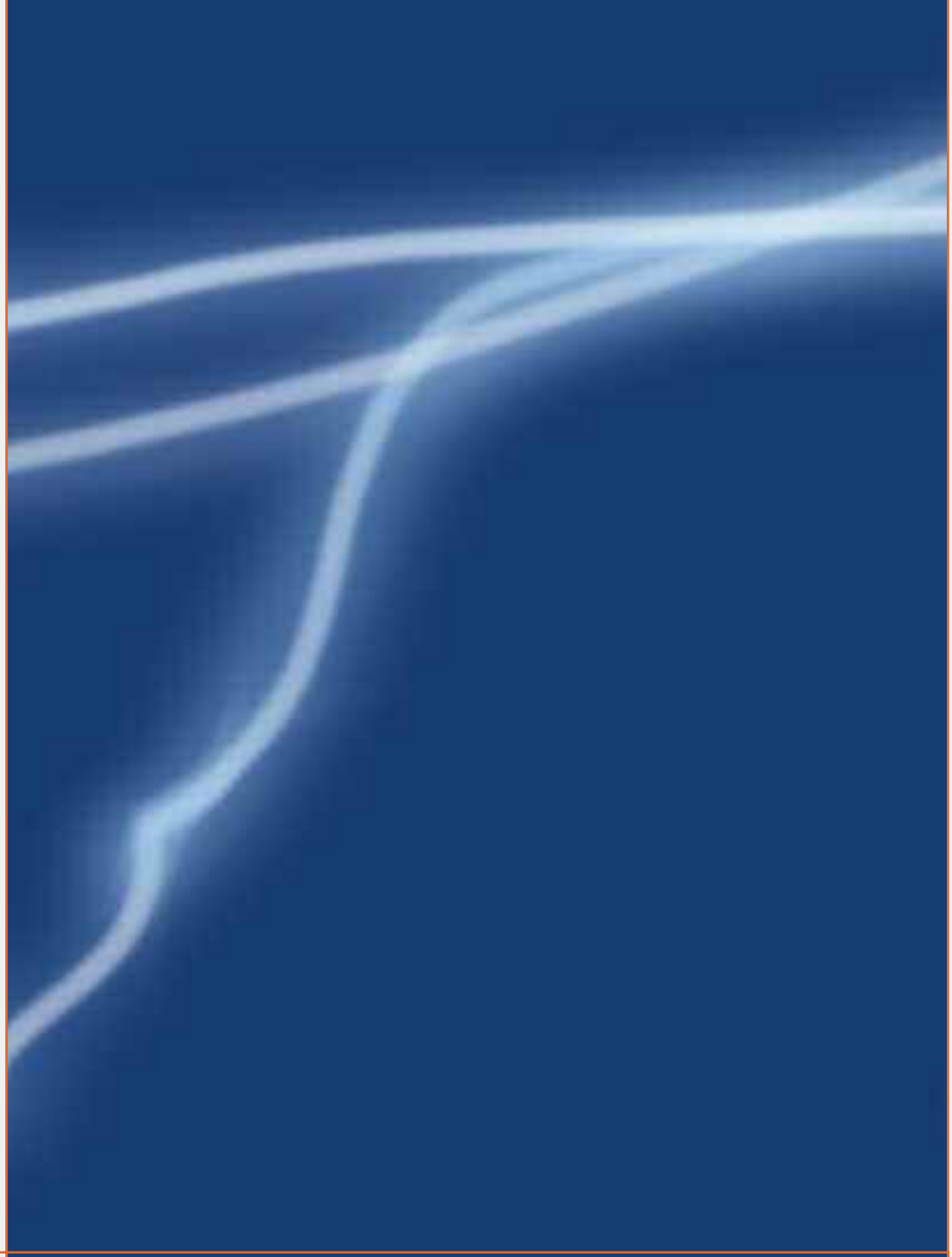
Specifications

Flow rate (mL/min)	5-240
Pressure limit (PSI/bar)	80/5.5
Wetted parts	316 stainless steel, LCP, PTFE
Cartridge capacity	2
Dimensions (W x D x H)	7.5” x 7.5” x 18.1” (19 cm x 19 cm x 46 cm)
Weight (lbs/kg)	6.6/3
Power	110-120 V AC, 50-60 Hz
	220-240 V AC, 50-60 Hz

Ordering Information

Item	Part Number
FlashMaster Personal Plus	
Dual cartridge personal flash system with two plungers for North America	FMP+-1N
Dual cartridge personal flash system with two plungers for United Kingdom	FMP+-1U
Dual cartridge personal flash system with two plungers for Europe	FMP+-1E
Dual cartridge personal flash system with two plungers for Japan	FMP+-1J


75
FLASH
Biotage



Development-Scale FLASH™ Chromatography Systems

For the Purification of Multi-gram Quantities of Synthetic Compounds

FLASH 75i AND 150i

FLASH 75i™ and FLASH 150i™: Reliable Gram-scale Purification

Gram-scale purification of reaction mixtures can be a straightforward process with the proper tools. Biotage FLASH 75i and FLASH 150i systems provide the tools needed for accurate, efficient gram-scale purification. Determine the elution conditions with TLC and purify on a FLASH 75i or 150i system or scale-up directly from a smaller Biotage FLASH cartridge using the Biotage scale-up table (see Table 1).

Cartridge	Diameter (mm)	Bed Length (cm)	Packing Wt. (g) (nom)	Column Vol. (mL)	Easy ΔCV = 6	Typical ΔCV = 2	Difficult ΔCV = 1
FLASH 75S	75	9	200	320	5 - 10	1 - 5	0.2 - 1
FLASH 75M	75	15	400	535	10 - 20	2 - 10	0.4 - 2
FLASH 75L	75	30	800	1,070	20 - 40	4 - 20	0.8 - 4
							Sample Range (g)

Table 1. Biotage FLASH 75 suggested sample sizes, based on TLC evaluation

FLASH 75i and FLASH 150i systems are designed for rapid, efficient gram-scale (1–320 g) purifications. Their operation requires no electricity or computer control—just compressed air to push solvent through the cartridge and to exert radial compression on the cartridge.

Biotage's patented radial compression technology reduces the chance of void and channel formation, resulting in a higher bed density. Compounds can then be collected in narrower bands for higher purity and yield.

FLASH 75i systems

Available in three lengths to accommodate easy, moderate, and difficult separations, FLASH 75i system packages include all the components necessary to begin your purification: a FLASH 75i radial-compression module, a fully integrated air manifold, a solvent reservoir, a sample-injection module, a start-up kit with all necessary tubing, a grounding kit, and a user's manual.

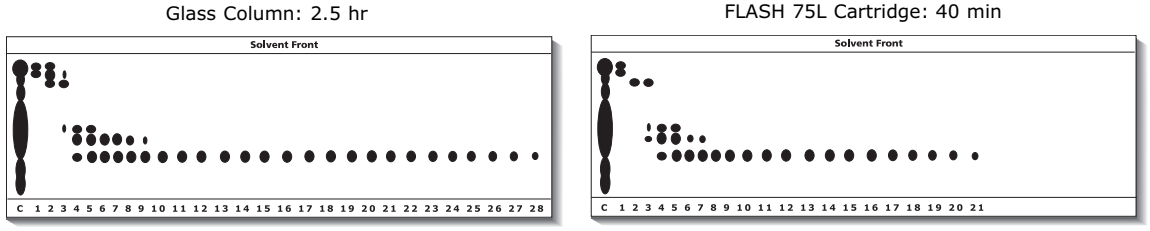


Figure 1. Glass column vs. FLASH 75L cartridge

Routinely operating at a flow rate of 250 mL/min, the FLASH 75i systems and FLASH 75i cartridges allow you to scale-up and quickly complete runs, saving hours, even days, of purification time compared to using glass-column flash purification.

FLASH 75i

FLASH 75™ cartridges, available in sizes containing 200, 400, and 800 grams of media, are built to withstand operating pressures up to 100 psig. The cartridges are constructed of rugged, medium-density polyethylene and resist cracking and splitting. There is no breakable glass and all of the silica is completely self-contained, eliminating any exposure to silica dust or contaminants.

FLASH 75i cartridges are available with a variety of media

- KP-SIL™ 40-63 µm, 60 Å, silica
- KP-C18-HS™ 35-70 µm, 90 Å, C18-bonded silica
- KP-NH™ 40-75 µm, 100 Å, amine-functionalized
- Mitsubishi Diaion™ HP20 and HP20SS SDVB resins
- FLASH WAC
- KP-C18-WP
- KP-C4-WP

FLASH 75i Features and Benefits

- Faster and safer than glass column flash purification
- Simple design and straightforward operation provide direct scale-up capability from TLC or smaller-scale flash
- Radial compression enhances purification performance by increasing effective bed density and minimizing channels and voids
- High-pressure (100 psig) capability allows faster flow rates and provides increased throughput
- Three lengths accommodate purification of gram-to-multigram sample loads
- Scalable to FLASH 150i and FLASH 400i systems

FLASH 75 Specifications

Cartridge	Size (mm x mm)	Sample Size (g)	Flow Rate (mL/min)	SIM* Vol. (mL)	Res. Vol. (L)
FLASH 75iS	75 x 90	0.2 – 10	250	100	4
FLASH 75iM	75 x 150	0.4 – 20	250	500	12
FLASH 75iL	75 x 300	0.8 – 40	250	500	12

*SIM, sample-injection module for low-solubility samples or viscous oils

FLASH 75

FLASH 75 System Ordering Information

Item	Description	Part Number
Systems		
FLASH 75S	75S compression module, air manifold, SIM 100™, 4-L solvent reservoir, tubing, grounding kit, and manual	SF-022-19161
FLASH 75M	75M compression module, air manifold, SIM 500™, 12-L solvent reservoir, tubing, grounding kit, and manual	SF-022-19041
FLASH 75L	75L compression module, air manifold, SIM 500, 12-L solvent reservoir, tubing, grounding kit, and manual	SF-022-19071
FLASH 75L Plus	75L Plus compression module, interchangeable 75S barrel, air manifold, SIM 500 (including 25 frits), 12-L solvent reservoir, 10 FLASH 75L cartridges (800 g, KP-Sil), 10 FLASH 75S cartridges (200 g, KP-Sil), tubing, grounding kit, and manual	SF-222-19071
Accessories		
FLASH 75S Compression Module	Powder-coated aluminum barrel with stainless-steel endcaps, V-band clamps, pressure indicator, an ASME-rated safety-relief valve, and mounting bars	FC-022-19161
FLASH 75M Compression Module	Powder-coated aluminum barrel with stainless-steel endcaps, V-band clamps, pressure indicator, an ASME-rated safety-relief valve, and mounting bars	FC-022-19041
FLASH 75L Compression Module	Powder-coated aluminum barrel with stainless-steel endcaps, V-band clamps, pressure indicator, an ASME-rated safety-relief valve, and mounting bars	FC-022-19071
FLASH 75S Barrel	Powder-coated aluminum barrel with pressure-relief valve and mounting bars; accepts FLASH 75S cartridges	FB-012-19160
FLASH 75M Barrel	Powder-coated aluminum barrel with pressure-relief valve and mounting bars; accepts FLASH 75M cartridges	FB-012-19040
FLASH 75L Barrel	Powder-coated aluminum barrel with pressure-relief valve and mounting bars; accepts FLASH 75L cartridges	FB-012-19070
SIM 100™ Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 100 mL	SIM-0102
SIM 500™ Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 500 mL	SIM-0502

Ordering Information

FLASH 75 System Ordering Information

Item	Description	Part Number
Accessories		
SIM 100 Top Frits	25 x 1.5” frits for the SIM 100 module	FTF-0125
SIM 500 Top Frits	25 x 3” frits for the SIM 500 module	FTF-0225
SIM Bottom Frit Holder	25 stainless-steel frits and sealing rings; replaces old-style SIM bottom frits	FSS-0075
SIM 100 Bottom Frits	25 frits and sealing rings for SIM 100 or 500; used with frit holder #FSS-0075	FBS-1025
Grounding Kit	Grounding kit includes Teflon®-coated wires and clips to dissipate static charges	FGD-15075
Three-way Injection Valve	Three-way vertical injection valve for direct liquid injections complete with Luer-Lok injection port	FIV-075-0000
4-L Solvent Reservoir	4 L stainless-steel solvent reservoir, ASME rated, complete with solvent shut-off and relief valves	FN-004-41201
12-L Solvent Reservoir	12 L stainless-steel solvent reservoir, ASME rated, complete with solvent shut-off and relief valves	FN-012-41201
Air Manifold	Air manifold; safely regulates the flow of air pressureand solvent(s) to FLASH 75 systems	AM-190
SIM 100 Start-up Kit	100 mL SIM, a cartridge extraction tool, tubing, user’smanual and grounding kit	SU-275-0100
SIM 500 Start-up Kit	500 mL SIM, a cartridge extraction tool, tubing, user’s manual and grounding kit	SU-275-0500
FLASH 75 Start-up Kit	Cartridge extraction tool, tubing, user’s manual, and grounding kit	SU-075-2000

AUTOFLASH 75 Compression Modules

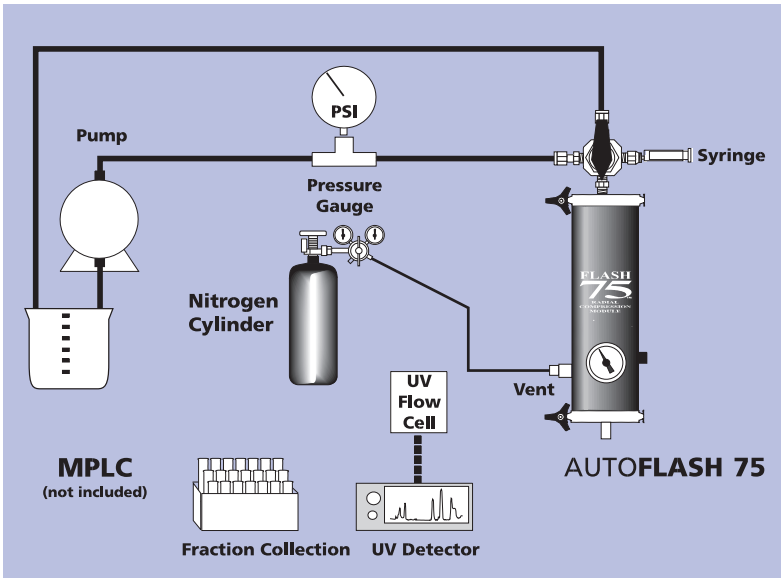


Figure 2. The Biotage AUTOFLASH 75 kit is designed for use with medium-pressure liquid chromatography pumps (MPLC) systems.

AUTOFLASH 75 compression modules are designed to provide FLASH 75 capacity and performance for your medium-pressure liquid chromatography (MPLC) system. AUTOFLASH 75 compression modules come with a pressure gauge, one start-up kit with all the tubing and fittings required to connect to an MPLC system, and a four-way valve with Luer-Lok adapter for direct sample injection.

AUTOFLASH 75 compression modules use Biotage's standard FLASH 75 (75 mm ID) prepacked cartridges (see page 246).

AUTOFLASH 75 systems can utilize our patented sample-injection modules, the SIM 100, and SIM 500.

Ordering Information

Item	Description	Part Number
AUTOFLASH 75S Compression Module	75S compression module, pressure gauge, 4-way injection valve, tubing, start-up kit, and manual	AF-005-19160
AUTOFLASH 75M Compression Module	75M compression module, pressure gauge, 4-way injection valve, tubing, start-up kit, and manual	AF-005-19040
AUTOFLASH 75L Compression Module	75L compression module, pressure gauge, four-way injection valve, tubing, start-up kit, and manual	AF-005-19070
AUTOFLASH 75S Barrel	Powder-coated aluminum barrel with pressure gauge and mounting bars, uses FLASH 75S cartridges	03711

Ordering Information

AUTOFLASH 75 Ordering Information

Item	Description	Part Number
AUTOFLASH 75M Barrel	Powder-coated aluminum barrel with pressure gauge and mounting bars; uses FLASH 75M cartridges	03710
AUTOFLASH 75L Barrel	Powder-coated aluminum barrel with pressure gauge and mounting bars; uses FLASH 75L cartridges	03706
Accessories		
AUTOFLASH SIM 100	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 100 mL; for use with AUTOFLASH 75 System	SIM-5102
AUTOFLASH SIM 500	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 500 mL; for use with AUTOFLASH 75 System	SIM-5502
AUTOFLASH MPLC Start-Up Kit	Contains all required tubing, nuts, and ferrules to connect an AUTOFLASH system to an MPLC pump	AFSU-1000

FLASH 150i systems

FLASH 150i system packages include an easy-to-install radial compression module, fully integrated air manifold, solvent reservoir, sample-injection module (SIM), start-up kit with all necessary tubing, grounding kit, and a user's manual. FLASH 150M (Medium) or FLASH 150L (Long) pre-packed cartridges are ordered separately.

FLASH 150 compression modules are mounted onto stable and robust portable bases (included in the system package), which are fitted with casters for easy mobility.

The FLASH 150 cartridges (150-mm ID) are available in two lengths: 30 cm (2.5 kg, FLASH 150M) and 60 cm (5 kg, FLASH 150L). Each cartridge is constructed of rugged, medium-density polyethylene to resist cracking or splitting. There is no breakable glass and all of the silica is self-contained, eliminating any exposure to contaminated silica dust. These high performance cartridges are built to withstand operating pressures up to 100 psig.

FLASH 150 cartridges are available with a variety of media

- KP-SIL, 40-63 µm, 60 Å, silica
- KP-C18-HS, 35-70 µm, 90 Å, C18-bonded silica
- Mitsubishi Diaion™ HP20 and HP20SS SDVB resins
- FLASH-WAC
- KP-C18-WP, 40-63 µm, 300 Å, C18-bonded silica
- KP-C-WP, 40-63 µm, 300 Å, C4-bonded silica

See page 248 for more information on cartridges.

With flow rates as high as 1.0 L/min, these systems allow you to complete runs and scale-up faster, saving hours, even days, of separation time (Tables 1 and 2, Figure 4).

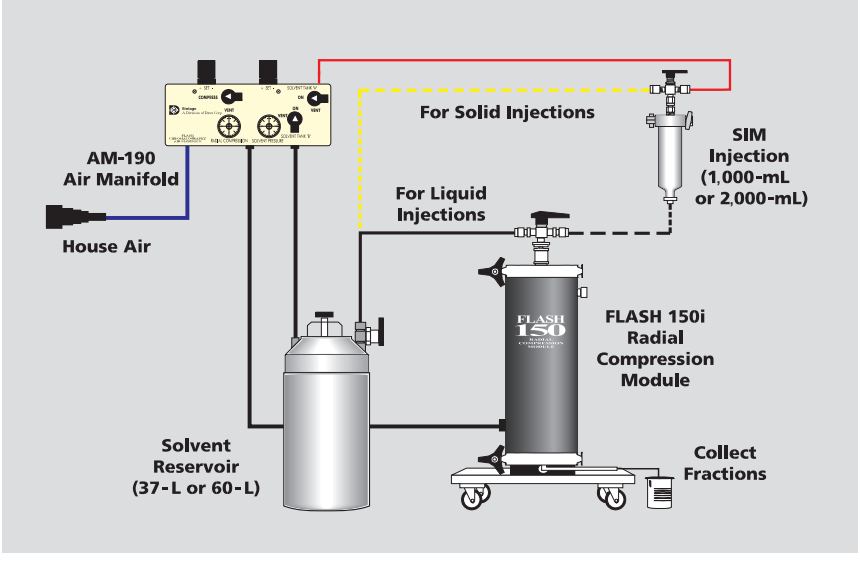


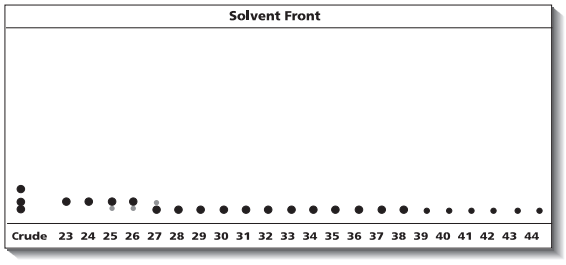
Figure 3. Purify kilogram-per-day quantities of promising drug candidates with the Biotage 150i system and our 150-mm ID, pre-packed FLASH 150 cartridges

FLASH 150i

	FLASH 150M	Glass Column
Column size	150 mm x 30 cm	120 mm x 66 cm
Silica amount	(2.5 kg)	(3 kg)
Sample load	180 g	450 g
Flow rate	500 mL/min	70 mL/min
No. of fractions	45	30
Purification time	90 min	430 min
Pure compound	70.5 g/run	45 g/run
Percent recovery	87%	22.2%
Purification Throughput	120 g/hr	63 g/hr

Table 1. A comparison of FLASH 150 vs. a traditional glass column purification shows the power and performance of the FLASH 150i system. In this application the FLASH 150 system saved a customer nearly four weeks of purification time on a 1-kilogram project.

FLASH 150M



Glass Column

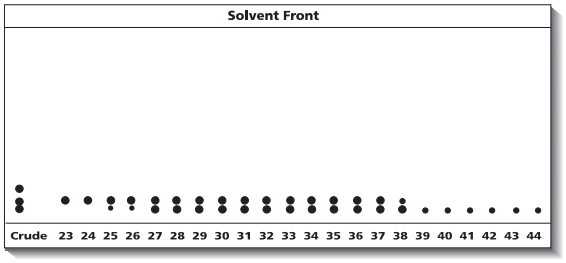


Figure 4. The TLC of the collected fractions in the FLASH 150M vs. glass column comparison shows more pure fractions were collected vs. the glass column due to a lighter load. The actual amount of pure compound per run, however, was 57% higher with the lighter load with a 4x improvement in compound recovery. Those improvements along with a faster flow rate yielded a throughput enhancement of 2x over the glass column.

FLASH 150 Specifications

Cartridge	Dimensions (mm x mm)	Sample Size (g)	Flow Rate (mL/min)	SIM Volume (mL)	Reservoir Volume (L)
FLASH 150M™	150 x 300	3–160	500-1000	1000	37
FLASH 150L™	150 x 600	6–320	500-1000	2000	60

Cartridge	Dimensions (mm x mm)	Packing Wt. (kg)	Column Volume (L)
FLASH 150M	150 x 300	2.5	4.3
FLASH 150L	150 x 600	5	8.6

Table 2. Biotage FLASH 150 sample sizes, based on TLC evaluation

*ΔCV = the difference in column volumes at which two compounds elute, calculated from the thin-layer chromatography Rf values as 1/Rf1 - 1/Rf2.

FLASH 150 Ordering Information

Item	Description	Part Number
Systems		
FLASH 150M System	150M compression module, air manifold, SIM 1000™, 37-L solvent reservoir, tubing, and manual	SF-022-25071
FLASH 150L System	150L compression module, air manifold, SIM 2000™, 60-L solvent reservoir, tubing, and manual	SF-022-25151

FLASH 150 Ordering Information

Item	Description	Part Number
Accessories		
FLASH 150M Compression Module	150M powder-coated aluminum barrel with stainless-steel endcaps, set on a portable base; V-band clamps; ASME-rated relief valve	FC-022-25071
FLASH 150L Compression Module	150L powder-coated aluminum barrel with stainless-steel endcaps, set on a portable base; V-band clamps; ASME-rated relief valve	FC-022-25151
FLASH 150M Barrel	Powder-coated aluminum barrel with pressure-relief valve; uses FLASH 150M cartridges	FB-012-25070
FLASH 150L Barrel	Powder-coated aluminum barrel with pressure-relief valve; uses FLASH 150L cartridges	FB-012-25150
SIM 1000 Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 1000 mL	SIM-1002
SIM 2000 Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 2000 mL	SIM-2002
SIM Top Frits	25 - 3" frits for either the SIM 1000 or SIM 2000	FTF-0225
SIM Bottom Frits	25 frits and sealing rings for SIM 1000 and SIM 2000	FBS-1025
Grounding Kit	Grounding kit includes Teflon®-coated wires and clips to dissipate static charges	FGD-15075
Three-way Injection Valve	Three-way 1/4" injection valve for direct liquid injections; complete with Luer-Lok injection port	FIV-150-0000
37-L Solvent Reservoir	37-L stainless-steel solvent reservoir; ASME rated; with solvent shut-off and relief valves	FN-037-41200
60-L Solvent Reservoir	60-L stainless-steel solvent reservoir; ASME rated; with solvent shut-off and relief valves	FN-060-41200
Air Manifold	Air manifold safely regulates the flow of air pressure and solvent(s) to FLASH 150 systems	AM-190
SIM 1000 Start-up Kit	1000-mL SIM, cartridge extraction tool, all required tubing, user's manual and grounding kit	SU-150-1022
SIM 2000 Start-up Kit	2000-mL SIM, cartridge extraction tool, all required tubing, user's manual and grounding kit	SU-150-2022
FLASH 150 Start-up Kit	Cartridge extraction tool, all required tubing, user's manual, and grounding kit	SU-150-0002

Spare Parts

Spare Parts

Item	Description	Part #

Spare Parts: Microwave Synthesis

Accessories

Crimper	Hand operated, used to crimp 20 mm caps on vials	353671
Decapper	Hand operated, used to decap 20 mm caps on vials	353913

Microwave Synthesis Spare Parts

Connection Set	Air adapters to connecting MAOS to facilities	353480
Vial Rack (5mL)	Holds 30 0.5-5 mL vials	353478
Vial rack (20mL)	Holds 12 10-20 mL vials	354798
8-rack (5mL)	Holds four 0.5-5 mL vials	355391
8-rack (20mL)	Holds two 10-20 mL vials	355390
Cavity Air Guide	Cavity Air Guide Emrys™ EXP	354839
Cavity Air Guide	Cavity Air Guide Initiator™ EXP	354974
Cavity Lid Seal	O-ring (blue) for EXP MAOS for venting on vials	354180
Vent Screw	Vent Screw Replacement for vial venting	354878
Vial Adapter	Designed to make 0.2-0.5 mL vials fit into the microwave cavity (qty 10)	355459
Vial Adapter	Designed to make 10-20 mL vials fit into the microwave cavity (qty 12 pieces)	355367
O-rings	Replacement O-rings for 10-20 mL adapters (qty 10)	354838
Waste tray insert	Waste tray insert (qty 5)	355366
Service lid insert		354715
Air hose x 2 m		351088
Air Control Unit		352281
Getting Started Guide		355422

Spare Parts: Purification

FLASH i-series Spare Parts

The i-series of FLASH products preceded the current FLASH+™ line.

V-band Clamp	3" V-band clamp for 1-L solvent reservoirs	08526
Gasket	3" solvent reservoir gasket, polyethylene	01617
Stopcock Valve	2-way stop flow valve, polypropylene	03274
Hose Barb Adapter	Female Luer to 1/8" tube	01986
Luer-Lok® Collar	Male Luer-Lok to 1/8" tube, w/ collar	03229
Luer-Lok Kit	1 female plastimate Luer-Lok port 1 finger-tight nut 1 front 1/4" ferrule 1 back 1/4" ferrule	02838
Air Tubing	1/4" OD polyethylene tubing (6')	03275
Air Fitting	1/4" OD 3/8" Male NPT brass bushing to 1/4" insta-tite fitting	03072
Ferrule Kit	1/4" PFA front ferrules (6) 1/4" PFA back ferrules (6)	03062
Nut and Ferrule Kit	Finger-tight nuts (2) 1/4" PFA front ferrules (2) 1/4" PFA back ferrules (2)	03061
Reducing Union	1/4" x 1/8" reducing union (four required per set)	04144

Spare Parts

Item	Description	Part #
FLASH 12i™ Spare Parts		
O-ring Kit	Chemraz® O-ring (1) Retaining ring (1) Instruction sheet	03046
Collection Tube Kit	For fraction collection, 1/16" OD tubing, FEP (12") tubing Union, 1/16" to 1/16", SS 1/16" OD tubing, SS (3.5") 1/8" to 1/16" reducing union	03071
Syringe	Disposable 2-mL polypropylene (5)	03276
Reducing Union	1/4" to 1/16" tube to tube	02979
Dip Tube	For solvent reservoir	01889
Nuts and Ferrules	1/4" and 1/8" stainless steel nuts and ferrules (three sets of each)	NF-15075
FLASH 12i Compression Module	For use with FLASH 12 Cartridges	FC-022-15024
FLASH 12i/40i Start-Up Kit	Frame and tubing	SU-242-0000
FLASH 12S Barrel	Short barrel	02954
FLASH 12M Barrel	Medium barrel	02942
Distribution Head	Upper flow-distribution head	02843
Distribution Head	Lower flow-distribution head	02946
Reducing Union	1/4" x 1/8" reducing union	04144
FLASH 40i™ Spare Parts		
FLASH 40i Compression Module	For use with FLASH 40 cartridges	FC-022-17024
FLASH 40S Barrel	Short barrel	01800
FLASH 40M Barrel	Medium barrel	01818
FLASH 40L Barrel	Long barrel	06981
FLASH 40i Spare Parts Kit	Tubing, O-ring, gasket, V-band clamp	01985
FLASH 12i/40i Start-Up Kit	Frame and tubing	SU-242-0000
O-ring Kit	Chemraz® O-ring (1) Retaining ring (1) Instruction sheet	03216
Collection Tube Kit	For fraction collection, 1/8" tubing, FEP (3') Tube with Luer-Lok® adapter	01888
Barrel Adapter	Threaded barrel adapter connects head assembly to 40S or 40M barrel	01790
Syringe	Disposable 10-mL polypropylene syringe	03277
Reducing Union	1/4" to 1/16" tube to tube	02979
Nut and Ferrule	1/4" and 1/8" stainless steel nuts and ferrules (three sets of each)	NF-15075
Head Assembly	SIM™ Receiver-head assembly	06090
Reducing Union	1/4" x 1/8" reducing union	04144
SIM 500™, 1000™, 2000™ Spare Parts		
Gasket	3" polyethylene	01617
Gasket	3" Viton	01615
Gasket	3" EPDM	01616
Clamp	3" SS sanitary clamp	00444
Frits	Top, 3" frits (25)	FTF-0225
Frits	Bottom frit and sealing rings (25) for the stainless steel frit holder	FBS-1025
Insertion Tool	Top-frit insertion tool, 3" diameter	01534

Spare Parts

Item	Description	Part #
Injection Valve		
Ferrule	1/4" PFA ferrule (6)	03062
Nut and Ferrule Kit	1/4" SS nut w/ PFA ferrule (2)	03061
Luer-Lok® Kit	Female Luer-Lok injection kit	02838
FLASH Miscellaneous Spare Parts		
Tubing	1/8" OD FEP tubing Sold by the foot	00088
Tubing	1/4" OD FEP tubing Sold by the foot	00089
Air Tubing	1/4" OD RED air tubing Sold by the foot	00546
Air Tubing	1/4" OD YELLOW air tubing Sold by the foot	01354
Air Tubing	1/4" OD GREEN air tubing Sold by the foot	00547
Air Tubing	1/4" OD BLUE air tubing Sold by the foot	01487
FLASH+ Spare Parts		
E-Clip	Retaining ring	03024
V-band Clamp	3" V-band clamp for 1-L solvent reservoirs	08526
Reducing Union	1/4" x 1/8" reducing union (four required per set)	04144
FLASH 12+™ Spare Parts		
Lower ZIF O-ring	Chemraz® 107 O-ring	04593
Upper ZIF O-ring	Chemraz 108 O-ring	02948
Barrel O-ring	Chemraz 108 O-ring	02948
FLASH 25+™ Spare Parts		
Lower ZIF O-ring	Chemraz 208 O-ring	06178
Upper ZIF O-ring	Chemraz 209 O-ring	06221
Barrel O-ring	Chemraz 209 O-ring	06221
FLASH 40+™ Spare Parts		
Lower ZIF O-ring	Chemraz 215 O-ring	07765
Upper ZIF O-ring	Chemraz 218 O-ring	08557
Barrel O-ring	Chemraz 218 O-ring	08557
Reducing Union	1/4" x 1/8" reducing union (four required per set)	04144

Biotage recommends annual replacement of Chemraz O-rings to maintain FLASH+ compression modules.

Spare Parts

Item	Description	Part #
V1 SP4 Spare Parts		
The V1 SP4 system preceded the current SP4™ system.		
Lipseal	0.500 OD x .312 ID 302 SST Spring	08192
Ring Wear	0.500 OD x .370 ID Quad1	06785
UV lamp	For Sp4 Detector	09427
Valve	Solenoid 2-Way NO 24VDC 100 PSI 1/4-28 Prots	08746
UV Collect Valve	UV Collect valve for Horizon and SP4	09321
O-Ring	014 Chemraz	05654
O-Ring	007 Chemraz	06026
Ferrule	Flangeless 1/8 Tefzel	04030
Nut	1/8" Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless, 3/16 Tubing	09312
Nut	3/16 Flangeless, 5/16-24 Peek Natural	09311
Ferrule	Flangeless 1/16 Tefzel	04009
Nut	1/6" Flangeless Fer 1/4-28 Peek	04794
Tubing	1/6" OD x .030" ID x 1.83 Long Flash Collector	08173
Inlet Filters	Solvent inlet filter disks, 3/8"	01801
Reducing Union	1/4" x 1/8" reducing union (four required per set)	04144
Horizon Spare Parts		
Tube Assembly	Compression module outlet to fraction collector arm, 1/8"	08079
Tube Assembly	Compression module outlet to UV detector inlet, 1/8"	08085
Spare Parts Kit	Kit, spare tubing & fittings horizon 1/8"	08442
Tube Assembly	Flow control outlet to UV detector outlet, 1/8"	08761
Tube Assembly	Flow control valve to three-way collect valve to waste, 1/8"	08762
Valve	UV collect valve	09321
Cell	0.3 mm flow cell	08632
Valve	Stop flow control valve	08770
Lamp	UV lamp for Horizon Detector	09427
Cell	0.1 mm flow cell	08856
Window	Replacement windows for flow cells	08857
Tubing Kit	Upgrade tubing for outlet of compression module to UV collect valve	09263
Reducing Union	1/4" x 1/8" reducing union (four required per set)	04144
ZIF-SIM™ Spare Parts		
E-Clip	Retaining ring	03024
ZIF-SIM Tubing Kit	Luer fitting with 1/8" tubing, 1/8" knurled nut, connects ZIF-SIM outlet to compression module	01903

Spare Parts

Item	Description	Part #
ZIF-SIM 10™ Spare Parts		
Frit Insertion Tool	Polypropylene frit insertion tool	0087
Upper O-ring	Chemraz 111 O-ring	00656
Lower O-ring	Chemraz 109 O-ring	06176
ZIF-SIM 35™ Spare Parts		
Frit Insertion Tool	Polypropylene frit insertion tool	0088
Upper O-ring	Chemraz 208 O-ring	06178
Lower O-ring	Chemraz 206 O-ring	06177
ZIF-SIM 60™ Spare Parts		
Frit Insertion Tool	Polypropylene frit insertion tool	0184
Upper O-ring	Chemraz® 211 O-ring	08555
Lower O-ring	Chemraz 209 O-ring	06221
Quad™ Spare Parts		
Filter Kit	Replacement filters 1/4" x 1/8" reducing union (4 required per set) solvent inlet filters (12)	QFILT-0000
Reducing Union	1/4" x 1/8" reducing union (four required per set)	04144
Inlet Filter Packs	Solvent inlet filters (12)	QFRT-012
Quad Check Valve	Check disc	05516
1/8” Fitting Kit	1/8” Peek flangeless fittings 1/8” Peek nut 1/8” Tefzel ferrule	QFTT-4795
1/8" Peek Nut	1/8” Peek nut	04795
1/8" Tefzel Ferrule	1/8” Tefzel ferrule	04030
1/16” Fitting Kit	1/16” Peek flangeless fittings 1/16” Peek nut 1/16” Tefzel ferrule	QFTT-4794
1/16" Peek Nut	1/16” Peek nut	04794
1/16" Tefzel	Ferrule 1/16” Tefzel ferrule	04009
Upper O-Ring Kit	Upper O-ring Kit, Chemraz 108 and 107 O-rings Retaining Clip	QUOR-001
Upper O-ring	Chemraz 108 O-ring	02948
Lower O-ring	Chemraz 107 O-ring	04593
Retaining Clip	Retaining clip	03024
Lower O-Ring Kit	Chemraz® 108 O-ring Retaining clip	QLOR-001
Parallex Flex™ Spare Parts		
Needle	Tapered-tip needle	02922
Rotor for Inject Valve	6-port rotor, 0.040" ID	03947
2-mL Loading Loop	1/16" OD x 0.040" ID, SS	02789
5-mL Syringe	Gas-tight syringe	02935
5-mL Loading Loop	1/16" OD x 0.040" ID, SS	02788
10-mL Syringe	Gas-tight syringe	02751
Labels	Labels for barcode printer	06461
Switching valve	Five port loop switching valve	02748
UV Detector		
UV Lamp	Deuterium	09414
Gasket Set	Gaskets, offset flow cell UV4	03944
Pump		
Check Valve	Check-valve assembly	06403
Plunger	Sapphire plunger w/ holder	06404

Spare Parts

Item	Description	Part #
Belt	Motor belt	06407
3-way valve	Gradient 3-way proportioning valve	06408
Seal	Seal	06405
Seal	Seal	06406
Fraction Collector		
Ferrule	1/8" Tube Short Tefzel	02727
Nut	1/8" Tube x 1/4" - 28 Tefzel	02728
Ferrule	1/16" Tube Short Tefzel	02729
Nut	1/16" Tube x 1/4" - 28 Tefzel	05694
Seal Kit	Valve, Check, 25 psi, Kalrez	03451
Fuses		
Fuse	1 A	03120
Fuse	10 A	03188
Fuse	2 A	03191
Tubing		
Reservoir Pressure Tubing	1/4" OD LDPE, BLUE air line	01487
	Sold by the foot	
Peek Tubing	1/16" 0.020 ID	03263
	Sold by the foot	
Teflon® Tubing		
General-Purpose	1/4" OD, 0.040" wall	00089
Waste	1/8" OD	00088
Detector-to-fraction Collector	1/16" OD connects to inlet valve	02879
	Sold by the foot	
Unions		
Y Union	1/4" Instatite	01478
Ferrules and Nuts		
Ferrule Set	1/4" 316 SS*	01634
Nut	1/4" SS*	01635
Ferrule	1/16", SS*	02726
Nut	1/16" compression nut, SS*	02725
MVP Valve Connections		
Ferrule	1/16 inch, w/ SS* locking ring	02445
Nut	1/16 inch, Delrin®	02446
VICI Valve Connections		
Nut	1/16 inch, for SS* tubing	03318
Ferrule	1/16 inch, SS*	03319

**SS = Stainless Steel*

SP1™ Spare Parts

Fraction Collector		
Guide	Needle Horizon Flash Collector	08072
UV collect valve Needle	1/6 inch OD x .030 Inch ID x 1.83L	08173
Nut	1/6 inch Flangeless Fer 1/4-28 Peek	04794
Ferrule	Flangeless 1/16 Tefzel	04009
Valve Assembly	UV Collect 3-Way	09341
Tube Assembly	1/4 inch Trough Drain Tube	08432
Ferrule	Set 1/4 316 SS	01634
Nut	1/4 Tube 316 SS	01635
Tubing	1/4 OD x .040 Wall FEP Teflon	00089
Fuse	5 X 20MM 2.5A / 250V	09367

Spare Parts

Item	Description	Part #
Adapter	40mm to 25mm Flash+ Module Rack	07482
Adapter	40mm to 12mm Flash+ Module Rack	07481
Operator's Manual	CD SP1	09624
Pump		
Disk	3/16 inch Balls Assembly Quad3	05516
Lipseal	0.500 OD x .312 ID 302 SST Spring	08192
Ring	0.500 OD X .370 ID Quad1	06785
Tee	Female Branch 1/8 T x 1/8 FNPT x 1/8 T	9566
Nut	1/8 inch Flangeless Fer 5/16-24 Peek	4795
Ferrule	Flangeless 1/8 Tefzel	4030
Nut	1/8 Flangeless 1/4-28 Peek	08399
Tube Assembly	Solvent Inlet 5' Color Red SP4B/SP1	09664-01
Tube Assembly	Solvent Inlet 5' Color Blue SP4B/SP1	09664-02
Tube Assembly	Solvent Inlet 5' Color Green SP4B/SP1	09664-03
Tube Assembly	Solvent Inlet 5' Color Gold SP4B/SP1	09664-04
Filter	Inlet Solvent for 3/16 inch OD Tubing 20 um Porosity 316 SST	09376
Reducing Union	1/4 inch x 1/8 inch reducing union (4 required per set)	04144
Tubing	3/16 OD x .125 ID Teflon FEP	09314
Nut	Flangeless 3/16 T x 5/16-24 Peek Natural	09311
Ferrule	Flangeless 3/16 Tubing	09312
Tube Assembly	Compression Module Outlet to Flow Path Module Inlet, SP4B	09665
Tube Assembly	Flow Path Module Outlet to Compression Module Inlet, SP4B	09666
Union	1/4 T X 1/8 T W/ Knurled Nut & PFA Ferrules	04144
Tubing	1/8 OD x .062 ID FEP	00088
Nut	1/8 inch Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless 1/8 Tefzel	04030
Tube Assembly	Collect Valve to Flow Cell Outlet & Waste Sp1	09695
Nut	1/8 T Short Flangeless, 1/4-28 PEEK	08394
Nut	1/8 Flangeless 1/4-28 Peek Blue	08372
Nut	1/8 Flangeless 1/4-28 Peek	08399
Ferrule	Flangeless 1/8 Tefzel	04030
UV Detector		
Lamp	Mercury UV Fixed Wavelength 254nm	09427
Lamp	UV Variable Wavelength	09830
0.1 mm Flow Cell	Replacement cell 0.1 mm pathlength	08856
0.3 mm Flow Cell	Replacement cell 0.3 mm pathlength	08632
0.1 mm Flow Cell	Replacement Dual Wavelength	09843
0.3mm Flow Cell	Replacement Dual Wavelength	09869

SP4™ Spare Parts

Fraction Collector

UV collect valve Needle	1/6 inch OD x .030 Inch ID x 1.83L	08173
Nut	1/6 inch Flangeless Fer 1/4-28 Peek	04794
Ferrule	Flangeless 1/16 Tefzel	04009
Valve Assembly	UV Collect 3-Way	09321
Fuse	5 X 20MM 2.5A / 250V	09367
Adapter	40mm to 25mm Flash+ Module Rack	07482
Adapter	40mm to 12mm Flash+ Module Rack	07481
Operator's Manual	CD SP4	09653
Software SP4		09701

Spare Parts

Item	Description	Part #
Pump		
Disk	3/16 inch Balls Assembly Quad3	05516
Lipseal	0.500 OD x .312 ID 302 SST Spring	08192
Ring	0.500 OD X .370 ID Quad1	06785
Tube Assembly	Solvent Inlet 5' Color Red SP4B/SP1	09664-01
Tube Assembly	Solvent Inlet 5' Color Blue SP4B/SP1	09664-02
Tube Assembly	Solvent Inlet 5' Color Green SP4B/SP1	09664-03
Tube Assembly	Solvent Inlet 5' Color Gold SP4B/SP1	09664-04
Filter	Inlet Solvent for 3/16 inch OD Tubing 20 um Porosity 316 SST	09376
Tubing	3/16 OD x .125 ID Teflon FEP	09314
Nut	Flangeless 3/16T x 5/16-24 Peek Natural	09311
Ferrule	Flangeless 3/16 Tubing	09312
Tube Assembly	Compression Module Outlet to Flow Path Module Inlet, SP4B	09665
Tube Assembly	Flow Path Module Outlet to Compression Module Inlet, SP4B	09666
Union	1/4 T X 1/8 T W/ Knurled Nut & PFA Ferrules	04144
Tube Assembly	Flow Path Module UV Det Outlet to Flow Cell Inlet SP4B	09667
Nut	1/8 Flangeless 1/4-28 Peek	08399
Tube Assembly	Waste Outlet 6' SP4B	09668
Ferrule	Set 1/8 316 SS	01037
Tubing	1/8 OD x .062 ID FEP	00088
Nut	1/8inch Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless 1/8 Tefzel	04030
Nut	1/8 T Short Flangeless, 1/4-28 Peek	08394
Pump		
Nut	1/8 Flangeless 1/4-28 Peek Blue	08372
Nut	1/8 Flangeless 1/4-28 Peek	08399
Nut	1/8inch Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless 1/8 Tefzel	04030
Tube Assembly	1/4 inch Trough Drain Tube Horizon Flash Collector	08432
Ferrule,	Set 1/4 316 SS	01634
Nut	1/4 Tube 316 SS	01635
Tubing	1/4 OD x .040 Wall FEP Teflon	00089
UV Detector		
Lamp	Mercury UV Fixed Wavelength 254nm	09427
Lamp	UV Variable Wavelength	09830
0.1 mm Flow Cell	Replacement flow cell for Horizon Detector	08856
0.3 mm Flow Cell	Replacement flow cell for Horizon Detector	08632
0.3mm Flow Cell	Replacement Dual Wavelength for SP and Isolera	09869
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

Spare Parts

Item	Description	Part #
FlashMaster Spare Parts & Accessories		
Plunger	FlashPack Plunger Assembly, 12mm	109219
Plunger	FlashPack Plunger Assembly, 16mm	109220
Plunger	FlashPack Plunger Assembly, 20mm	109221
Plunger	FlashPack Plunger Assembly, 27mm	109222
Plunger	FlashPack Plunger Assembly, 37mm	109223
Plunger	FlashPack Plunger Assembly, 40mm	109224
O-ring	12mm Plunger O-ring	00-012-010
O-ring	16mm Plunger O-ring	00-016-010
O-ring	20mm Plunger O-ring	00-020-010
O-ring	27mm Plunger O-ring	00-027-010
O-ring	37mm Plunger O-ring	00-037-010
O-ring	40mm Plunger O-ring	00-040-010
O-ring	FlashPack Module Luer Tip assy, O-ring	00-000-011
Spring	FlashPack Luer Tip Assy, Spring	00-000-020
Spring & O-ring	FlashPack Luer Tip Assy, Spring and O-ring	00-000-030
Luer Tip Assy	FlashPack Luer Tip Assy	00-000-040
Filter	Solvent Line Filter	00-000-002
Valve	Shot Off Valve	FM-SCL/P-000
Seal	Rotor Seal for Main Valco Valve, EMTST12	SSAST12MWE
O-ring	FlashPack Module Luer Tip ASM O-ring, 1EA	00-000-010
Flangeless Fitting	FlashPack 1/16" Flangeless Fitting, PK/5	00-000-050
Flangeless Fitting Kit	Kit, FlashPack 1/8 Flangeless Fitting, PK/5	00-000-060
Tefzel Ferrule Kit	Kit, FlashPack 1/16", Tefzel Ferrule, PK/10	00-000-070
Tefzel Ferrule	Kit, FlashPack 1/8", Tefzel Ferrule, PK/5	00-000-080
Outlet	FlashMaster Check Valve Ass. Outlet	00-000-081
Outlet	Peek Anti Back-Flow Purge Check Valve Outlet	00-000-084
Arm	Positional Output Arm for FM Personal	00-000-086
Fittings Kit	FM Personal Fittings Kit	00-000-001
Outlet Line	ASM, Eluent Outlet Line to FC	00-000-202
Nut	1/8" PPS Superflangeless Nut, (Qty 10)	900263
Ferrule	1/8" Superflangeless Ferrule, (Qty 10)	900264
Diverter Valve	Fraction Collector Diverter Valve (Parker)	901686
Diverter Valve	High Flow rate Fraction Collector	302134
Needle	1.6 Inch SS Needle for 203/204 Fraction Collector	901684
Fraction Collector	203 Fraction Collector	901633
Long Needle	ASM, Long Needle FM	302162
USB Serial Interface	FM USB/Serial Interface	901730
Check Valves	Oakwade Check Valves (current)	901753
Fraction Collector	204 Fraction Collector	901634
SW Upgrade	FM II Software Upgrade, 2.X to current USB	901780
SW Update	FM II Software Update, 3.1 to current Parallel	901623
SW Upgrade	FM II Software Upgrade, 2.X to current Parallel	901658
SW Update	FM II Software Update, 3.1 to current USB	901782
Starter Kit	FM Personal Column Starter Kit	901711
Starter Kit	FM Personal Series ACC/PLUNG Starter Kit	901712
Quick Cards	FlashMaster Quick Cards	901597
Diverter Valve	Fraction Collector Diverter Valve, Gilson	170734

Item	Description	Part #
Service Rates		
Hourly rate		
Off-Site Service	Per hour	SER-002-LR
In-House Service	Per hour	SER-001-HR
Daily rate		
Off-Site Service	Per day	SER-002-DR
Travel Charges		
Zone A	Local travel 1-50 miles or 1-75 km	SER-0ZA-TR
Zone B	Local travel 51-100 miles or 76-150 km	SER-0ZB-TR
Zone 1	Travel 101-200 miles or 151-300 km	SER-0Z1-TR
Zone 2	Travel 201-500 miles or 301-750 km	SER-0Z2-TR
Zone 3	Travel 501-1000 miles or 751-1500 km	SER-0Z3-TR
Zone 4	Special Travel >1000 miles or >1500 km	SER-0Z4-TR
Service Contracts, Planned Maintenance and Installations		
2 Channel Flex	Installation/Training 2 Channel Flex	SER-FX2-IN
2 Channel Flex	2 Channel Flex Platinum Service Contract	SER-FX2-PL
2 Channel Flex	2 Channel Flex Gold Service Contract	SER-FX2-GLD
2 Channel Flex	PM-Planned Maintenance 2 Channel Flex	SER-FX2-PM
2 Channel Flex	PM Kit 2 Channel Flex	10468
4 Channel Flex	Installation/Training 4 Channel Flex	SER-FX4-IN
4 Channel Flex	4 Channel Flex Platinum Service Contract	SER-FX4-PL
4 Channel Flex	4 Channel Flex Gold Service Contract	SER-FX4-GLD
4 Channel FlexMUX	4 Channel FlexMUX Platinum Service Contract	SER-FMX-PL
4 Channel Flex	PM-Planned Maintenance 4 Channel Flex	SER-FX4-PM
4 Channel Flex	PM Kit 4 Channel Flex	10469
Parallex	Parallex Platinum Service Contract	SER-PAR-PL
ParallexMUX	ParallexMUX Platinum Service Contract	SER-PMX-PL
Advancer	Installation/Training Advancer	SER-ADV-IN
Advancer	Advancer Platinum Service Contract	SER-ADV-PL
FlashMaster II	Installation/Training FlashMaster II	SER-FM2-IN
FlashMaster II	FlashMaster II Platinum Service Contract	SER-FM2-PL
FlashMaster II	FlashMaster II Gold Service Contract	SER-FM2-GLD
FlashMaster Solo	Installation/Training FlashMaster Solo	SER-FMS-IN
FlashMaster Solo	FlashMaster Solo Platinum Service Contract	SER-FMS-PL
FlashMaster Solo	FlashMaster Solo Gold Service Contract	SER-FMS-GLD
FlashMaster II & Solo	PM-Planned Maintenance FM II/FlashMaster Solo	SER-FMS-PM
FlashMaster II & Solo	PM Kit FlashMaster II and FlashMaster Solo	901786
Horizon	Installation/Training Horizon	SER-HOR-IN
Horizon	Horizon Platinum Service Contract	SER-HOR-PL
Horizon	Horizon Gold Service Contract	SER-HOR-GLD
Horizon	PM-Planned Maintenance Horizon / Pioneer	SER-HOR-PM
Horizon	PM Kit Horizon / Pioneer	10433
Initiator	Installation/Training Initiator / EXP	SER-IN1-IN
Initiator	Initiator / EXP Platinum Service Contract	SER-IN1-PL
Initiator	Initiator / EXP Gold Service Contract	SER-IN1-GLD
Initiator	PM-Planned Maintenance Initiator / EXP	SER-IN1-PM
Initiator	PM Kit Initiator / EXP	355656
Initiator 8	Installation/Training Initiator 8 / 8EXP	SER-IN8-IN
Initiator 8	Initiator 8 / 8 EXP Platinum Service Contract	SER-IN8-PL

Spare Parts

Item	Description	Part #
Initiator 8	Initiator 8 / 8 EXP Gold Service Contract	SER-IN8-GLD
Initiator 8	PM-Planned Maintenance Initiator 8 / 8 EXP	SER-IN8-PM
Initiator 8	PM Kit Initiator 8 / 8 EXP	355656
Initiator 60	Installation/Training Initiator 60 / 60EXP	SER-I60-IN
Initiator 60	Initiator 60 / 60 EXP Platinum Service Contract	SER-I60-PL
Initiator 60	Initiator 60 / 60 EXP Gold Service Contract	SER-I60-GLD
Initiator 60	PM-Planned Maintenance Initiator 60 / 60 EXP	SER-I60-PM
Initiator 60	PM Kit Initiator 60 / 60 EXP	355656
Isolera One	Installation/Training Isolera One	SER-IS1-IN
Isolera One	Isolera One Platinum Service Contract	SER-IS1-PL
Isolera One	Isolera One Gold Service Contract	SER-IS1-GLD
Isolera Four	Installation/Training Isolera Four	SER-IS4-IN
Isolera Four	Isolera Four Platinum Service Contract	SER-IS4-PL
Isolera Four	Isolera Four Gold Service Contract	SER-IS4-GLD
SP1	Installation/Training SP1	SER-SP1-IN
SP1	SP1 Platinum Service Contract	SER-SP1-PL
SP1	SP1 Gold Service Contract	SER-SP1-GLD
SP1	PM-Planned Maintenance SP1	SER-SP1-PM
SP1	PM Kit SP1	10466
SP4	Installation/Training SP4 Old	SER-S4O-IN
SP4	SP4 Old Platinum Service Contract	SER-S4O-PL
SP4	Installation/Training SP4 New	SER-S4N-IN
SP4	SP4 New Platinum Service Contract	SER-S4N-PL
SP4	SP4 Gold Service Contract	SER-SP4-GLD
SP4 New	PM-Planned Maintenance SP4 New	SER-S4N-PM
SP4 New	PM Kit SP4	10466
Pioneer™	Pioneer Platinum Service Contract	SER-PIO-PL
Pioneer	PM-Planned Maintenance Pioneer / Horizon	SER-HOR-PM
Pioneer	PM Kit Pioneer / Horizon	10433
Quad3™	Installation/Training Quad3 / UV	SER-QUA-IN
Quad3	Quad3 Platinum Service Contract	SER-QU3-PL
Quad3	Quad3 Gold Serivce Contract	SER-QU3-GLD
Quad3	PM-Planned Maintenance Quad3	SER-QU3-PM
Quad3	PM Kit Quad3	10434
Quad UV	Quad UV Platinum Service Contract	SER-QUV-PL
Quad UV	Quad UV Gold Service Contract	SER-QUV-GLD
Quad UV	PM-Planned Maintenance Quad UV	SER-QUV-PM
Quad UV	PM Kit Quad UV	10465
Quest 205™	Installation/Training Quest 205	SER-Q05-IN
Quest 205	PM-Planned Maintenance Quest 205	SER-Q05-PM
Quest 205	PM Kit Quest 205	900824
Quest 205	Quest 205 Platinum Service Contract	SER-Q05-PL
Quest 210	Installation/Training Quest 210	SER-Q10-IN
Quest 210	Quest 210 Platinum Service Contract	SER-Q10-PL
Quest 210	PM-Planned Maintenance Quest 210	SER-Q10-PM
Queset 210	PM Kit Quest 210	900823
Synthesizer	Synthesizer Platinum Service Contract	SER-SYN-PL
Synthesizer	Synthesizer Gold Service Contract	SER-SYN-GLD
Synthesizer	PM-Planned Maintenance Synthesizer	SER-SYN-PM
Synthesizer	PM Kit Synthesizer	355657
Liberator™	Liberator Platinum Service Contract	SER-LIB-PL
Liberator	PM-Planned Maintenance Liberator	SER-LIB-PM
Liberator	PM Kit Liberator	355657

Spare Parts

Item	Description	Part #
Creator™	Creator / EXP Platinum Service Contract	SER-CRE-PL
Creator	Creator / EXP Gold Service Contract	SER-CRE-GLD
Creator	PM-Planned Maintenance Creator / EXP	SER-CRE-PM
Creator	PM Kit Creator	355658
Optimizer™	Optimizer / EXP Platinum Service Contract	SER-OPT-PL
Optimizer	Optimizer / EXP Gold Service Contract	SER-OPT-GLD
Optimizer	PM-Planned Maintenance Optimizer / EXP	SER-OPT-PM
Optimizer	PM Kit Optimizer	355658
V-10™	Installation/Training V-10	SER-V10-IN
V-10	V-10 Platinum Service Contract	SER-V10-PL
V-10	V-10 Gold Service Contract	SER-V10-GLD
Advantage 2410™	Installation/Training Advantage 2410	SER-A24-IN
Advantage 2410	Advantage 2410 Return to Factory Platinum Service Contract	SER-A24-PL
Advantage 3400™	Installation/Training Advantage 3400	SER-A34-IN
Advantage 3400	Installation/Training Advantage 3400 Accessories	SER-ASA-IN
Advantage 3400	Advantage 3400 Complete System Platinum Service Contract	SER-ACS-PL
Advantage 3400	Advantage 3400 Complete System Gold Service Contract	SER-ACS-GLD
Advantage 3400	Advantage 3400 Back Plane System Platinum Service Contract	SER-ABS-PL
Advantage 3400	Advantage 3400 Basic System Gold Service Contract	SER-ABS-GLD
Advantage 3400	PM-Planned Maintenance Advantage 3400 Complete System	SER-ACS-PM
Advantage 3400	PM Kit Advantage 3400 Complete	901784
Advantage 3400	PM-Planned Maintenance Advantage 3400 Basic System +4 mos.	SER-ABS-PM
Advantage 3400	PM Kit Advantage 3400 Back Plane	901559
Advantage 4100™	Installation Training Advantage 4100	SER-A41-IN
Atlantis™	Installation Atlantis 4 Chamber	SER-AT4-IN
Endeavor®	Installation/Training Endeavor	SER-END-IN
Endeavor	Endeavor Platinum Service Contract	SER-END-PL
Endeavor	Endeavor Gold Service Contract	SER-END-GLD
Endeavor	PM-Planned Maintenance Endeavor	SER-END-PM
Endeavor	PM Kit Endeavor	900828
Surveyor™	Surveyor Platinum Service Contract	SER-SUR-PL
Surveyor	PM-Planned Maintenance Surveyor	SER-SUR-PM
Surveyor	PM Kit Surveyor	900829
Trident™	Trident Platinum Service Contract	SER-TRI-PL
Trident	PM-Planned Maintenance Trident	SER-TRI-PM
Trident	PM Kit Trident	900825
T-Workstation	T-Workstation Platinum Service Contract	SER-TWO-PL
T-Workstation	PM-Planned Maintenance T-Workstation	SER-TWO-PM
T-Workstation	PM Kit T-Workstation	900826

Biotage Terms & Conditions of Sale

1. GENERAL

1.1 In these Terms & Conditions: The **Buyer** or **Customer** means the person, firm, company or other organization who or which has ordered Products from the Company; The **Company** means Biotage Sweden AB, a Swedish corporation existing under the laws of Sweden and any Affiliates to the Company; **Affiliates** means any corporation, partnership or other entity that controls, is controlled by, or is under common control with the Company, a corporation or other entity shall be regarded as in control of another corporation or entity if it owns, directly or indirectly, at least fifty percent (50%) of the voting or equity rights of the other corporation or entity authorized to cast votes in any election of directors or, in the case of a non-corporate entity, with the power to direct the management and policies of such non-corporate entity; The **Contract** means any contract for the sale and purchase of Products between the Company and the Buyer being any quotation of the Company which is accepted by the Buyer or any order of the Buyer's which is accepted by the Company whichever first occurs; The **Consumables** means Products used for sample preparation, Cartridges and accessories used for chromatography, vials and accessories used for synthesis; The **System** means instrumentation products included in any chromatography, synthesis or evaporation system listed in Exhibit A; The **Biotage Software** means any software used in Biotage instrumentation and in companion with instrumentation; The **Goods** means all items manufactured or supplied by the Company including the Consumables, the Systems and the Biotage Software; and The **Products** means any Goods agreed to be supplied by the Company.

1.2 These Terms & Conditions shall be incorporated into each Contract and shall govern each Contract. These Terms & Conditions may not be varied or waived except with the express written agreement of the Company. The failure of the Company to enforce its rights under the Contract at any time for any period of time shall not be construed as a waiver of any such rights.

2. PRICES AND QUOTATIONS

2.1 The price of the Products will be the Company's quoted price in the currency pursuant to the local price list, exclusive of any duties, value added or other taxes. All quotations issued by the Company for the supply of Products shall remain open for acceptance for the period stated in the quotation or, if none is stated, for thirty (30) days. In all other cases, prices payable are those currently in effect. Unless otherwise agreed in writing, extra charges will be made for all applicable handling, freight, content, packaging, insurance or similar costs and a handling charge may be made for small orders.

2.2 The Company shall not modify prices at any time before delivery to the Buyer unless to reflect any changes to its costs resulting from any alteration in or addition to the Buyer's requirements.

3. PAYMENT

3.1 Unless otherwise agreed in writing, payment in full shall be made to the Company in the currency invoiced no later than thirty (30) days from the date of invoice.

3.2 In addition to the prices invoiced, the Customer shall pay any tax, duty, customs or other fee of any nature imposed upon the transaction by any federal, state or local government authority. In the event the Company is required to prepay any such tax or fee, the Customer shall reimburse the Company.

3.3 In the event of late payment the Company reserves the right:

(i) to suspend deliveries and/or cancel any of its outstanding obligations; and

(ii) to charge interest at an annual rate equal to 12 % on all unpaid amounts calculated on a day to day basis until the actual date of payment.

3.4 Customers must themselves pay any bank charges that are incurred in making the payment. Full payment instructions are set out on the invoice.

4. CHANGES AND RETURNS

4.1 The Company reserves the right to make any change on prior notice in the specification of the Products, which does not materially affect the performance or price thereof. The Buyer shall confirm or cancel any order promptly on receipt of such

notice. The absence of such Buyer's confirmation or cancellation shall be deemed as acceptance of change of Product specification.

4.2 Returns of any Product must be authorized by the Company in advance. The Company shall be contacted for a return authorization number and shipping instructions. A restocking charge will be applied to shipments returned for exchange or credit.

5. DELIVERY

5.1 The Company will select the method of shipment and the carrier to be used, unless otherwise agreed. Unless otherwise agreed, shipment will be FCA (named place), Incoterms 2000. The Company will not be responsible for any loss or damage to the Products following delivery to the carrier. Damaged items cannot be returned without authorization.

5.2 If the Buyer fails to accept delivery of the Products within a reasonable period after receiving notice from the Company that they are ready for delivery, the Company may dispose of or store the Products at the Buyer's expense.

5.3 The Company will use all reasonable endeavors to avoid delay in delivery on the notified delivery dates. Failure to deliver by the specified date will not be a sufficient cause for cancellation, nor will the Company be liable for any direct, indirect, consequential or economic loss due to delay in delivery.

5.4 The Buyer shall notify the Company within five (5) working days in writing of any short delivery or defects reasonably discoverable on careful examination. The Company's sole obligation shall be, at its option, to replace or repair any defective Products or refund the purchase price of any undelivered Products.

5.5 Where delivery of any Product requires an export license or other authorization before shipment, the Company shall not be responsible for any delay in delivery due to delay in, or refusal of, such license or authorization.

6. RISK AND TITLE

6.1 The Buyer shall bear the risk of loss to the Products after delivery to the carrier. Full legal and equitable title and interest in the Products shall pass to the Buyer on delivery to the carrier.

6.2 To the extent there is any software included with the Products, the software is being licensed to the Buyer, not sold; and all right, title and interest therein shall remain in Company or its licensors. Use of such software shall be in accordance with the software license delivered with the applicable Product.

7. RESTRICTED USE

7.1 With respect to certain Products, use restrictions are a condition to the purchase which Buyer must satisfy by strictly abiding by the restriction as set forth in the Company's catalogue and/or on the Product and accompanying documentation. In no event shall Products stipulated by Company as intended for research and development use be used in a manufacturing process or in manufactured products or in human subjects. The Products shall in no event be used in medical or clinical applications, unless otherwise expressly stated by the Company, and Buyer is solely liable to ensure compliance with any regulatory requirements related to the Buyer's use of Products.

7.2 Any warranty granted by Company to the Buyer shall be deemed void if any Products covered by such warranty are used for any purpose not permitted hereunder.

7.3 The Buyer shall indemnify Company and hold Company harmless from and against any and all claims, damages, losses, costs, expenses and other liability of whatever nature that Company suffers or incurs by reason of any such unintended use.

8. WARRANTY

8.1.1 Consumables. The Company warrants that its Consumables meet the Company's specifications at the time of shipment. All warranty claims on Products must be made in writing and delivered to the Company within thirty (30) days of receipt of the Products ("Warranty Period"). The Company's sole liability and Buyer's exclusive remedy for a breach of this warranty is limited to replacement or refund at the sole option of the Company.

8.1.2 Systems. The Company warrants for a period of twelve (12) months from the date of shipment ("Warranty Period") that its Systems shall be free from defects in material and workmanship under normal use and service and when used in compliance with the applicable operating instructions. The Company's sole liability and Buyer's exclusive remedy for a breach of this warranty is limited to replacement, repair or refund at the sole option of the Company. This warranty does not apply to any consumable items included in the System such as, but not limited to, tubing, fittings, o-rings and gaskets, or any other part that comes in contact with the sample path. This warranty does not apply to any computer hardware delivered for use with the System. Such computer hardware will be subject to applicable manufacturer's warranties if any.

8.1.3 Software. The Company warrants for a period of twelve (12) months from the date of shipment ("Warranty Period") that the Biotage Software will, when used in the designated operating environment, perform materially in accordance with the applicable specifications. The Company does not warrant that the operation of the computer programs or software will be uninterrupted or error free. The warranty shall not apply to any Biotage Software that has been improperly installed or modified by Customer or any third party or which has been the subject of neglect, misuse, abuse, misapplication or alteration or has been used in violation of the applicable software license agreement. This warranty applies only to the most current version of the Biotage Software that was supplied to the Customer by the Company. The Company's sole liability and Buyer's exclusive remedy for a breach of this warranty is limited to correction or replacement or refund of the Biotage Software, at the sole option of the Company. This warranty does not apply to any third party operating system software included with the personal computer provided to the Customer by the Company. Such third party computer software will be subject to applicable manufacturer's warranties, if any.

8.1.4 Spare Parts and Repairs. The warranty period concerning repair work carried out and spare parts delivered is ninety (90) days and begins after the latter of the finishing of the repair work or the delivery of the spare parts. The warranty period shall, however, end no later than upon expiry of the initial Warranty Period applicable in relation to the original Products delivered. A repair or exchange of spare part does not extend the initial Warranty Period

8.1.5 All warranty claims on Biotage must be made in writing and delivered to the Company within the respective Warranty Period and as soon as a warranty claim is discovered by the Buyer. Any warranty claim presented by Customer to the Company hereunder shall reasonably detail the circumstances giving raise to the warranty claim.

8.2 THE COMPANY HEREBY EXPRESSLY DISCLAIMS, AND BUYER HEREBY EXPRESSLY WAIVES, ANY WARRANTY REGARDING RESULTS OBTAINED THROUGH THE USE OF THE PRODUCTS, INCLUDING WITHOUT LIMITATION ANY CLAIM OF INACCURATE, INVALID, OR INCOMPLETE RESULTS. ALL OTHER WARRANTIES, REPRESENTATIONS, TERMS AND CONDITIONS (STATUTORY, EXPRESS, IMPLIED OR OTHERWISE) AS TO QUALITY, CONDITION, DESCRIPTION, MERCHANTABILITY, FITNESS FOR PURPOSE OR NON-INFRINGEMENT (EXCEPT FOR THE IMPLIED WARRANTY OF TITLE) ARE HEREBY EXPRESSLY EXCLUDED.

9. LIMIT OF LIABILITY

9.1 The Company shall have no liability under the warranties contained in Section 8 in respect of any defect in the Products arising from: specifications or materials supplied by the Buyer; fair wear and tear; willful damage or negligence of the Buyer or its employees or agents; abnormal working conditions at the Buyer's premises; failure to follow the Company's instructions (whether oral or in writing); lack of maintenance; misuse or alteration or repair of the Products without the Company's approval; service or repair of the Products by any other party than the Company or an authorized service partner of the Company; or if the total price for the Products has not been paid; or through any cause beyond the Company's reasonable control.

9.2 THE COMPANY SHALL IN NO EVENT BE LIABLE FOR ANY INDIRECT OR CONSEQUENTIAL, OR PUNITIVE DAMAGES OF ANY KIND FROM ANY CAUSE ARISING OUT OF THE SALE, USE OR INABILITY TO USE ANY PRODUCT, INCLUDING WITHOUT LIMITATION, LOSS OF PROFITS, GOODWILL OR BUSINESS INTERRUPTION, EVEN IF COMPANY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

9.3 The exclusion of liability in these Terms & Conditions shall not apply in respect of death or personal injury caused by the Company's negligence.

9.4 The Company shall not be bound by any representations or statements on the part of its employees or agents, whether oral or in writing, including errors made in catalogues and other promotional materials.

10. INTELLECTUAL PROPERTY RIGHTS

10.1 Where the Buyer supplies materials, designs, drawings, and specifications to the Company to enable the Company to manufacture non-standard or custom made Products, the Buyer warrants that such manufacture will not infringe the intellectual property rights of any third party.

10.2 All intellectual property rights in the Products shall at all times remain vested in the Company.

11. HEALTH, SAFETY AND WASTE

The Buyer shall ensure that:

(i) the specification of the Products is safe for the intended use;
(ii) the Products are handled in a safe manner; and
(iii) any waste originating from the Products is disposed of in accordance with any relevant regulations.

12. INDEMNITIES

Except where the claim arises as a result of the negligence of the Company, the Buyer shall indemnify the Company in respect of any claim which may be made against the Company:

(i) arising in connection with the Buyer's use of the Products;
(ii) alleging that the use to which the Products are put infringes the intellectual property rights of any third party.

13. INSOLVENCY

In the event that the Buyer becomes bankrupt or, being a company, goes into liquidation (other than for the purposes of reconstruction or amalgamation), the Company shall be entitled immediately to terminate the Contract without notice and without prejudice to any other rights of the Company hereunder.

14. FORCE MAJEURE

14.1 The Company shall not be liable in respect of the non-performance of any of its obligations to the extent such performance is prevented by any circumstances beyond its reasonable control including but not limited to strikes, lock outs or labor disputes of any kind (whether relating to its own employees or others), fire, flood, explosion, natural catastrophe, military operations, blockade, sabotage, revolution, riot, civil commotion, war or civil war, plant breakdown, computer or other equipment failure and inability to obtain equipment.

14.2 If an event of force majeure exceeds thirty (30) days the Company may cancel the Contract without liability.

15. GOVERNING LAW

This Contract shall be governed by and construed in accordance with the substantive laws of Sweden, exclusive of its choice of law provisions, and the parties hereby submit to the exclusive jurisdiction of the courts of Sweden. Either party shall have the right to take proceedings in any other jurisdiction for the purposes of enforcing a judgment or order obtained from a Swedish court.

16. PRODUCT-SPECIFIC TERMS AND CONDITIONS

Additional terms and conditions govern the sale of certain Products. These additional terms and conditions are available at www.biotage.com and/or specified in the quotation if the Product is a custom product. Such additional terms and conditions shall take precedent in the event of any inconsistency with these Terms & Conditions.

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