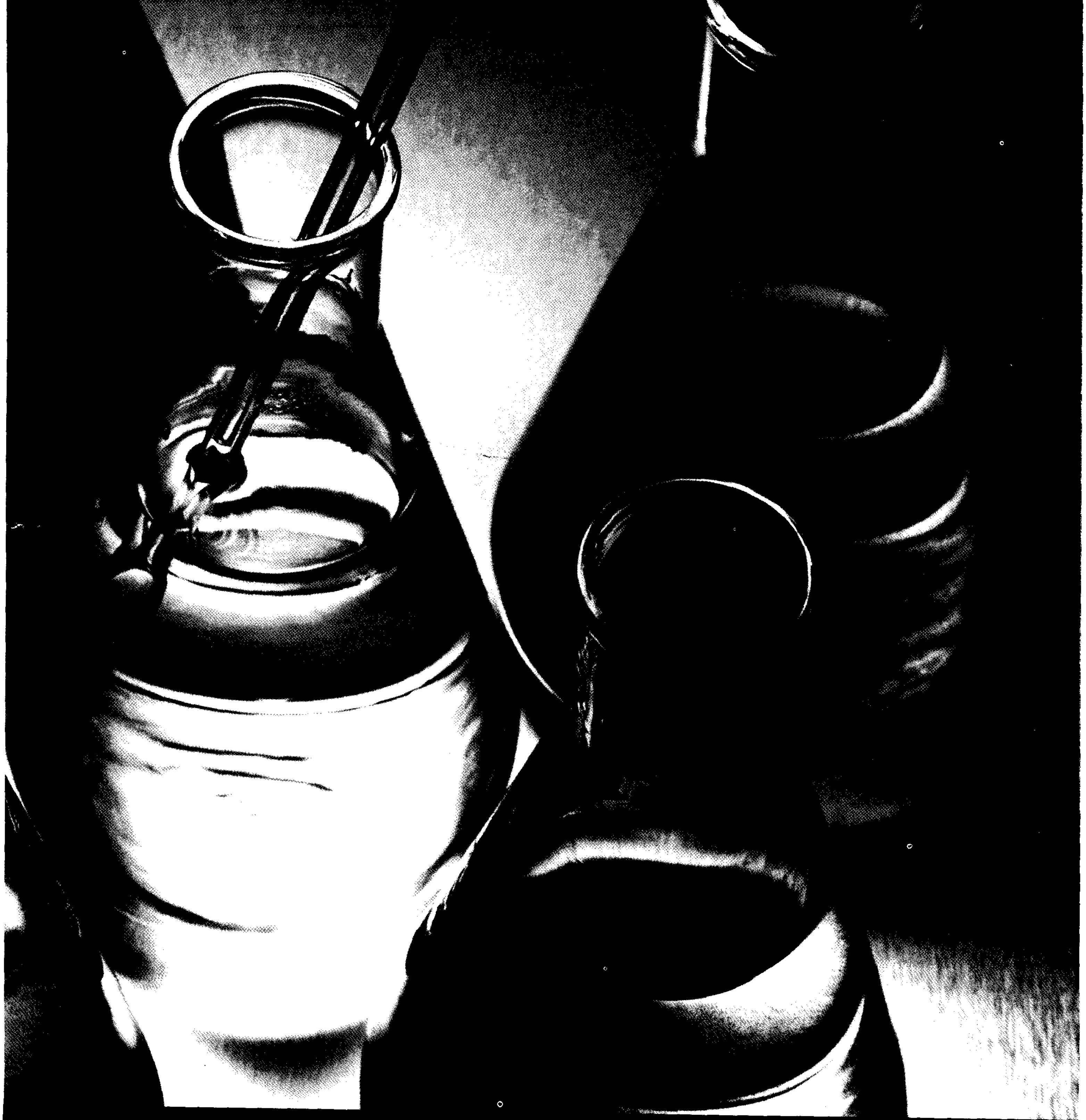
RESINS AND REAGENTS

FOR ACCELERATING SYNTHESIS AND PURIFICATION



ARGONAUT
TECHNOLOGIES

Welcome
to the Argonaut Resins Catalog

Argonaut Technologies develops and commercializes technology aimed at accelerating the discovery of new organic molecules. Our goal is to provide innovative technology that quickly and easily helps chemists capture the vast productivity gains offered by high speed parallel organic synthesis.

We provide resins for solid-phase and solution-phase organic synthesis. For solid-phase synthesis our resins are designed to reduce the time required to develop solid-phase protocols from existing solution-phase methodology. These unique resins perform under a wide variety of reaction conditions, permitting the synthesis of a range of interesting molecules.

To accelerate solution-phase synthesis and purification, we have developed scavenger resins and polymer-bound reagents. This line of products increases product purity and significantly reduces or eliminates the time and effort required for workup and purification by traditional methods.

Quality Products

Argonaut is known for the quality of its products. We perform extensive quality control tests on each resin lot, including:

- Loading capacity
- Bead size distribution
- Total extractables
- Chemical structure
- Elemental analysis
- Loss on drying
- Bead shape and appearance

This extensive testing results in excellent lot-to-lot and bead-to-bead consistency and very low levels of impurities in the products you synthesize.

Expertise

Argonaut's chemists are experienced synthetic organic chemists and have published widely in the academic literature and in Argonaut Application Notes. When you purchase resins from Argonaut you gain access to our technical resources for advice and support. Calling (888) 598-1350 (in North America) and +(650) 598-1350 (outside North America) will always bring you into contact with one of our specialists.

We are also always ready to discuss your needs for custom chemistries.

Customer Service

We have made it easy for you to order from us by whatever means best suits your needs – by telephone, fax, written requests and the Internet (see page III for details). If you already know what products you need, you can place an order 24 hours a day by fax or through the ArgoStore, Argonaut's online store. For those who prefer personal assistance for help with technical issues, a custom product or a bulk purchase discount agreement, help is only a telephone call away during regular working hours.

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How to Place an Order

KIMBERLY M. WOLFSON
INSIDE SALES REPRESENTATIVE
887 INDUSTRIAL ROAD, SUITE G • SAN CARLOS, CALIFORNIA 94070

Ordering by Phone

Monday-Friday 8 am to 5 pm PST

1-888-598-1350

1-650-598-1350 (outside U.S.) For a list of local distributors visit our Website: www.argotech.com

1. Have the list of items you would like to order ready.
2. Purchase orders and major credit cards (VISA, MasterCard and American Express) are accepted.

Ordering by Fax

24 hours a day, 7 days a week

1-650-598-1359

1. Send a fax copy of your purchase order
2. Be sure to include complete address information and telephone number

Ordering over the Internet

Use your credit card to order resins and Quest supplies from the Argonaut online store.

1. Go to the Argonaut Website at www.argotech.com and click on the link to the ArgoStore.
2. Search the store by part number, if you know it or browse the product categories until you find the items you need.
3. Click on the items you wish to purchase and provide shipping and billing information over a secure link.

Ordering by Mail

1. Mail a copy of your purchase order
2. Be sure to include complete address information and telephone number.

Order Processing
Argonaut Technologies
887 Industrial Road, Suite G
San Carlos, CA 94070

Expedite your order by including the following information:

1. Bill to, ship to address (please include phone and fax numbers) or current Argonaut Account number
2. Copy of Purchase Order
3. Product information - part number, description, quantity
4. Include a state tax exemption certificate or resale certificate for those orders that are not taxable.

Resin Discount Programs

See page VII for further details.

Terms and Conditions

See page IV for a list of Terms and Conditions of Sale.

Standard Terms and Conditions of Sale for Consumable Products

Price

Quote prices are valid for 30 Days from the date of the quote unless cancelled in writing by Seller. Shipping charges, insurance, duties and taxes are not included in prices and will be invoiced, if applicable, as separate items. For a current price list visit our Website: www.argotech.com.

Packing and Loss or Damage in Transit

Equipment will be packed for shipment in a manner suitable for air or truck. Unless otherwise indicated on the sales order acknowledgment, all sales are F.O.B. shipping point and all risk of loss or damage to product in transit is upon Buyer. Payment will be made in accordance with the Terms of Payment listed below.

Taxes

Buyer is responsible for the ultimate payment of all taxes which may be assessed or levied on or on the account of materials sold hereunder to the Buyer whether termed a gross receipts tax, use tax, property tax, sales tax or otherwise. Where Buyer claims that this transaction is not subject to any such tax or that Buyer is exempt or that Seller is not required to collect such tax, Buyer agrees to provide Seller with any documentation necessary to support such a claim, to allow Seller to document its decision not to collect such tax(es), and to indemnify Seller from any subsequent claims that such tax(es) were due.

Terms of Payment

Payment terms are net 30 from day of invoicing. Seller reserves the right in its sole discretion to require alternative payment terms, including, without limitation, sight draft, letter of credit or full or partial payment in advance.

Delivery Dates

The scheduled shipping date shown on the sales order acknowledgment is our best estimate of the time of the order will be shipped. Seller may make, and invoice, partial payments. Seller assumes no liability for loss, general damages, or special or consequential damages due to delays.

Returned Goods

Credits will not be issued for goods returned without prior approval. Please call Order Administration for required approval and return procedures. Returns may be subject to a restocking fee.

Termination

Upon any termination or cancellation of a sales order by Buyer, either in whole or in part, Buyer agrees to promptly pay appropriate termination or cancellation charges invoiced by Seller.

Quality and Testing Program for
Resins and Reagents

Use our high quality resins to produce consistent results with lower reagent costs. Argonaut Technologies' extensive QC testing guarantees high standards and minimum lot-to-lot variability for seven important parameters:

- **Loading capacity:**

The functional group content of a resin is referred to as *loading* for solid-phase synthesis resins and *capacity* for polymer reagents and scavengers for parallel-solution phase chemistry. Loading and capacity are reported in units of mmol/g.

At Argonaut we do not rely solely on elemental analysis to quantify the loading and capacity of our resins. All of our resins are tested functionally in model reactions to estimate the actual loading or capacity of the resin.

Resins for solid-phase organic synthesis are tested for resin loading. Typically this is performed by loading a model chromophore onto a sample of the resin followed by cleavage and measurement of the amount recovered. Polymer reagent and scavenger capacity is measured by conversion or uptake of a substrate in a model reaction or reagent scavenging, respectively.

Precise loading and capacity data enable the user to calculate stoichiometry accurately.

- **Bead size distribution:**

Argonaut resins are guaranteed to be 95% within a specified range to ensure uniform reaction kinetics, better compound yield, and higher purity. Uniform, specific-sized beads are desirable for split and mix applications.

- **Total extractables:**

Minimal resin impurities facilitate product purification and characterization.

- **Chemical structure:**

Argonaut uses FT-IR or 13C-NMR for chemical verification and purity.

- **Elemental analysis:**

Additional testing to verify chemical structure and loading capacity.

- **Loss on drying:**

This parameter assures low levels of residual solvent and accurate weighing.

- **Bead shape:**

Spherical shape and low levels of broken beads prevent clogging of frits and synthesis apparatus.

Certificate of Analysis

PS-Isocyanate
Lot: 00451

Property	Assay	Specification	Property
Scavenging Capacity	Excess Benzylamine Scavenging, 3 Hour, DCM, RT	NLT 1.0 mmol/g NMT 1.7 mmol/g	1.55 mmol/g
Mean Bead Size	Image Analysis	75-150 µm	101 µm
Chemical Structure	FTIR	Consistent with Structure	Passed

Certified by ______________________ **Date:** February 19, 1999

Material Specifications
PS-Isocyanate

Lot: 00451

Vendor: Argonaut Technologies
Qty: 1200 grams
Qty of QC Testing/Retain Sample: 10 grams

Property	**Assay**	**Specification**	**Property**
Scavenging Capacity	Excess Benzylamine Scavenging, 3 Hour, DCM, RT	NLT 1.0 mmol/g NMT 1.7 mmol/g	1.55 mmol/g
Capacity	Elemental N Analysis	NLT 1.0 mmol/g NMT 1.7 mmol/g	1.66 mmol/g
Residual Cl	Elemental Cl Analysis	For Information Only	0.58 mmol/g
Total Extractables	Dichloromethane Extraction	NMT 0.5 wt.%	0.10 wt.%
Loss on Drying	6 Hour Drying at 25°C and 1mmHg	NMT 1.0 wt.%	0.46 wt.%
Bead Shape	Microscopy	Spherical and <2% Broken	Passed
Mean Bead Size	Image Analysis	75 - 150 μm	101μm
Chemical Structure	FTIR	Consistent with Structure	Passed

Accepted: X **Rejected:** ____

By ____________________ **Date:** February 19, 1999

Custom Resin Synthesis

Argonaut Technologies currently offers a wide variety of common linkers on our three different resin types. Custom linker synthesis is also available to meet specific customer needs. Our chemistry expertise in both analytical and process scales guarantees the successful synthesis of resin to custom requirements. For further information on this service please contact us at (650) 598-1350 and ask to speak with the Product Manager for Resins.

Bulk Resin Manufacturing

Argonaut offers bulk resin manufacturing with guaranteed specifications, single large lots, competitive pricing, and on-time delivery. For large-scale manufacturing of custom resins, we work closely with our customers through all stages of development, from small batch trials to large-scale resin production.

Custom Packing in ArgoCaps®

Argonaut will custom-pack resin into polycarbonate capsules. ArgoCaps are a convenient and time-saving method for delivering fixed unit doses of resin to a reaction vessel. In addition, these convenient resin packages protect resins from moisture, while being easy to dissolve with a wide range of organic solvents.

ArgoCaps are available in two sizes: #5 and #3 capsules. The capsules are filled volumetrically. The fill weight is therefore dependent on the resin density.

Typical values for the fill weight of ArgoCaps are:

ResinType	#3 ArgoCaps	#5 ArgoCaps
ArgoGel	160 mg	70 mg
ArgoPore	100 mg	40 mg
Polystyrene	150 mg	65 mg

Argonaut also offers custom resins filling of ArgoCaps with your resins. For additional information, please contact your Argonaut representative.

Resin Discount Programs

Argonaut Technologies is pleased to extend substantial price savings to our valued customers within a pre-negotiated "Resin Discount Program". Additional discounts are available for large quantity orders and educational institutions. For further information on resin discounts please contact us at (650) 598-1350 and ask to speak with a Resin Sales Representative.

Resins and Reagents for Solution-Phase Synthesis & Purification

Parallel solution-phase synthesis has been growing in popularity as an alternative to solid-phase methodology for generating libraries of organic compounds. However, product workup and purification are unfortunate bottlenecks that can limit its practicality.

Chemically-driven purification techniques provide an alternative to individual aqueous extraction, crystallization and flash chromatography. Argonaut Technologies has developed a variety of scavenger resins and polymer-bound reagents to facilitate a wide range of solution-phase reactions and workups making parallel solution-phase synthesis more practical.

Scavenger resins

Scavenger resins are added after a reaction is complete to quench and selectively react with excess reagents and/or reaction byproducts. The bound impurities can be removed by simple filtration and washing. Compound purities exceeding 85% can be achieved 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 before chromatography to help achieve maximum throughput, purity and yield. Argonaut Technologies makes scavengers for a variety of electrophiles and nucleophiles. Since the reactive functionality is polymer-bound, seemingly incompatible combinations of these scavengers e.g. acids with bases, can be used together to remove mixtures of impurities.

Resin capacity is determined by measuring the uptake of a model substrate. This provides a better measure of scavenging capacity than loading based on elemental analysis.

Polymer-bound reagents

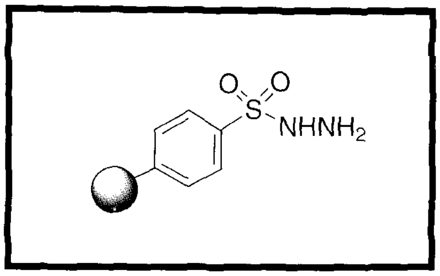
Polymer-bound reagents perform in a manner similar to their small molecule equivalents with minimal optimization needed for a given synthetic transformation. They are particularly useful for multistep reactions, saving time and reducing solvent requirements.

A subset of polymer-bound reagents - Catch and Release™ resins - allow for the "catching" of a small molecule as an activated polymer intermediate. The resin is washed to remove byproducts and a second transformation is performed to "release" the product into solution. Argonaut's polymer-bound reagents include acids, bases and coupling agents among others.

Resin Type

In this catalog, the product names provide information about the resin type that is used for each scavenger and reagent. PS designates a lightly cross-linked polystyrene and MP a more highly cross-linked macroporous resin.

Lightly cross-linked resins typically require the use of solvents that will swell the resin to allow 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. With macroporous resins, the functional groups are accessed through the pore network which is not usually dependent on solvent.



Electrophile Scavenger

PS-TsNHNH$_2$

Application:	Scavenging aldehydes and ketones
Typical Scavenging Conditions:	3 equiv. relative to carbonyl, 1 - 3 h, 20 °C, CH_2Cl_2. Ketones and hindered aldehydes are accelerated by the addition of acetic acid (~10%) and/or heat.
Compatible Solvents:	CH_2Cl_2 (7 mL/g), dichloroethane (7 mL/g), THF (6.5 mL/g), DMF (7.2 mL/g), and other swelling solvents

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 loading 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 acetic acid (5 - 10%) may be required for ketones and hindered aldehydes. Acetic acid is also required for sequestering aldehydes in DMF. Complete removal of common aldehydes occurs in 0.5 to 3 hours and removal of a ketone takes from 2 to 16 hours. 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.* one that swells polystyrene, and the product is isolated by concentration.

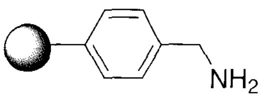
PS-TsNHNH$_2$ is also potentially useful as a polymeric reagent. Bound sulfonyl hydrazones, formed by condensation with carbonyl compounds, can be utilized in further synthetic transformations. The high accessibility of tosyl hydrazide functional groups in PS-TsNHNH$_2$ should afford high synthetic fidelity relative to other reported systems.[1-3]

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.

PS-TsNHNH$_2$

		PART #	QUANTITY
Resin Type:	1% Cross-linked polystyrene	800270	10 g
Capacity:	1.8 - 3.2 mmol/g (based on benzaldehyde uptake)	800271	25 g
Bead Size:	75-150 microns, 100-200 mesh (95% within)	800272	100 g



Electrophile Scavenger

PS-NH_2

Application:	Scavenging acid chlorides, sulfonyl chlorides, isocyanates and other electrophiles.
Typical Scavenging Conditions:	3 - 6 equiv relative to acid chloride, 1 - 4 h, 20 °C. If an additional resin-bound base is present: 1.5 - 3 equiv
Compatible Solvents:	CH_2Cl_2 (9.1 mL/g), THF (7.7 mL/g), DMF (6.5 mL/g)

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

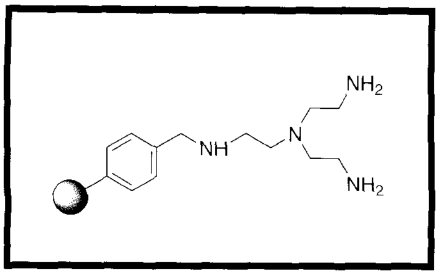
References

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

PS-NH_2

Resin Type:	1% Cross-linked polystyrene
Capacity:	1.0 - 1.6 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)

PART #	QUANTITY
800263	10 g
800264	25 g
800265	100 g



Electrophile Scavenger

PS-Trisamine

Application:	Scavenging acid chlorides, sulfonyl chlorides, isocyanates, and other electrophiles
Typical Scavenging Conditions:	3 - 6 equiv relative to acid chloride, 1 - 4 h, 20 °C. If an additional resin-bound base is present: 1.5 - 3 equiv
Compatible Solvents:	CH_2Cl_2 (7 mL/g), THF (6 mL/g), DMF (5.2 mL/g) and other swelling solvents

PS-Trisamine is used for the removal of excess electrophilic reagents during the quenching and purification of reaction mixtures.[1]

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 hour using 3.5 equivalents PS-Trisamine (For data, see Technical Section). 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 hour.

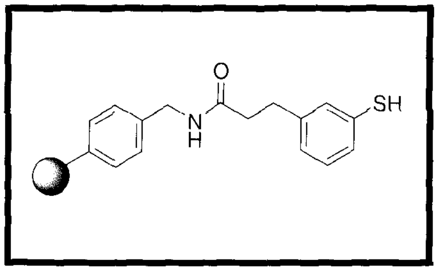
References

1. Booth, R. J.; Hodges J. C. *J. Am. Chem. Soc*, **1997**, *119*, 4882.

PS-Trisamine

Resin Type:	1% Cross-linked polystyrene
Capacity:	3 - 4 mmol/g (based on benzoyl chloride uptake)
Bead Size:	75-150 microns, 100-200 mesh (95% within)

PART #	**QUANTITY**
800228	10 g
800229	25 g
800230	100 g



Electrophile Scavenger

PS-Thiophenol

Application:	Scavenging alkylating agents
Typical Scavenging Conditions:	2 - 3 equiv relative to nucleophile, 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 diisopropylethylamine (DIEA, 2 equiv) and MP-Carbonate (2 equiv). Scavenging is best performed in THF/ethanol or DMF
Compatible Solvents:	DMF (7.0 mL/g), THF (7.0 mL/g) , CH_2Cl_2 (7.0 mL/g), and other swelling solvents

PS-Thiophenol is based on an aminomethyl resin with a tethered thiophenol functionality. The resin is designed for the scavenging of 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.

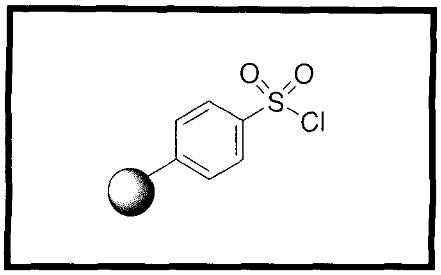
Effective scavenging of active halides requires either the use of the potassium thiolate salt (formed with potassium trimethylsilanolate) or the presence of diisopropylethylamine (DIEA) and MP-Carbonate resin. The solvent used for the scavenging reaction is critical for good scavenging rates. Both 1:1 THF/ethanol (THF/EtOH) mixtures and dimethylformamide (DMF) were found to be effective solvents. Low levels of scavenging were observed in pure THF, indicating that removal of alkyl halides from a reaction carried out in THF would require the addition of ethanol to accelerate the reaction. It is likely that addition of ethanol may be necessary to accelerate the scavenging process in other solvents, as well.

PS-Thiophenol is stable with long-term storage at 4°C. Stability studies have shown no loss in capacity over a period of 18 months.

PS-Thiophenol

Resin Type:	1% Cross-linked polystyrene
Capacity:	1.0 - 1.5 mmol/g (based on benzyl bromide uptake)
Bead Size:	75-150 microns, 100-200 mesh (95% within)

PART #	QUANTITY
800273	10 g
800274	25 g
800275	100 g



Nucleophile Scavenger

PS-TsCl High Loading

Application:	Scavenging of alcohols, amines and other nucleophiles
Typical Scavenging Conditions:	3 equiv relative to nucleophile, 20% pyridine or 6 equiv of triethylamine, THF or 1, 2-dichloroethane, 3-6h
Compatible Solvents:	Dichloromethane (4.5 mL/g), tetrahydrofuran (9.9 mL/g), dimethylformamide (9.0 mL/g), and other solvents that swell gel-type polystyrene
Incompatible Solvents:	Water, methanol, isopropyl alcohol, ethyl ether, and hexanes
Recommended Agitation:	Gentle stirring or swirling

PS-TsCl-HL is the resin-bound equivalent of tosyl chloride. This high-loading resin (2.0-3.0 mmol/g) is useful for the scavenging of various nucleophiles, including amines, hydrazines, alcohols and organometallics.

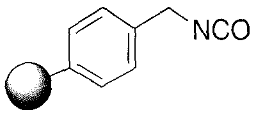
Scavenging reactions typically use 3 equivalents of resin per equivalent of substrate to be scavenged. The resin can be used in conjunction with a polymer-bound base, e.g. MP-carbonate or PS-DIEA, if a soluble base is not present in the reaction mixture. Various solvents may be used, including 1,2-dichloroethane (DCE), dichloromethane (DCM), tetrahydrofuran (THF) and N,N-dimethylformamide (DMF), with a temperature range from 20 to 50 °C.

Scavenging reactions may also be performed in THF or DMF. In these cases, THF was found to give lower scavenging efficiency when compared to DCE. Reactions done in DMF were successful, however, reaction mixtures became discolored. For data on the comparative scavenging of various nucleophiles, please refer to the Technical Section.

PS-TsCl-HL

Resin Type:	1% Cross-linked polystyrene
Capacity:	2.0 - 3.0 mmol/g (based on uptake of aniline and confirmed by Volhard titration)
Bead Size:	75-150 microns, 100-200 mesh (95% within)

PART #	QUANTITY
800364	10 g
800365	25 g
800366	100 g



Nucleophile Scavenger

PS-Isocyanate

Application:	Scavenging nucleophiles, including amines and alkoxides
Typical Scavenging Conditions:	2 - 3 equiv relative to nucleophile, 1 - 16 h, 20 °C
Compatible Solvents:	CH_2Cl_2 (9.5 mL/g), dichloroethane (7.2 mL/g), THF (8.2 mL/g), toluene (7.8 mL/g), incompatible with water and alcohols

PS-Isocyanate is produced from aminomethyl resin by a superior process which gives high conversion with minimal urea formation as determined by IR spectroscopy.

The resin can readily scavenge excess nucelophiles and is often used to drive reactions to completion, thereby facilitating workup and purification.[1-5] The reaction of nucleophiles with the isocyanate moiety occurs without liberation of small molecule byproducts.

Removal of nucleophiles from solution generally requires a 2 - 3 equiv of PS-Isocyanate depending on substrate reactivity. Comparative scavenging of amines and alcohols of varying reactivity was tested as a function of time and temperature. Typical aliphatic amines are completely sequestered by two equivalents of PS-Isocyanate within 1 hour. Two equivalents of PS-Isocyanate sequestered 89% and 99% aniline at room temperature and 60 °C for 16 hours, respectively. A less reactive aromatic amine, 2-aminobenzophenone, was not completely sequestered even at elevated temperatures. Alcohols were not reactive towards PS-Isocyanate at room temperature, suggesting that aliphatic amines can be selectively sequestered in the presence of alcohol functionalities. For details please refer to the Technical Section.

Upon completion of the scavenging, the product is washed away from the resin with a solvent that dissolves the product and swells polystyrene, but is not nucleophilic enough to react with the resin. CH_2Cl_2 is preferred, but dichloroethane, THF and toluene are also good choices.

A twelve month stability study on PS-Isocyanate indicates that the resin is stable at room temperature with no loss of activity observed.

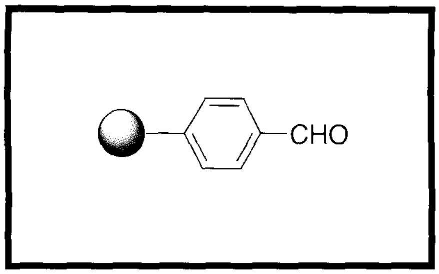
References

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.

PS-Isocyanate

Resin Type:	1% Cross-linked polystyrene
Capacity:	1.0 - 1.7 mmol/g (based on benzylamine uptake)
Bead Size:	75-150 microns, 100-200 mesh (95% within)

PART #	QUANTITY
800260	10 g
800261	25 g
800262	100 g



Nucleophile Scavenger

PS-Benzaldehyde

Application:	Scavenging nucleophiles including primary amines, hydrazines, reducing agents
Typical Scavenging Conditions:	3 equivalents relative to nucleophile, 50 °C, DCE 1-16 h
Compatible Solvents:	CH_2Cl_2 (8.1 mL/g),1,2-dichloroethane (7.4 mL/g), THF (7.3 mL/g), toluene (7.0 mL/g), and other solvents that swell gel-type polystyrene.
Incompatible Solvents:	Water, alcohols, ethyl ether, hexane

PS-Benzaldehyde[1,2] is the resin-bound equivalent of benzaldehyde. This resin is useful for scavenging various nucleophiles, including primary amines, hydrazines, and carbon-based nucleophiles such as Meldrum's acid and organometallics. The loading 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 1,2-dichloroethane (DCE), dichloromethane (DCM), and N,N-dimethylformamide (DMF), with a temperature range from 20 °C to 50 °C. For data on comparative scavenging of nucleophiles by PS-Benzaldehyde, please refer to the Technical Section.

PS-Benzaldehyde is stable at room temperature with no loss of activity observed.

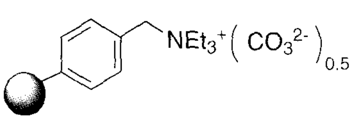
References

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-Benzaldehyde

Resin Type:	1% Cross-linked polystyrene
Capacity:	1.0 - 1.6 mmol/g (based on uptake of phenylhydrazine and confirmed by nitrogen analysis of the 2,4 DNP derivative)
Bead Size:	75-150 microns, 100-200 mesh (95% within)

PART #	QUANTITY
800360	10 g
800361	25 g
800362	100 g



Polymer-Bound Base

MP-Carbonate

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 equiv of diisopropylamine as a soluble transfer base.

Typical Scavenging Conditions: 3 equiv relative to substrate, 0.5 to 2 h, 20 °C

Resin Swelling: CH_2Cl_2 (3 mL/g), dichloroethane (3 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 like carboxylic acids or acidic phenols.

Removal of excess carboxylic acids or acidic phenols, *e.g.* phenol or nitrophenol, from solution generally requires 3 - 4 equiv of MP-Carbonate. Removal of excess hindered phenol requires larger amounts of resin, typically up to 5-fold excess MP-Carbonate. Complete removal takes from 30 minutes to 2 hours. Upon completion of the scavenging, the resin is rinsed three times with a suitable solvent, including CH_2Cl_2, THF, or ethanol. Representative acids and phenol scavenging examples are presented in the Technical Section.

MP-Carbonate is also very useful for neutralizing alkylammonium salts, *e.g.* hydrochlorides and trifluoroacetates, to generate the free base. Applications include neutralizing reactants, products and ammonium salts of volatile amines, *e.g.* diisoproylethylamine (DIEA) or triethylamine, 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 equiv) can be added as a soluble transfer base.

Use gentle magnetic stirring, swirling or overhead stirring for large resin quantities (>5 g). Due to the large bead size of this resin, effective mixing may not be achieved with Quest 210. Optimal mixing may be achieved with resin cartridges or filter plates using rotatory or orbital mixing.

References

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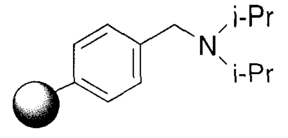
MP-Carbonate

Resin Type: Macroporous polystyrene
Capacity: 2.5 - 3.5 mmol/g (based on nitrogen elemental analysis)
Bead Size: 350-1250 microns, 18-52 mesh (95% within)

PART #	QUANTITY
800267	10 g
800268	25 g
800269	100 g



Polymer-Bound Base

PS-DIEA

Application:	Tertiary amine base
Typical Application Conditions:	2 - 3 equiv relative to limiting reagent
Resin Swelling:	CH_2Cl_2 (3.0 mL/g), THF (4.2 mL/g), DMF (2.5 mL/g)

PS-DIEA is a high loading tertiary amine base which is a resin-bound equivalent of diisopropylethylamine. PS-DIEA is useful in applications requiring a tertiary amine base and where the resin-bound ammonium salt byproducts are 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 the benzylic position by analogy to other resin-bound amine bases, *e.g.* morpholinomethyl polystyrene. Although the benzylic amine linkage is typically susceptible to cleavage by electrophiles, to form small molecule impurities, *e.g.* amides or carbamates,[2,3] 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 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).

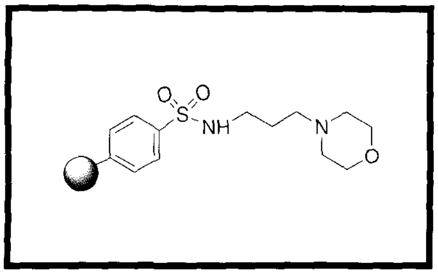
References

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-DIEA

Resin Type:	1% Cross-linked polystyrene
Capacity:	3 - 4 mmol/g (based on nitrogen analysis)
Bead Size:	105-1000 microns, 22-165 mesh (95% within)

PART #	QUANTITY
800279	10 g
800280	25 g
800281	100 g



Polymer-Bound Base

PS-NMM

Application:	Tertiary amine base
Typical Reaction Conditions:	2 - 3 equiv of PS-NMM resin relative to electrophile
Compatible Solvents:	CH_2Cl_2 (7.8 mL/g), tetrahydrofuran (5.8 mL/g), dimethylformamide (8.7 mL/g), methanol (2.2 mL/g)

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 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 (CH_2Cl_2, 16 h), whereas treatment of morpholinomethyl polystyrene under similar conditions led to 90% cleavage of the NMM group from the resin.

Representative uses of PS-NMM resin in the formation of amides, sulfonamides, and carbamates are provided in the Technical Section.

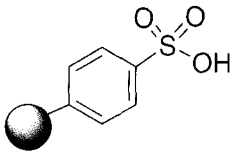
References

1. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.

PS-NMM

Resin-Type:	1% Cross-linked polystyrene
Capacity:	1.5 - 2.5 mmol/g based on nitrogen analysis.
Resin-Type:	1% cross-linked poly(styrene-co-divinylbenzene
Bead Size:	75-150 microns, 100-200 mesh (95% within)
Application:	Tertiary amine base

PART #	QUANTITY
800282	10 g
800283	25 g
800284	100 g



Polymer-Bound Acid

MP-TsOH

Application:	Scavenging and "Catch and Release"of amines
Typical Scavenging Conditions:	Approx. 2 - 3 equiv of resin relative to amine, 0.5 - 1 h, 20 °C
Resin Swelling:	CH_2Cl_2 (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 & Haas).[1-2, 6-7] However, 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 predominately restricted to the surface of the macroporous framework and 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.[8] Representative amine scavenging examples as a function of time are provided in the Technical Section.

MP-TsOH is 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.[3-5] MP-TsOH (1.4 mmol/g) has approximately double the sulfonic acid capacity of SCX media (approx. 0.7 mmol/g). In addition, MP-TsOH circumvents the contamination of amine products with fine particulates that may occur with silica-derived SCX columns. This problem is presumably due to dissolution of silica by methanol used to elute amine products from the media. Representative amine scavenging examples in cartridges are provided in the Technical Section.

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2. Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**. *38*, 513.
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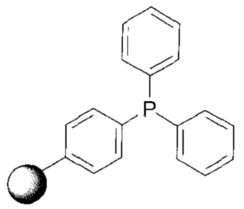
8. Stahlbush, J.R.; Strom, R.M.; Byers, R.G.; Henry, J.B.; Skelly, N.E. "Prediction and Identification of Leachables from Cation Exchange Resins," 48th Annual Meeting International Water Conf., Pittsburgh, PA (Nov. **1987**), IWC-87-10.

MP-TsOH

Resin-Type:	Macroporous polystyrene
Capacity:	1.1 - 1.6 mmol/g based on uptake of benzylamine
Bead Size:	300-450 microns, 38-50 mesh (mean value)

PART #	QUANTITY
800285	10 g
800286	25 g
800287	100 g



Polymer-Bound Phosphine

PS-Triphenylphosphine

Application:	Chlorination of acids and alcohols, Wittig and Mitsunobu reactions, scavenging of alkyl halides
Typical Chlorination Conditions:	0.5 equiv of acids or alcohols in CCl_4, 2 h, 80 °C
Typical Mitsunobu Reaction Conditions:	1.0 equiv of alcohol, 1.0 equiv of phenol, 1.0 equiv of resin, and 1.0 equiv of diethyl azodicarboxylate (DEAD) at room temperature for 16 h
Typical Wittig Reaction Conditions:	2.0 equiv of ylide resin, 8.0 equiv of sodium bis(dimethylsilyl)amide/ tetrahydrofuran (NaHMDS/THF), resin washing with THF, followed by 1.0 equiv of carbonyl compound in THF at room temperature for 16 h
Typical Alkyl Halide Scavenging Conditions:	3.0 equiv of resin, dimethylformamide (DMF, 10 mL/g resin) 20°C, 16 h
Compatible Solvents:	DMF (3.5 mL/g), THF (4.1 mL/g), dichloromethane (4.9 mL/g), benzene (3.1 mL/g) and other solvents that swell gel-type polystyrene
Incompatible Solvents:	Water, ethanol, isopropyl alcohol, diethyl ether (2.1 mL/g) and other solvents that do not swell gel-type polystyrene

PS-Triphenylphosphine is a resin-bound equivalent of triphenylphosphine. This resin can readily convert acids or alcohols to the corresponding acyl or alkyl chlorides in CCl_4.[2-4] The conditions are mild and products are formed in high yield. PS-Triphenylphosphine may also be utilized for Mitsunobu reactions to prepare aryl ethers in high yield.[5] Removal of hydrazide byproducts is readily accomplished using a silica SPE cartridge. PS-Triphenylphosphine resin can be utilized to synthesize olefins via the Wittig reaction.[1,6] The resin gave superior results for Wittig reactions when compared to alternative polymer-bound Triphenylphosphine (2 % DVB), in which case starting materials were recovered. PS-Triphenylphosphine may also be used as a scavenger for alkyl halides.

For more information about these reactions and for yield and purity data, please see the Technical Section.

References

1. Bernard, M.; Ford, W.T. *J. Org. Chem.* **1983**, *48*, 326
2. Relles, H. M.; Schluenz, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 6469.
3. Regen, S. L.; Lee, D. P. *J. Org. Chem.* **1975**, *40*, 1669.
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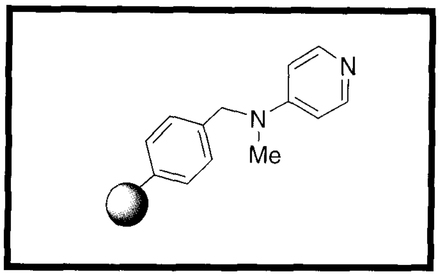
PS-Triphenylphosphine

Resin Type:	1% Cross-linked polystyrene
Capacity:	1.0 - 1.5 mmol/g (based on uptake of benzyl bromide)
Bead Size:	75-150 microns, 100-200 mesh (95% within)

PART #	QUANTITY
800378	10 g
800379	25 g
800380	100 g



Polymer-Bound Catalyst

PS-DMAP

Application:	Catalyst for acylation reactions, "Catch and Release" applications
Typical Catalysis Conditions:	10 mol % (0.1 equiv) relative to alcohol, overnight, 110 °C.
Resin Swelling:	Toluene (1.8 mL/g), CH_2Cl_2 (3.8 mL/g), DMF (2.6 mL/g), THF (1.9 mL/g)
Recommended Agitation:	Gentle stirring or swirling

PS-DMAP is a polymer-bound equivalent of dimethylaminopyridine (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 use of PS-DMAP as a catalyst for the esterification of tertiary alcohols was investigated using 1-methylcyclohexanol.[1,2] The results indicate the PS-DMAP reaction was 95% complete relative to 98% complete with DMAP.

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.[3,4] The electrophilic partner is reacted 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.[5] By using the nucleophile as the limiting reagent, the product can be isolated in high purity by filtration, with the excess electrophile remaining bound to the resin.

Examples of the use of PS-DMAP to form amides & sulfonamides by Catch and Release are given in the Technical Section.

References

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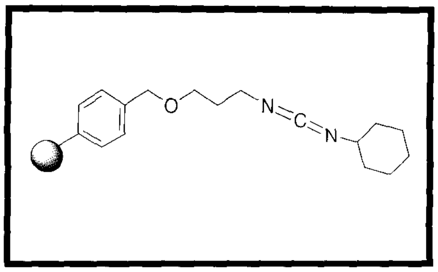
5. Patchornik, A. *Chemtech*, **1987**, 58.
6. Based upon experimental findings for "Catch and Release" applications, an average of 25% of the total DMAP sites are available for reaction on PS-DMAP resin.

PS-DMAP

Resin Type:	4% Cross-linked polystyrene
Capacity:	1.1 - 1.8 mmol/g (based on nitrogen analysis). Approximately 0.35 mmol/g capacity for acyl/sulfonyl chloride in "Catch and Release" applications.
Bead Size:	200-600 microns, 30-80 mesh (95% within)

PART #	QUANTITY
800288	10 g
800289	25 g
800290	100 g



Polymer-Bound Coupling Agent

PS-Carbodiimide

Application:	Coupling agent for amide and ester synthesis, pentafluorophenyl (PFP) and other activated ester formation
Typical Acid/Amine Coupling:	2 equiv of resin, 1.5 equiv of acid, 1.0 equiv of amine in dichloromethane overnight at room temperature
Compatible Solvents:	Dichloromethane (7.0 mL/g), dichloroethane (6.9 mL/g), tetrahydrofuran (6.5 mL/g), dimethylformamide (4.5 mL/g), and other solvents that swell polystyrene
Incompatible Solvents:	Water, methanol, isopropyl alcohol, ethyl ether and other solvents that do not swell gel-type polystyrene
Storage:	5° C freezer recommended, however, the resin has been found to be stable at room temperature for over six months

PS-Carbodiimide is a neutral, tethered carbodiimide that may be used for the synthesis of amides, esters, and activated esters. Amide formation may be conducted either with or without HOBt. Excess HOBt may be scavenged after the reaction using PS-Trisamine resin.[2] The shelf stability of PS-Carbodiimide at room temperature was found to be superior to the charged P-EDC resin making PS-Carbodiimide a reliable and shelf-stable reagent for coupling reactions.

PS-Carbodiimide has been found to give superior results relative to N-Cyclohexylcarbodiimide-N'-Me PS resin[3] (**Figure 1**) and the quaternary carbodiimide resin P-EDC.[4]

In general, PS-Carbodiimide affords amides in high yield and purity without evidence of residual amine or carboxylic acid. The carboxylic acid, normally used in excess relative to the amine, remains bound to the resin during work-up. PS-Carbodiimide may also be used for the synthesis of pentafluorophenyl (PFP) activated esters and N-hydroxysuccinimidyl esters.[5]

References

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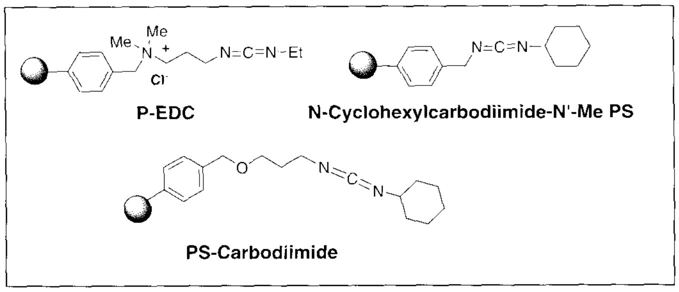
5. Adamczyk, M.; Fishpaugh, J.R.; Mattingly, P.G. *Tetrahedron Lett.* **1995**, *36*, 8345.

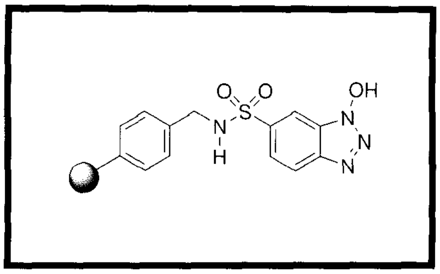
FIGURE 1. Structures of Carbodiimide Resins



PS-Carbodiimide

Resin Type:	1% Cross-linked polystyrene
Capacity:	0.9-1.4 mmol/g (based on generation of Ac_2O from AcOH, measured by ^1H NMR)
Bead Size:	75-150 microns, 100-200 mesh (95% within)
Resin Type:	1% cross-linked poly(styrene-co-divinyl benzene)

PART #	QUANTITY
800369	10 g
800370	25 g
800371	100 g



Polymer-Bound Coupling Agent

PS-HOBt

Application:	Coupling of acids and amines (Catch and Release), protecting group (Fmoc, Cbz or Boc) transfer
Typical Acid Loading Conditions:	Two treatments of 2 equiv of acid, 2 equiv of bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP) and 4 equiv of N,N-diisopropylethylamine (DIEA) in dimethylformamide (DMF) at room temperature for 3 hours
Typical Protecting Group Loading Conditions:	3 equiv of FmocCl or CbzCl and 5 equiv of pyridine in CH_2Cl_2 at room temperature for 1 h
Compatible Solvents:	DMF (7.5 mL/g), tetrahydrofuran (4.8 mL/g), dichloromethane (3.0 mL/g), and other solvents that swell gel-type polystyrene
Incompatible Solvents:	Water, methanol, isopropyl alcohol, ethyl ether and other solvents that do not swell gel-type polystyrene

PS-HOBt is a resin-bound equivalent of 1-hydroxybenzotriazole (HOBt) which is attached via a sulfonamide linkage.[1] The resin reacts readily with carboxylic acids in the presence of PyBrOP and DIEA to give a variety of functionalized polymers which can be used as acylation reagents for amines in organic synthesis.[1-5] We have found that in the cleavage of resin-bound activated esters with amines the use of DIEA improves the overall reaction yield. In most cases, amides are formed in high purity and no further purification is needed.

PS-HOBt may also be used for the protection of amines. This resin is an effective activating reagent for transfer of protecting groups, e.g. Fmoc and Cbz, to amines.[6] For more details please refer to the Technical Section.

Resin-bound activated esters and protecting groups can be stored at 0-5 °C for extended periods. PS-HOBt is stable and recyclable which makes it attractive for use in automated synthesis. The resin is ready for re-use after washing to remove any remaining reagents.

References

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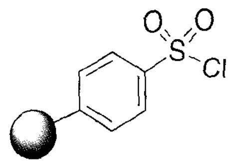
PS-HOBt

		PART #	QUANTITY
Resin Type:	1% Cross-linked polystyrene	800373	10 g
Capacity:	0.6-1.0 mmol/g (based on benzoylation of benzylamine)	800374	25 g
Bead Size:	75-150 microns, 100-200 mesh (95% within)	800375	100 g



Electrophilic Activation

PS-TsCl

Application: Loading of alcohols followed by nucleophilic displacement (Catch and Release), scavenging of nucleophiles

Typical Alcohol Loading Conditions: 2 - 5 equiv of alcohol in CH_2Cl_2/pyridine (1:1), 5 - 10 h, 20 °C

Compatible Solvents: dichloromethane (12 mL/g), THF (8.6 mL/g), DMF (12.5 mL/g), and other swelling solvents

PS-TsCl is a chlorosulfonated polystyrene resin that is a resin-bound equivalent of tosyl chloride and has a loading capacity of 1.0 - 2.0 mmol/g . The resin readily reacts with nucleophiles to give a variety of sulfonyl functional polymers which can be used as polymeric supports, reagents and catalysts in organic synthesis.[1-6]

PS-TsCl can be employed in Catch and Release applications, where soluble substrates are reacted with PS-TsCl to form an activated polymer intermediate, *e.g.* a tosylate. After purification by washing, the polymeric intermediate is subjected to a second transformation that releases the product from the resin. This has been applied to synthesis of tertiary amines (for more details, see the Technical Section).

Loading of primary alcohols to PS-TsCl resin typically requires reaction with a 3 - 5 equiv of alcohol for 5 hours at room temperature in CH_2Cl_2/pyridine solvent mixture (1:1, 100 mg resin/mL) under an inert atmosphere. The resin is washed with DCM (3x), DMF (5x), DMF/H_2O (3:1, 5x), THF (3x), DCM (3x), and dried under vacuum. The sulfonate formation may be monitored using a simple bead staining test. For more details please see the Technical Section.

Sulfonate resins may be cleaved using secondary amines to produce tertiary amines. Cleavage of the sulfonate resin is accomplished using 2 equiv of secondary amine in the presence of 6 equiv of diisopropylethylamine in CH_3CN at 70 °C for 18 h, or 80 °C for 8 h. Alternatively, cleavage using volatile secondary amines may be performed using 6 equiv of secondary amine at 60 °C for 8 h.

References

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PS-TsCl

Resin Type: 1% Cross-linked polystyrene

Capacity: 1.0 - 2.0 mmol/g (based on sulfur analysis)

Bead Size: 75-150 microns, 100-200 mesh (95% within)

PART #	QUANTITY
800276	10 g
800277	25 g
800278	100 g

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Solution Phase Toolbox

Includes:	PART #	QUANTITY
10 gram quantities of each: PS-Trisamine, PS-Thiophenol, PS-Isocyanate, PS-TsNHNH$_2$, MP-Carbonate, PS-DMAP, PS-DIEA, PS-NMM, PS-TsCl, MP-TsOH Product information and procedure cards ArgoScoop™ (calibrated scoop for convenient resin measuring)	800266	10 g of each

Scavenger Kit

Includes:	PART #	QUANTITY
PS-Trisamine, PS-Thiophenol, PS-Isocyanate, PS-TsNHNH$_2$, MP-Carbonate, PS-TsCl(HL), PS-Benzaldehyde	800368	10 g of each

Coupling Kit

Includes:	PART #	QUANTITY
PS-HOBt, PS-Isocyanate, PS-DMAP, MP-Carbodiimide	800377	10 g of each

Polymer Tosyl Kit

Includes:	PART #	QUANTITY
PS-Isocyanate, MP-Carbonate, PS-TsCl	800293	10 g of each

Base Kit

Includes:	PART #	QUANTITY
MP-Carbonate, PS-DMAP, PS-DIEA, PS-NMM	800294	10 g of each

Card Set, Solution Phase Toolbox

Includes:	PART #
Product information and procedure cards	800382

ArgoScoop™

Includes:	PART #	QUANTITY
Pre-calibrated measuring scoop	900131	1

Resins for Solid Phase Synthesis

Argonaut offers three distinctive resins for solid phase synthesis, each with a variety of linkers that provide flexibility in the attachment of different functional groups and the selection of different reactions and cleavage conditions.

ArgoPore®

ArgoPore resins are based on a highly cross-linked macroporous polystyrene framework which provides low and predictable swelling in all solvents. The unique porous design means:

- rapid diffusional access of reagents to reaction sites
- removal of byproducts using virtually any solvent
- suitability for reactions with low solubility (e.g. ionic) intermediates and low temperatures
- a wide range of reaction conditions, including protic solvents, e.g., water

This facilitates the direct transfer of reaction conditions from known solution phase chemistry to solid phase. ArgoPore is also ideally suited for automation with its unique handling properties: rapid washing/drying and free-flowing beads which do not stick to glass reaction vessels.

ArgoGel®

ArgoGel resins are based on a novel grafted polyethyleneglycol-polystyrene (PEG/PS) copolymer. The flexible PEG grafts provide a solution-like environment for resin-bound molecules, resulting in high resolution ^{1}H and ^{13}C NMR spectra and fast reaction rates. These properties make ArgoGel resins ideal for new chemistry development.

ArgoGel's high-quality beads have very low leachable PEG impurities, and are compatible with a wide range of solvents, including water. ArgoGel's unique bifurcated linkage means high loading and great stability.

1% Cross-linked Polystyrene

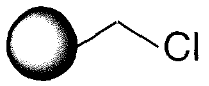
1% Cross-linked poly(styrene-co-divinylbenzene) resin is a commonly used solid support that provides a cost-effective choice for many reactions in organic solvents. Argonaut's polystyrene resins offer high purity (total extractables are typically less than 0.2%) and high-loading capacities. The **Solid Phase Toolbox** includes seven of these polystyrene resins with different linkers, along with product information cards and a calibrated resin scoop.

ArgoCaps®

These pre-weighed resin capsules significantly reduce resin weighing/dispensing time. The capsules are made of a polymer that protects resins from moisture, yet readily dissolves in DCM and other solvents. ArgoCaps are available in two sizes, filled with any of Argonaut resins or custom filled with your own resin.

A Selection Guide to Base Resins for Solid Phase Organic Synthesis

Resin Performance Characteristics	ArgoGel® PEG-Grafted Polystyrene	ArgoPore® Macroporous Polystyrene	1% Cross-linked Polystyrene
Degree of mobility	Very Flexible	Rigid	Moderately Flexible
Solvent compatibility	Compatible with most solvents including water, methanol, ethanol; not compatible with ethyl ether, hydrocarbons and certain alcohols	Compatible with all solvents (precondition with water compatible solvent prior to use with aqueous conditions)	Not compatible with highly polar protic solvents (ie. water, methanol)
Swelling	High in all solvents	Low in all solvents	High in DCM, THF, DMF low in water and methanol
Ease of drying (especially water, *in vacuo*)	Fair	Excellent	Fair
Suitability for monitoring by NMR (^{1}H and ^{13}C)	Excellent	Poor	Fair
Suitability for monitoring by IR	Fair	Good	Good
Ease of washing (removal of excess reagent and/or impurities)	Fair (requires larger volumes of solvents)	Good (requires minimal solvent)	Fair (requires larger volumes of solvents)
Ability to use solvent/reagent combination from solution phase chemistries	Good	Good	Fair
Typical loading values	0.35 - 0.45 mmol/g	0.6-1.1 mmol/g	0.6-2.0 mmol/g
Suitability for low temperature reactions	Fair	Excellent	Fair



-Cl Functionalized Resins

ArgoGel-Cl

ArgoPore-Cl

Chloromethylpolystyrene (PS-Cl)

Application: Linker for acids, secondary amines, base resin for other linkers
Reaction Conditions Tolerated: Acidic, neutral, mildly basic
Typical Cleavage Conditions: Alkoxide in alcohol or alcohol/THF
Cleaved Products: Esters, amines

The chloromethyl polystyrene derivative (commonly known as Merrifield[1] resin) and chloro functional ArgoGel may be used for direct loading of carboxylic acids via their cesium salts.[2,3]

ArgoPore-Cl and PS-Cl are also useful as a linker for secondary amines.[4] Both phenols and thiols readily undergo nucleophilic displacement of Cl using standard etherification conditions (e.g. 3-5 equiv. of potassium or sodium phenolate (thiolate) DMF, 80°C 12h) to form aryl and thioether derivatives. This provides a useful method to incorporate linkers. We have also found that it is possible to monitor nucleophilic displacements of ArgoGel-Cl by gel-phase ^{13}C NMR.

References
1. Merrifield, R.B.; *J.Am. Chem. Soc.* **1963**, *85, 2149.*
2. Gisin, B.F., *Helv. Chem. Acta* **1993**, *56, 1476.*
3. Frenette, R.; Friesen *Tetrahedron Lett.* **1994**, *49, 9177.*
4. Conti, P. et al *Tetrahedron Lett.* **1997**, *38, 2915.*

ArgoGel-Cl

Resin Type: PEG-grafted polystyrene
Capacity: 0.40-0.50 mmol/g (derived from ArgoGel-OH)
Bead Size: 120-230 microns, 65-125 mesh (95% within)
Resin Swelling: CH_2Cl_2 (7.4 mL/g), THF (5.8 mL/g), DMF (5.5 mL/g), toluene (5.5 mL/g), methanol (4.2 mL/g), water (4.1 mL/g)

PART #	QUANTITY
800016	10 g
800036	25 g
800017	100 g

ArgoPore-Cl

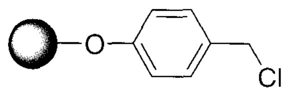
Resin Type: Macroporous polystyrene
Capacity: 0.8-1.3 mmol/g (determined by Volhard titration)
Bead Size: 105-250 microns, 60-140 mesh (95% within)
Resin Swelling: CH_2Cl_2 (5.4 mL/g), THF (5.1 mL/g), DMF (5.2 mL/g), toluene (5.2 mL/g), methanol (5.5 mL/g), water (5.1 mL/g)

PART #	QUANTITY
800051	10 g
800052	25 g
800053	100 g

PS-Cl

Resin Type: 1% Cross-linked polystyrene
Capacity: 1.4-1.7 mmol/g (determined by Volhard titration)
Bead Size: 75-150 microns, 100-200 mesh, (95% within)
Resin Swelling: CH_2Cl_2 (8.7 mL/g), THF (8.3 mL/g), DMF (6.0 mL/g)

PART #	QUANTITY
800257	10 g
800258	25 g
800259	100 g



-Cl Functionalized Resins

ArgoGel-Wang-Cl

Application:	Linker for amines, acids, alcohols
Reaction Conditions Tolerated:	Mildy acidic, neutral, midly basic
Typical Cleavage Conditions:	Resin-bound secondary amines may be sulfonylated ($ArSO_2Cl$, DIEA, DCM), converted to ureas (RNCO, DMF), or amides (RCOCl, DIEA, DCM) prior to cleavage with 95:5 TFA/Et_3SiH, 8h). Esters are cleaved by analogy to ArgoGel-Wang. Cleavage of ArgoGel-Wang-derived ethers using TFA cleavage conditions (20% TFA/DCM, 2h) generates the alcohols and variable amounts of the corresponding trifluoroacetate esters (20-30%). To overcome this we have utilized oxidative cleavage.[1]
Cleaved Products:	Ureas, amides, sulfonamides, alcohols, acids

The 4-alkoxybenzyl chloride moiety commonly known as Wang-Cl Linker, is useful for the attachment of carboxylic acids, amines and alcohols.[2]

Primary amines react with ArgoGel-Wang-Cl to form secondary amines. Aliphatic amines react with ArgoGel-Wang-Cl (10 equiv., DMF, 12h) at room temperature, while aromatic amines require more forcing conditions (e.g. 10 equiv. aniline, 3 equiv. DIEA, NMP, 60 °C, 10h). Resin-bound secondary amines may be sulfonylated ($ArSO_2Cl$, DIEA, DCM), converted to ureas (RNCO, DMF), or amides (RCOCl, DIEA, DCM) prior to cleavage with 95:5 TFA/Et_3SiH, 8h). Cleavage efficiencies of amides and ureas are likely to be sensitive to the nature of the amine and acyl substituents. Resin-bound tertiary amines derived from displacement of ArgoGel-Wang-Cl may be cleaved using α-chloroethyl chloroformate (ACE-Cl)/ MeOH.[3]

Carboxylic acid derivatives are readily coupled to ArgoGel-Wang-Cl using cesium carbonate (2.5 equiv. RCO_2H, 4.0 equiv. Cs_2CO_3, DMF, 60 °C, 6h). Alcohols can be attached to ArgoGel-Wang-Cl using the appropriate sodium alkoxide (3 equiv., DMF, 60 °C, 12h). Chloride displacement may be monitored by gel-phase ^{13}C NMR by observing the shift in the benzylic carbon (∂ 45.5 ppm) to the 60-70 ppm range.

References

1. Deegan, T.L.; Gooding, O.W.; Baudart, S.; Porco, J.A., Jr. *Tetrahedron Lett.* **1997**, *38*, 4973.
2. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, 42, 3021 and references cited therein.
3. Conti, P.; Demont, D.; Cals, J.; Ottenheijm, H.C.J.; Leysen, D. *Tetrahedron Lett.* **1997**, *38*, 2915.

ArgoGel-Wang-Cl

Resin Type: PEG-grafted polystyrene
Capacity: 0.35-0.45 mmol/g (derived from AG-Wang)
Bead Size: 120-230 microns, 65-125 mesh (95% within)
Resin Swelling: CH_2Cl_2 (7.9 mL/g),
THF (5.9 mL/g), DMF (5.8 mL/g),
toluene (5.3 mL/g), methanol (4.0 mL/g),
water (3.9 mL/g)

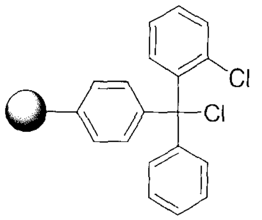
PART #	QUANTITY
800043	10 g
800044	25 g
800045	100 g

ArgoPore-Wang-Cl

This product may be available for custom synthesis. Please contact Argonaut Technologies for further information.

PS-Wang-Cl

This product may be available for custom synthesis. Please contact Argonaut Technologies for further information.



-Cl Functionalized Resin

Polystyrene-Chlorotrityl-Cl

Chemical Name:	1-chloro-1-(2-chlorophenyl)-1-phenyl-methylpolystyrene
Application:	Links carboxylic acids, amines, alcohols, imidazoles, and phenols
Reaction Conditions Tolerated:	Neutral, basic
Typical Cleavage Conditions:	1-5% TFA in DCM with 5% triisopropyl silane (alcohols, amines) or 1:1:8 AcOH/TFE/DCM (carboxylic acids)

This resin is used to immobilize alcohols and other compounds. A versatile resin invented for attachment of carboxylic acids in peptide synthesis,[1] PS-Chlorotrityl-Cl has since been used to immobilize alcohols,[2] phenols,[3] amines,[4] and hydroxylamine.[5] The 2-chlorotrityl linker is very sterically hindered such that cleavage by even reactive and unhindered nucleophiles is limited. It is also generally stable to basic conditions. Cleavage is accomplished using 1 – 50% TFA in DCM. Triisopropyl silane (5% by volume) may be added as a cation scavenger.

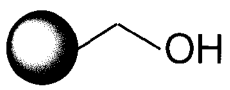
References

1. Barlos, K., Chatzi, O. Stavropoulos, G. Int. *J. Pept. Protein. Res.* **1991**, *37*, 513-520.
2. Wenschuh, H.; Beyermann, M.; Haber, H.; Seydel, J. K.; Kraus, E.; Bienert, M.; Carpino, L. A. *J. Org. Chem.* **1995**, *60*, 405-410.
3. Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. *Tetrahedron Lett.* **1998**, *39*, 2447-2448.M
4. Hoekstra, W. J.; Greco, M. N.; Yabut, S. C. *Tetrahedron Lett.* **1997**, *38*, 2629-2632.
5. Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311-3314.

Polystyrene-Chlorotrityl-Cl

Resin type	1% Cross linked polystyrene
Capacity:	1.0-1.5 mmol/g (determined by UV quantitation of the Fmoc chromophore.after loading Fmoc-Gly-ol
Bead Size:	100-200 mesh (75-150 microns)
Resin Swelling:	CH_2Cl_2 (6.2 mL/g), THF (6.7 mL/g), DMF (4.3mL/g), MeOH 2.8 mL/g)

PART #	QUANTITY
800384	10 g
800385	25 g
800386	100 g



-OH Functionalized Resins

ArgoGel-OH
ArgoPore-OH

Application:	Linker for acids
Reaction Conditions Tolerated:	Acidic, neutral, mildly basic
Typical Cleavage Conditions:	Alkoxide in alcohol or alcohol/THF
Cleaved Products:	Esters, acids

Hydroxyl functional resins may be used for attachment of carboxylic acids and acid chlorides. Carboxylic acids are readily coupled onto hydroxyl functional resins using DMAP-catalyzed esterification conditions (e.g. 5 equiv of diisopropyl carbodiimide/methylene chloride/catalytic DMAP). Some substituted amino acids, aromatic and hindered carboxylic acids require the use of 1-(Mesityene-2-sulfonyl)-3-nitro-1H-1,2,4-triazole (MSNT).[1] The resins may also be converted to the REM linker (acrylate ester linker) which is used to load secondary amines and affords tertiary amines in the cleavage step.[2]

ArgoGel-OH may also be used to attach linkers through deprotonation of the terminal alcohol with KOtBu/THF and alkylation of the resulting alkoxide with alkylating agents.

References

1. Nielsen, J.; Lyngso, L.O. Tetrahedron Lett. **1996**, 37, 8439; Blankemeyer Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, 31, 1701.
2. Murphy, J.R. et al; *Tetrahedron Lett.* **1996**, 37, 3209.

ArgoGel-OH

Resin Type:	PEG-grafted polystyrene
Capacity:	0.4-0.5 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size:	120-230 microns, 65-125 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (7.5 mL/g), THF (5.8 mL/g), DMF (6.0 mL/g), toluene (5.2 mL/g), methanol (4.7 mL/g), water (3.9 mL/g)

PART #	QUANTITY
800003	10 g
800032	25 g
800004	100 g

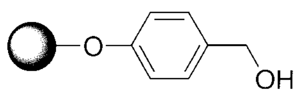
ArgoPore-OH

Resin Type:	Macroporous polystrene
Capacity:	0.6-1.1 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size:	105-250 microns, 60-140 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (5.7 mL/g), THF (5.8 mL/g), DNF (5.5mL/g), toluene (5.8 mL/g), methanol (5.0mL/g), water (5.7 mL/g)

PART #	QUANTITY
800175	10 g
800176	25 g
800177	100 g

PS-OH

This product may be available as a custom synthesis. Please contact Argonaut Technologies for further information.



-OH Functionalized Resins

ArgoGel-Wang
ArgoPore-Wang
PS-Wang

Application:	Linker for acids, amines, phenols
Reaction Conditions Tolerated:	Mildly acidic, neutral, midly basic
Typical Cleavage Conditions:	Ester and carbamate linked products are generally cleaved with trifluoroacetic acid/dichloromethane mixtures. Carbamate cleavage via amine-mediated cyclization to hydantoins[1,2] and quinazoline-2,4-diones[3] has also been effected.
Cleaved Products:	Acids, phenols, amines

This resin is modified with p-hydroxybenzyl alcohol (commonly known as Wang linker). Carboxylic acids are readily coupled onto hydroxyl functional resins using DMAP-catalyzed esterification conditions (e.g. 5 equiv of diisopropyl carbodiimide/methylene chloride/catalytic DMAP). Some substituted amino acids, aromatic and hindered carboxylic acids require the use of 1-(Mesityene-2-sulfonyl)-3-nitro-1H-1,2,4-triazole (MSNT).[4] Amines can be attached to Wang resin using the 4-nitrophenyl carbonate derivative of the linker.[2,3] Wang may also be used as an effective linker for phenols; in this case the Mitsunobu reaction is the preferred method to load the resin.[3]

References

1. Mathews, J.; Rivero, R.A. *J Org Chem.* **1997**, 62, 6090
2. Gouilleux, L.J.; Fehrentz, J.A.; Winternitz, F.; Martinez, J., *Tetrahedron Lett.* **1996**, 37, 7031.
3. *c.f.* (a) Krchnak, V.; Flegelova, Z.; Weichsel, A.S.; Lebl, M., *Tetrahedron Lett.* **1995**, *36*, 6193. (b) Rano, T.A.; Chapman, K.T., *Tetrahedron Lett.* **1995**, 36, 3789.
4. Nielsen, J.; Lyngso, L.O. Tetrahedron Lett. **1996**, 37, 8439; Blankemeyer Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, *31*, 1701.

ArgoGel-Wang

Resin Type: PEG-grafted polystyrene
Capacity: 0.35-0.45 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine.
Bead Size: 120-230 microns, 65-125 mesh (95% within)
Resin Swelling: CH_2Cl_2 (7.9 mL/g), THF (6.1 mL/g), DMF (6.1 mL/g), toluene (4.8 mL/g), methanol (4.5 mL/g), water (4.0 mL/g)

PART #	QUANTITY
800013	10 g
800035	25 g
800014	100 g

ArgoPore-Wang

Resin Type: Macroporous polystyrene
Capacity: 0.5-1.0 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size: 105-250 microns, 60-140 mesh (95% within)
Resin Swelling: CH_2Cl_2 (3.5 mL/g), THF (3.3 mL/g), DMF (3.3 mL/g), toluene (3.3 mL/g), methanol (3.3 mL/g), water (3.4 mL/g)

PART #	QUANTITY
800055	10 g
800056	25 g
800057	100 g

PS-Wang

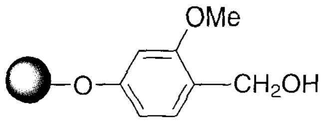
Resin Type: 1% Cross-linked polystyrene
Capacity: 1.0-1.4 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size: 100-200 mesh, 75-150 microns (95% within)
Resin Swelling: CH_2Cl_2 (6.3 mL/g), THF (8.0 mL/g), DMF (7.0 mL/g)

PART #	QUANTITY
800351	10 g
800295	25 g
800296	100 g

Wang Linker Kit

Includes: PS-Wang, ArgoGel-Wang, ArgoPore-Wang

PART #	QUANTITY
800356	10 g of each



-OH Functionalized Resins

ArgoGel-MB-OH

Application:	Linker for acids, amines, phenols
Reaction Conditions Tolerated:	Neutral, mildly basic
Typical Cleavage Conditions:	Mildly acidic (5% TFA/DCM, 1-2h, or glacial acetic, 60 deg. C, 12h).[1]
Cleaved Products:	Acids, amines, phenols

ArgoGel modified with a 3-methoxy-4-hydroxylmethylphenoxy linker. Aliphatic carboxylic acid derivatives are readily coupled to ArgoGel-MB-OH using DIC/DMAP. Alpha-amino acid derivatives generally require a double-coupling to obtain full loading. Aromatic carboxylic acid derivatives are optimally coupled using 1-(Mesitylene-2-sulfonyl)-3-nitro-1H-1,2,4-triazole (MSNT) and N-methylimidazole (NMI) in dichloromethane.[2] Gel-phase ^{13}C NMR can be used to monitor esterifications and evaluate their efficiency. Amines may be attached to ArgoGel-MB-OH through a carbamate linkage using the 4-nitrophenyl carbonate derivative of the linker. ArgoGel MB-OH can also be an effective linker for phenols, in which case the Mitsunobu reaction is the preferred method for attachment.[3]

References

1. cf. Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Tetrahedron Lett.* **1988**, *29*, 4005; Florsheimer, A.; Riniker, B. Peptides **1990**, *131*.
2. Nielsen, J.; Lyngso, L.O. Tetrahedron Lett. **1996**, *37*, 8439; Blankemeyer Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, *31*, 1701.
3. cf. (a) Krchnak, V.; Flegelova, Z.; Weichsel, A.S.; Lebl, M. *Tetrahedron Lett.* **1995**, 36, 6193. (b) Rano, T.A.; Chapman, K.T. *Tetrahedron Lett.* **1995**, 36, 3789.

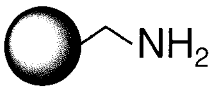
ArgoGel-MB-OH

Resin Type:	PEG-grafted polystyrene
Capacity:	0.35-0.45 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size:	120-230 microns, 65-125 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (6.6 mL/g), THF (5.1 mL/g), DMF (5.1 mL/g), toluene (4.6 mL/g), methanol (3.9 mL/g), water (3.7 mL/g)

PART #	QUANTITY
800025	10 g
800039	25 g
800026	100 g

ArgoPore-MB-OH

This product may be available as a custom synthesis. Please contact Argonaut Technologies for further information.



-NH$_2$ Functionalized Resins
ArgoGel-NH$_2$
ArgoPore-NH$_2$
Aminomethyl polystyrene (PS-NH$_2$)

Aminomethyl functionalized resins[1] are useful as base resins for derivatization by acylation with carboxylic acid-containing linkers,[2] as shown in the table.

Linker	Functionality Attached	Cleavage Condition	Product Functionality
HMPA,AC[2]	Carboxylic acid	TFA	Carboxylic acid
PAL[3]	Carboxylic acid	TFA	Carboxamide
Sieber[4]	Carboxylic acid	TFA	Carboxamide
BAL[5]	Amine	TFA	Carboxamide sulfonamide, urea
Photochemical[6]	Carboxylic acid	*hv* (350 nm)	Carboxamide
Aliphatic [7] sulfonamide	Carboxylic acid	1) activate 2) Amine, OH	Carboxamide, carboxylic acid

References

1. Mitchell, A.R., et al. *J. Org. Chem.* **1978**, *30, 2845.*
2. Sheppard, R.C., et al. *Int. J. Pept. Protein Res.* **1982**, *20, 451.*
3. Alberecio, F., et al. *J.Org. Chem.* **1990**, *55, 3730.*
4. Sieber, P. *P. Tetrahedron Lett.* **1987**, *2107.*
5. Jensen, K.J. *Peptides - Chemistry and Biology: Proceedings of the Fourth American Peptide Symposium*, Mayflower Worldwide Limited, England, **1996**, *30.*
6. Holmes, C.P., et al. *J. Org. Chem.* **1995**, *60, 2318.*
7. Backes, B.J., et al. *J. Am. Chem. Soc.* **1996**, *188, 3055.*

ArgoGel-NH$_2$

Resin Type: PEG-grafted polystyrene
Capacity: 0.35-0.5 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size: 120-230 microns, 65-125 mesh (95% within)
Resin Swelling: CH_2Cl_2 (8.6 mL/g), THF (6.4 mL/g), DMF (7.0 mL/g), toluene (6.2 mL/g), methanol (4.9 mL/g), water (4.0 mL/g)

PART #	QUANTITY
800007	10 g
800033	25 g
800008	100 g

Argo-Pore-NH$_2$

Resin Type: Macroporous polystyrene
Capacity: 0.6-1.1 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size: 105-250 microns, 60-140 mesh (95% within)
Resin Swelling: CH_2Cl_2 (5.6 mL/g), THF (5.4 mL/g), DMF (5.6 mL/g), toluene (5.7 mL/g), methanol (5.2 mL/g), water (4.9 mL/g)

PART #	QUANTITY
800047	10 g
800048	25 g
800049	100 g

Product Name: ArgoPore-NH$_2$-High loading
Capacity: 1.1-1.6 mmol/g
Bead Size: 105-250 microns, 60-140 mesh (95% within)
Resin Swelling: CH_2Cl_2 (4.1 mL/g), THF (4.0 mL/g), DMF (4.1 mL/g), toluene (4.2 mL/g), methanol (4.0 mL/g), water (3.9 mL/g)

PART #	QUANTITY
800159	10 g
800160	25 g
800161	100 g

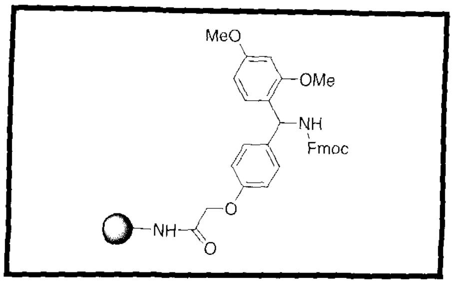
Product Name: ArgoPore-NH$_2$ -Low loading
Capacity: 0.2-0.6 mmol/g
Bead Size: 105-250 microns, 60-140 mesh (95% within)
Resin Swelling: CH_2Cl_2 (5.9 mL/g), THF (5.9 mL/g), DMF (5.9 mL/g), toluene (6.0 mL/g), methanol (5.8 mL/g), water (5.4 mL/g)

PART #	QUANTITY
800167	10 g
800168	25 g
800169	100 g

PS-NH$_2$

Resin Type: 1% Cross-linked polystyrene
Capacity: 1.0-1.6 mmol/g (determined by coupling of Fmoc-Gly, followed by UV quantification of Fmoc chromophore)
Bead Size: 100-200 mesh, 75-150 microns (95% within)
Resin Swelling: CH_2Cl_2 (9.1 mL/g), THF (7.7 mL/g), DMF (6.5 mL/g)

PART #	QUANTITY
800263	10 g
800264	25 g
800265	100 g



-NH_2 Functionalized Resins

ArgoGel-Rink-NH-FMOC
ArgoPore-Rink-NH-FMOC
PS-Rink-NH-FMOC

Application:	Linker for acids, aldehydes, sulfonyl chloride
Reaction Conditions Tolerated:	Neutral, basic
Typical Cleavage Conditions:	95:5 trifluoroacetic acid: water or 5% trifluoroacetic acid: dichloromethane
Products:	Amides, amines, sulfonamides, ureas

This resin is functionalized with a modified Rink linker.[1] The linker is stable to strong protic acids normally used for compound cleavage. As a result, colored linker-derived by-products are not formed during cleavage as is the case with the benzylic-phenoxy linked system. The linker is supplied in Fmoc-protected form and requires treatment with 20% piperidine/DMF prior to use. The derived resin-bound benzhydrylamine is commonly used in the solid phase synthesis of carboxamides and sulfonamides[2] and in condensation reactions.[3] ArgoPore-Rink has been applied to the synthesis of biaryls using a Suzuki coupling reaction.

References

1. Rink, H. *Tetrahedron Letters*, **1987**, *28*, 3787.
2. Beaver, K.A.; Siegmund, A.C.; *Tetrahedron Letters*, **1996**, *37*, 1145.
3. Sutherlin, D.P.; Stark, T.M.; Hughes, R.; Armstrong, R.W. *J. Org. Chem.*, **1996**, *61*, 8350 and references sited therein.

ArgoGel-Rink-NH-FMOC

Resin Type:	PEG-grafted polystyrene
Capacity:	0.30-0.40 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size:	120-230 microns, 65-125 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (7.0 mL/g), THF (5.1 mL/g), DMF (5.0 mL/g), toluene (4.7 mL/g), methanol (3.3 mL/g), water (3.3mL/g)

PART #	QUANTITY
800019	10 g
800037	25 g
800020	100 g

ArgoPore-Rink-NH-FMOC

Resin Type	Macroporous polystrene
Capacity:	0.5-1.0 mmol/g (determined by UV quantitation of Fmoc chromophore after loading Fmoc-glycine)
Bead Size:	*105-250 microns, 60-140 mesh (95% within)*
Resin Swelling:	CH_2Cl_2 (4.0 mL/g), THF (3.8 mL/g), DMF (3.9 mL/g), toluene (4.0 mL/g), methanol (3.9mL/g), water (3.7 mL/g)

PART #	QUANTITY
800059	10 g
800060	25 g
800061	100 g

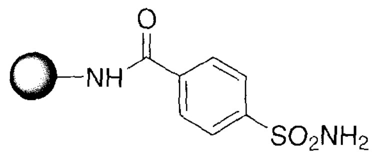
PS-Rink-NH-FMOC

Resin Type:	1% Cross-linked polystyrene
Capacity:	0.7-1.2 mmol/g (determined by UV quantification of Fmoc chromophore)
Bead Size:	100-200 mesh, 75-150 microns (95% within)
Resin Swelling:	CH_2Cl_2 (7.0 mL/g), THF (6.0 mL/g), DMF 5.8 mL/g)

PART #	QUANTITY
800353	10 g
800301	25 g
800302	100 g

Rink Linker Kit

		PART #	QUANTITY
Includes:	PS-Rink, ArgoGel-Rink, ArgoPore-Rink	800357	10 g of each



-NH$_2$ Functionalized Resins

ArgoGel-AS-SO$_2$NH$_2$
ArgoPore-AS-SO$_2$NH$_2$
PS-AS-SO$_2$NH$_2$

Application:	Linker for acids
Reaction Conditions Tolerated:	Acidic, basic
Typical Cleavage Conditions:	Activation/cleavage is effected by alkylation with (trimethylsilyl) diazomethane or iodoacetonitrile, followed by treatment with a nucleophile (amines, hydroxide, etc.) to release a carboxylic acid derivative (e.g. amide).[1]
Cleaved Products:	Acids, amides and esters

The Aryl sulfonamide or "safety-catch" linker is unique for the synthesis of carboxylic acid derivatives because acylsulfonamides are stable to both strongly basic and acidic conditions and are only activated for cleavage under a narrow range of conditions. This linker system has been successfully utilized by Ellman and co-workers in the elaboration of a phenylacetic acid core using a tandem Suzuki reaction/enolate alkylation protocol.[1] This chemistry was successfully reproduced on ArgoPore-AS-SO$_2$NH$_2$.

References

1. Backes, B.J.; Ellman, J.A., *J.Am. Chem. Soc.* **1994**, *116*, 11171.

ArgoGel-AS-SO$_2$NH$_2$

Resin Type:	PEG-grafted polystyrene
Capacity:	0.35-0.45 mmol/g (determined by sulfur analysis)
Bead Size:	120-230 microns, 65-125 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (6.8 mL/g), THF (4.9 mL/g), DMF (5.9 mL/g), toluene (3.9 mL/g), methanol (3.7 mL/g), water (3.6 mL/g)

PART #	QUANTITY
800010	10 g
800034	25 g
800011	100 g

ArgoPore-AS-SO$_2$NH$_2$

Resin Type:	Macroporous polystyrene
Capacity:	0.5-1.0 mmol/g (determined by sulfur analysis)
Bead Size:	105-250 microns, 60-140 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (4.4 mL/g), THF (4.2 mL/g), DMF (4.4 mL/g), toluene (4.4 mL/g), methanol (4.6 mL/g), water (2.9 mL/g)

PART #	QUANTITY
800063	10 g
800064	25 g
800065	100 g

PS-AS-SO$_2$NH$_2$

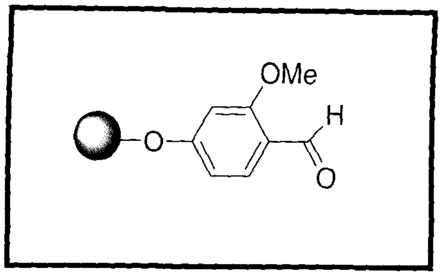
Resin Type:	1% Cross -linked polystyrene
Capacity:	0.9-1.3 mmol/g (determined by sulfur analysis)
Bead Size:	100-200 mesh, 75-150 microns (95% within)
Resin Swelling:	CH_2Cl_2 (3.7 mL/g), THF (7.1 mL/g), DMF (7.1 mL/g)

PART #	QUANTITY
800354	10 g
800304	25 g
800305	100 g

AS-SO$_2$NH$_2$ Linker Kit

Includes:	PS-AS-SO$_2$NH$_2$, ArgoGel-AS-SO$_2$NH$_2$, ArgoPore-AS-SO$_2$NH$_2$

PART #	QUANTITY
800359	10 g of each



-CHO Functionalized Resins

ArgoGel-MB-CHO
ArgoPore-MB-CHO
PS-MB-CHO

Application:	Linker for amines
Reaction Conditions Tolerated:	Mildly acidic, basic
Typical Cleavage Conditions:	Activated with an isocyanate, sulfonyl chloride or acyl derivative followed by treatment with 95:5 trifluoroacetic acid: water or 95:5 trifluoroacetic acid: triethylsilane. Efficiency depends on the nature of the amine and electrophile substituent
Cleaved Products:	Amides, sulfonamides, ureas, heterocycles

The MB-CHO, 4-Formyl-3-methoxy-phenoxy linker is useful for attachment of amines by reductive amination.[1] The PS-MB-CHO resin is often referred to as the AMEBA resin.[1a] The conditions for reductive amination on AP-MB-CHO and PS-MB-CHO are similar to those reported for AG-MB-CHO, with the exception that sodium borohydride in THF / ethanol (3:1) is used as the reducing agent.[1b] Activation with an isocyanate, sulfonyl chloride or acyl derivative is required prior to TFA cleavage.

References

1. (a) Fivush, et al., *Tetrahedron Letters*, **1997**, *38*, 7151. (b) Sarantakis,D., et al., *Tetrahedron Letters*, **1997**, *38*, 7325.

General References for MB-CHO Linker:
Bilodeau, M.T.; Cunningham, A.M., J. Org. Chem. **1998**, *63*, 2800. Kearney, P.C.; Fernandez, M.; Flygare, J. A. J. Org. Chem. **1998**, *63*, 196. Swayze, E., *Tetrahedron Letters*, **1997**, *38*, 8465.

ArgoGel-MB-CHO

Resin Type:	PEG-grafted polystyrene
Capacity:	0.35-0.45 mmol/g (determined by nitrogen analysis of the 2,4-dinitrophenyl hydrazone derivative)
Bead Size:	120-230 microns, 65-125 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (7.9 mL/g), THF (5.9 mL/g), DMF (5.9 mL/g), toluene (5.5 mL/g), methanol (4.0 mL/g), water (3.8 mL/g)

PART #	QUANTITY
800022	10 g.
800038	25 g.
800023	100 g

ArgoPore-MB-CHO

Resin Type:	Macroporous polystyrene
Capacity:	0.5-1.0 mmol/g (determined by nitrogen analysis of the 2,4-dinitrophenyl hydrazone derivative)
Bead Size:	105-250 microns, 60-140 mesh (95% within)
Resin Swelling:	CH_2Cl_2 (5.1 mL/g), THF (4.9 mL/g), DMF (5.0 mL/g), toluene (4.9 mL/g), methanol (4.9 mL/g), water (4.4 mL/g)

PART #	QUANTITY
800150	10 g
800151	25 g
800152	100 g

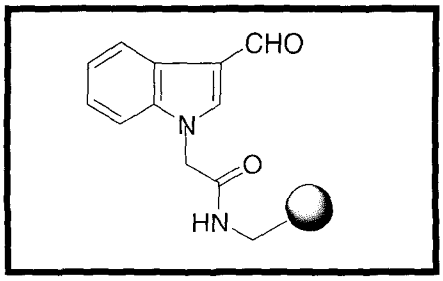
PS-MB-CHO

Resin Type:	1% Cross-linked polystyrene
Capacity:	1.0-1.4 mmol/g (determined by nitrogen analysis of the 2,4-dinitrophenyl hydrazone derivative)
Bead Size:	100-200 mesh, 75-150 microns (95% within)
Resin Swelling:	CH_2Cl_2 (8.4 mL/g), THF (7.5 mL/g), DMF (6.2 mL/g)

PART #	QUANTITY
800352	10 g
800298	25 g
800299	100 g

MB-CHO Linker Kit

		PART #	QUANTITY
Includes:	PS-MB-CHO, ArgoGel-MB-CHO, ArgoPore-MB-CHO	800358	10 g of each



-CHO Functionalized Resin

Polystyrene-Indole-CHO

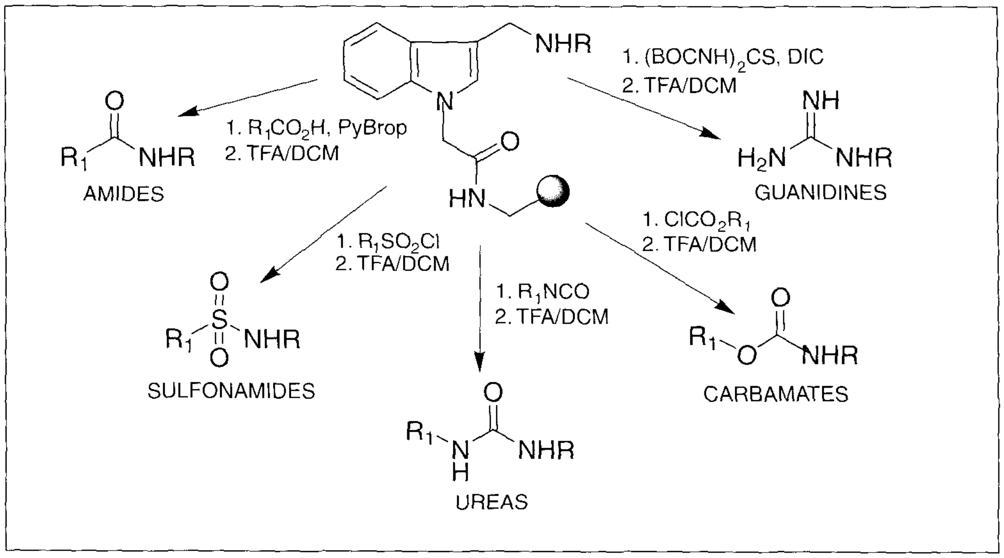
Chemical Name:	3-formyl-indol-1-yl-acetamidomethyl polystyrene
Application:	Linker for amines
Reaction Conditions Tolerated:	Mildly acidic, basic
Typical Cleavage Conditions:	Activation by acylation with an isocyanate, sulfonyl chloride, or other acyl derivative followed by treatment with 2 – 50% TFA in DCM (2 – 5% TFA/DCM is effective for most substrates).
Cleaved Products	Amides, ureas, sulfonamides, carbamates, guanidines, anilines

PS-Indole-CHO is used to attach amines by reductive amination. Activation with an isocyanate, sulfonyl chloride or acyl derivative can then be used as a diversity step resulting in the synthesis of amides, sulfonamides, and ureas. PS-Indole-CHO is similar to the Argonaut PS-MB-CHO but permits the use of milder cleavage conditions.

PS-Indole-CHO contains an indole-3-carboxaldehyde moiety that performs similarly to the Argonaut PS-MB-CHO product, while offering the advantage of milder cleavage conditions. Primary amines are attached to PS-Indole-CHO by reductive amination using $Me_4NBH(OAc)_3$ in DCE or $NaBH_3CN$ in MeOH. The secondary amines that are generated are then activated by an electrophile resulting in resin-bound amides, ureas, sulfonamides, carbamates and guanidines (**Scheme 1**). Cleavage requires as little as 2 – 5% TFA in DCM and results in pure products in high yields.[1]

Reference

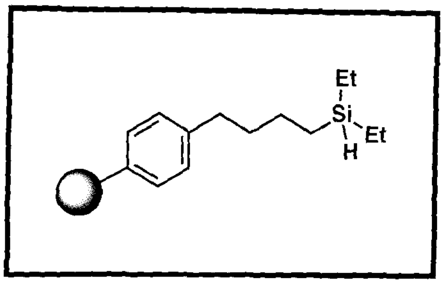
1. Estep, K. G.; Neipp, C. E.; Stramiello, L. M. S.; Adam, M. D.; Allen, M. P.; Robinson, S.; Roskamp, E. J. *J. Org. Chem.* **1998**, *63*, 5300-5301.



SCHEME 1

Polystyrene-Indole-CHO

		PART #	QUANTITY
Resin type	1% Cross-linked polystyrene		
Capacity:	0.9 – 1.3 mmol/g (determined by nitrogen analysis of the 2,4-dinitrophenyl hydrazone derivative).	800387 800388 800389	10 g 25 g 100 g
Bead Size:	100-200 mesh (75-150 microns)		



Silyl Functionalized Resins

PS-DES

Application:	Linker for alcohols, carbonyl groups, acetylenes, aromatic compounds, bound silane reagent precursor to bound silyl triflates
Reaction Conditions Tolerated:	Acidic, basic
Typical Cleavage Conditions:	AcOH/THF/water (6:6:1, 50-80 °C) for primary and secondary alcohols, TBAF (THF) or HF/pyridine/THF (25 deg. C) may also be used. Electron-rich and neutral aromatics cleaved using TFA/DCM, electron-poor using TBAF[1]
Cleaved Products	Alcohols, aromatics, acetylenes, heterocycles

PS-DES is a 1% cross linked polystyrene modified with a butyldiethylsilane linker. Silyl-derivatives are widely used to protect various functional groups such as alcohols, phenols, carboxylic acids, amines, acetylenes, and aromatic compounds.[2,3] They are inert to a wide range of synthetic transformations, but can be easily removed under selective conditions (e.g. HF/pyridine, fluoride ion). Typically, they are produced by the reaction of a silyl chloride and the corresponding functionality (alcohol, carboxylic acid, acetylene, Grignard or alkyllithium derivatives). Polymer-supported silyl chlorides and arylsilane derivatives[1,4-8] have a number of limitations:

- Polymeric silyl chlorides are reactive and unstable to hydrolysis leading to poor shelf life.
- Displacement of silyl chlorides is difficult to monitor using standard spectroscopic techniques.
- For many traceless applications, aromatic scaffolds are attached to a silicon-containing handle which is subsequently attached to the solid support.[9,10]

Argonaut's PS-DES[11] resin has a silane (Si-H) moiety which offers a number of unique advantages:

- Stability to moisture for long shelf life.
- Direct attachment of functional groups (e.g. alcohol,[12,13] carbonyl,[14] aromatic, or unsaturated derivatives) without prior transformation to activated silylating agents (e.g. silyl chloride).
- Efficient transformation into a reactive silyl chloride or silyl triflate[15] derivative which can be used immediately, before hydrolysis or degradation can occur.
- Ability to monitor reactions using IR spectroscopy by examination of the Si-H stretch (2100 cm^{-1}).

References

1. Woolard, F.X.; Paetsch, J.; Ellman, J.A. *J.Org. Chem.* **1997**, 62, 6102.
2. Greene, T.W.; Wuts, P.G.M. in *Protecting Groupsin Organic Synthesis, John Wiley and Sons,* **1991**, *68.*
3. Kocienski, P.J. in *Protecting Groups,* Thieme, **1994**, *28.*
4. Farral, M.J.; Frechet, J.M. *J.Org. Chem.* **1976**, *41*, 3877.
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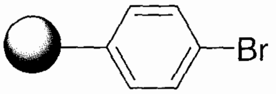
8. Stranix, B.R.; Liu H.Q.; Darling, G.D. *J. Org. Chem.* **1997**, *62*, 6183.
9. Boehm, T.L.; Showalter, H.D.H. *J. Org. Chem.* **1996**, *61*, 6498.
10. Newlander, K.A.; Chenera, B.; Veber, D.F.; Yim, N.C.F: Moore, M.L. *J Org. Chem,* **1997**, *62*, 6726.
11. Hu, Yonghan.; Porco, J.A. Jr.; Labadie, J.W.; Gooding, O.W.; Trost, B.M. *J. Org. Chem,* **1998**, *63*, 4518.
12. For alcoholysis of hydrosilanes with TBAF in solution, see: Tanabe, Y,; Okumura, H.; Maeda, A.; Murakami, M. *Tetrahedron Lett.* **1994**, *35*, 8413.
13. For rhodium-catalyzed alcoholysis of hydrosilanes in solution, see: Doyle, M.P.; High, K.G.; Bagheri, V.; Pieters, R.J.; Lewis, P.J.; Pearson, M.M. *J. Org. Chem.* **1990**, *55*, 25.
14. For hydrosilylation of carbonyl compounds on solution, see,: a) Ojima, I.; Nihonyanagi, M.; Kogure, T.; Kumagai, M.; Horiuchi, S.; Nakatsugawa, K.*J. Organomet. Chem.* **1975**, *94*, 449. b). Mukaiyama, T.; Izumi, J.; Shiina, I. *Chem. Lett.* **1997**, 187. c.) Fujita. M.; Hiyama, T.*J. Org. Chem.* **1998**, *53*, 5405.
15. Hu, Yonghan.; Porco, J.A. Jr. *Tetrahedron Lett.* **1999**, *40*, 3289.

PS-DES

Resin type	1% Cross linked polystyrene
Capacity:	1.1-1.6 mmol/g (determined by reduction of trityl bromide and quantitation of the triphenyl methane produced)
Bead Size:	100-200 mesh (75-150 microns)
Resin Swelling:	CH_2Cl_2 (8.4 mL/g), THF (8.2 mL/g), DMF (3.1 mL/g),

PART #	QUANTITY
800142	10 g
800143	25 g
800144	100 g



-Br Functionalized Resin

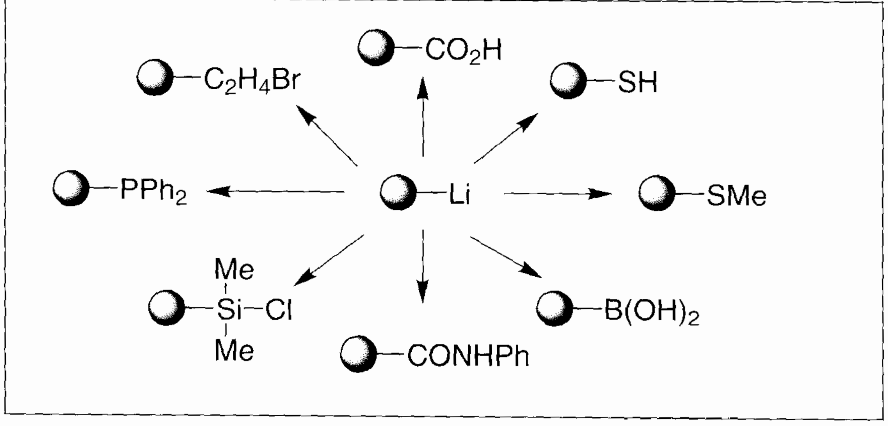
Polystyrene-Aryl-Br

Chemical Name:	Bromopolystyrene
Application:	Useful as a base resin for attachment of various linkers

PS-Aryl-Br is a functional base resin that may be converted into a variety of polymers containing carboxylic acid, thiol, sulfide, boronic acid, amide, silyl chloride, phosphine, alkyl bromide, aldehyde, alcohol, or trityl functional resins **(Scheme 1)**.[1] Lithiation of the polymer via halogen-metal exchange using butyllithium in toluene, followed by quenching with an appropriate electrophile provides a general route to a plethora of polymer supported products.

Reference

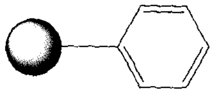
1. Farrall, M. J.; Frechet, J. M. *J. Org. Chem.* **1976**, *41*, 3877-3882.



SCHEME 1

Polystyrene-Aryl-Br

		PART #	**QUANTITY**
Resin type	1% Cross-linked polystyrene	800390	10 g
Capacity:	2.7 - 3.3 mmol/g as determined by elemental analysis for bromine	800391	25 g
Bead Size:	100-200 mesh (75-150 microns)	800392	100 g
Resin Swelling:	CH2Cl2 (7.5 mL/g), THF (8.2 mL/g), DMF (4.0mL/g), MeOH (2.8 mL/g)		



Unfunctionalized Resin

Polystyrene

Chemical Name: Polystyrene, unfunctionalized

A base resin composed of 1% crosslinked polystyrene-co-divinylbenzene serves as a starting material for many functional polymers.

Polystyrene

Resin type	1% Cross-linked polystyrene
Bead Size:	100-200 mesh (75-150 microns)
Resin Swelling:	CH_2Cl_2 (9.3mL/g), THF (9.5mL/g), DMF (5.4 mL/g), MeOH (2.8mL/g)

PART #	QUANTITY
800393	10 g
800394	25 g
800395	100 g
800396	1000 g

Solid Phase Toolbox

Solid Phase Toolbox

		PART #	QUANTITY
Includes:	PS-Wang, PS-MB-CHO, PS-Rink, PS-AS-SO_2NH_2, PS-NH_2, PS-Cl, PS-DES Product information cards ArgoScoop™ (calibrated scoop for convenient resin measuring)	800355	10 g of each

Linker Kits
for Solid Phase Resins

Wang Linker Kit

		PART #	QUANTITY
Includes:	PS-Wang, ArgoGel-Wang, ArgoPore-Wang	800356	10 g of each

Rink Linker Kit

		PART #	QUANTITY
Includes:	PS-Rink, ArgoGel-Rink, ArgoPore-Rink	800357	10 g of each

MB-CHO Linker Kit

		PART #	QUANTITY
Includes:	PS-MB-CHO, ArgoGel-MB-CHO, ArgoPore-MB-CHO	800358	10 g of each

AS-SO_2NH_2 Linker Kit

		PART #	QUANTITY
Includes:	PS-AS-SO_2NH_2, ArgoGel-AS-SO_2NH_2, ArgoPore-AS-SO_2NH_2	800359	10 g of each

Technical Information for Solid Phase Resins
ArgoPore®

Advantages of ArgoPore Macroporous Resins

The unique structure of ArgoPore facilitates the direct transfer of reaction conditions from known solution phase methods to solid phase. Many solid-phase resins require the use of non-protic solvents in order to swell the resin and expose the reaction sites. ArgoPore resins have a highly cross-linked, rigid, macroporous polystyrene framework. This framework makes the beads' internal reaction sites accessible without the need for swelling by solvent, so that it can be used with any solvent type. ArgoPore resins also provide access to polymer-supported intermediates requiring reaction conditions that would collapse gel-type resins such as low temperature and charged intermediates. The internal pore structure of ArgoPore offers numerous advantages for solid phase organic synthesis including:

- Access of reagents to reaction sites occurs by rapid diffusion through the rigid, open pore structure rather than through a swollen gel phase
- Accessibility of reaction sites independent of solvent type and temperature
- Low and predictable swelling in all solvents, including water
- Potential for the isolation of reactive sites from each other
- Resistance to bead cracking due to rapid and large volume changes during swelling (osmotic shock)
- Rapid removal of reagents and byproducts via solvent washing between synthetic steps
- Rapid removal of solvent between synthetic steps (drying)
- Reduced tendency to adhere to glass vessels

Development of ArgoPore Resins

The majority of solid-phase transformations described to date have employed lightly crosslinked (1-2%), gel-type polystyrene supports, (GPS) which have limitations related to the general requirement that the resins must be swollen in a suitable solvent to gain access to reactive sites. This gives rise to processes, such as gel-phase diffusion and solvent/reagent-polymer interactions, that must be considered when developing solid-phase reactions or transferring solution-phase chemistry to solid-phase. Macroporous[1] polystyrene resins are a well-known alternative to GPS resins for a variety of applications (*vide infra*). In the case of highly crosslinked (>8%) macroporous resins, chemical reactions involving functional groups occur primarily at the pore surface, with diffusion of reactants and products occurring through a pore network. We sought to develop a family of novel macroporous resin beads for solid-phase organic synthesis of small molecules with high levels of crosslinking and high surface area.

Macroporous polystyrene-co-divinylbenzene resins were invented in the 1950s and are widely used for ion-exchange, absorbents, and chromatographic separation media.[2] Macroporous resins have largely supplanted lightly crosslinked, gel-type resins for these applications due to their resistance to solvent-induced fracture and lower swelling volumes.

However, commercially available ion exchange resins and absorbents are not well suited for use as supports for solid-phase organic synthesis for a number of reasons.[3] The available functional group types are limited, loading is generally too high (3 - 5 mmol/g), and bead size too large (~0.5-1.0 mm). Loading to the maximum extent is desirable for ion exchange applications, but may lead to errors in synthesis when multiple steps are involved because not all sites are equally accessible. These large, highly loaded beads are also difficult to wash between synthetic steps due to a high percentage of small pores, i.e. pores < 20Å in diameter.[4] A few companies[5] produce amino-functionalized macroporous resins for oligonucleotide synthesis, but these feature low loading and small bead size, making them generally unsuitable for small molecule applications. ArgoPore was developed as a new macroporous support, designed for small-molecule applications. It has great utility in parallel and combinatorial synthesis by providing an alternative to 1% crosslinked polystyrene.

In the development of ArgoPore highly cross-linked polystyrene base resins ranging from 10 to 85% divinylbenzene (DVB) composition were investigated. The polymers were produced by analogy to published procedures employing free radical initiated suspension co-polymerization of styrene and DVB with an inert diluent (porogen) added to create the porous structure.[6] These polymers were tested for pore size distribution, mechanical stability, washing characteristics, and ease of functionalization. Ultimately, a composition near the middle of the range was selected for further development. This base resin was functionalized by aminomethylation and chloromethylation using conventional methods to afford functional ArgoPore resins. These have been further modified to provide a family of ArgoPore linker resins.

ArgoPore Characterization and Properties

Pore Profile

The internal pore structure of ArgoPore has been specifically designed for synthesis of organic molecules. The pore structure of macroporous resins is best characterized by nitrogen adsorption-desorption measurements.[6] ArgoPore resins were found to have high total surface area, a low percentage of micropores (6 volume % pores < 20Å), and a high percentage of mesopores (94 volume % pores 60-200Å) (**Table 1**). High surface area is desirable because ultimate loading is proportional to surface area. Low micropore volume is desirable because small pores are inaccessible to larger reagents and smaller reagents can become trapped leading to difficult washing operations. High mesopore volume is also desirable as mesopores facilitate bulk transport of reagents and solvents into and out of the bead.

Because the easiest way to obtain high surface area is to have a large number of small pores, it seems the ideal pore structure is a delicate balance between pore geometry and surface area. Macropores (pores >200Å) are undesirable because large pores do not provide adequate surface area for reasonable levels of functionalization. ArgoPore offers relatively high loading (0.6-1.2 mmol/g) in comparison with other macroporous resins due to its high surface area and uniform pore structure (**Table 1**).[7] It is important to note that the pore data presented in Table 1 are measured on polymer in the dry state. Further pore expansion occurs with solvent regain. The unique pore profile provides ArgoPore with its rapid washing, drying and diffusional access to reactive sites that is independent of solvent type.

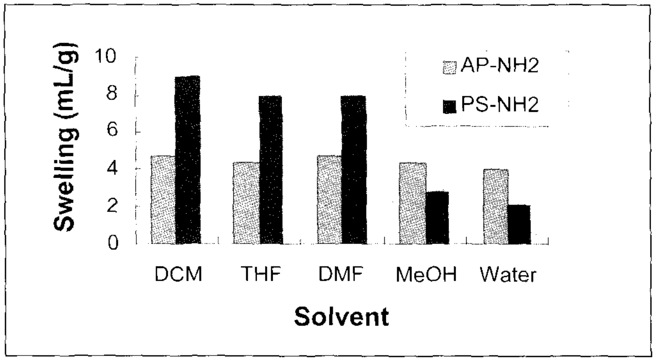
TABLE 1.
Typical Pore Data for Selected ArgoPore Resins

Resin	Average Pore Diameter (Å)	Pore Volume (mL/g)	Surface Area (m^2/g)
ArgoPore-NH_2	90	0.95	650
ArgoPore-Cl	90	0.95	650
ArgoPore-Wang-OH	90	0.75	500

Swelling Properties

Solvent-induced volume changes are an important consideration for solid supports. The density of dry ArgoPore resin is low, at 0.4 g/mL (2.5 mL/g swelling) relative to 1% crosslinked polystyrene due to its porous nature. In contrast to 1% crosslinked polystyrene resins, swelling for ArgoPore resins is relatively low and constant over a wide range of solvents, including MeOH and water (**Chart 1**). The volume increase of approximately 2x (from 2.5 to 4.5 mL/g) in the presence of solvent is attributed to pore expansion upon solvent regain rather than gel-phase swelling that is associated with lightly crosslinked polystyrene supports.

CHART 1.
Swelling of ArgoPore Versus Gel-Type Polystyrene



The swelling of ArgoPore is largely independent of the bound molecules (**Chart 2**). Attachment of the Rink linker and subsequent loading of cholanic acid (a steroidal carboxylic acid) causes a relatively small decrease in swelling. In fact, when normalized for the polystyrene composition, there is no significant swelling change due to the attached small molecule. In contrast, swelling changes dramatically upon small molecule attachment to the gel-type polystyrene which is highly dependent on the nature of bound molecules and not always predictable. This behavior can lead to "eruptions" of resins out of their reaction vessels (e.g. IRORI® radio-tagged microreactors) during synthetic operations.

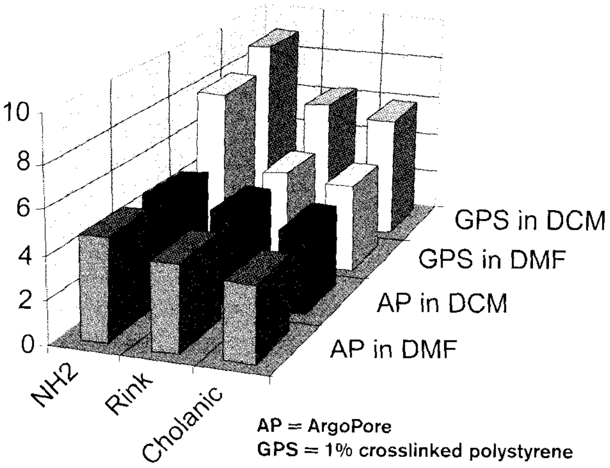


CHART 2.
The Effect of Small Molecule Attachment on Swelling

Washing Properties

A standard operation in solid-phase synthesis is the removal of impurities and byproducts between steps through resin washing. A great deal of time and solvent can be consumed by this activity. To compare washing properties of two resins, ArgoPore-Wang and 1% crosslinked polystyrene-Wang were each impregnated with a solution of biphenyl in DCM by agitation for 1 hour (100 mg resin, 4 mL solution, 32 mg/mL). Washing with 4 mL aliquots of DCM was continued and the release of biphenyl was monitored by GC using naphthalene as an internal standard. Biphenyl was removed at a higher rate, and with fewer washes, from ArgoPore relative to 1% crosslinked polystrene (**Table 2**). Wash times of two minutes were sufficient for bead-solution equilibration of impurities (longer wash times were not more effective). This profile was repeated with other impurities such as nitrobenzaldehyde and phenanthrene, with similar results. Equilibration of impurities between pore phase and bulk solution occurred more rapidly with ArgoPore than with 1% crosslinked polystyrene, resulting in shorter wash times.

It was also observed that removal of colored impurities and reactant neutralizations was more rapid with ArgoPore than with gel-type resins (and required fewer washes).

Protic solvents which do not swell polystyrene, including water, aqueous acids and aqueous bases, were found effective as wash solvents. This demonstrates an additional advantage offered by ArgoPore for product purification.

TABLE 2
Resin washing Study

	1% BIPHENYL REMOVED			
Resin	**Wash 1**	**Wash 2**	**Wash 3**	**Wash 4**
ArgoPore-Wang	91.1	8.00	0.01	0
PS-Wang	81.85	14.98	2.62	0.01

1% crosslinked polystyrene
Journal of Combinatorial Chemistry, 1999, Vol. 1. No. 6

It is important to note that ArgoPore must be wetted with an organic solvent, e.g. methanol or THF, in order to achieve effective absorption of water into the pore structure. Also, it is recommended that the final solvent wash after a reaction be methanol, as this leaves the pores in an open, accessible condition on drying.

Preparation of ArgoPore Resins for use

ArgoPore resins are supplied as free-flowing powders and are ready to use without pre-washing or purification. When aqueous reaction conditions are to be used, the resin must be rinsed with a water soluble organic solvent, *e.g.* methanol or THF, prior to addition of the aqueous media.

Typical particle size and loading capacity for ArgoPore Resins

ArgoPore resins are spherical beads with a particle size distribution of 90-250µm.

Loading values typically range from 0.6 - 1.1 mmole/g for functional resins, and 0.5 - 0.9 mmole/g for linker resins, based on standard analytical techniques. In addition, there is a high load and low load version of aminomethyl ArgoPore, with loading capacities of 1.1-1.6 and 0.2-0.6 mmol/g respectively.

Storage requirments

Refrigeration is recommended for long term storage of ArgoPore resins.

Temperature and agitation

Chemistry has been performed on ArgoPore at a temperature of 150° C . Temperature stability will vary with different reagents, however ArgoPore should be stable to 150° C unless particularly harsh reagents are present.

Any of three principal modes of agitation are recommended: (1) rocking in a shaker vessel (2) overhead paddle stirring at low speed (<30 rpm) or (3) Quest agitation. Although magnetic stirring can be performed successfully under selective conditions (i.e. low rpm, pea or flea stir-bar, short times), it is not recommended as a general procedure. Reagent transport in and out of the pore phase is governed by diffusion, so, stirring can be kept to a minimum or in some cases eliminated.

References-ArgoPore

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8. Given a surface area of 650 m2/g and a loading of 0.75 mmol/g, a simple calculation of loading density can be conducted assuming all loading is present at the surface. Thus, such a resin has a molecula density of 0.0093 molecules/$Å^2$ or approximately 1 molecule per 10 $Å^2$ of surface area.

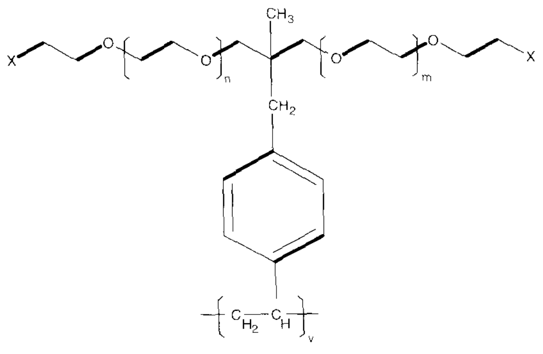
Technical Information for Solid Phase Resins
ArgoGel®

Advantages of ArgoGel

ArgoGel resins are specifically designed to facilitate the transition of organic synthesis between solution and solid phase. ArgoGels are poly(ethylene glycol) (PEG) grafted polystyrene where the linker is present at the terminus of the PEG chain. (**Figure 1**) Resin bound compounds are exposed to a solution-like environment due to the highly flexible nature of the PEG graft. A novel bifurcated graft-polystyrene linkage is incorporated in ArgoGel to allow higher loading and greater stability than analogous resins based on a benzylic ether linkage. ArgoGel's structure manifests itself in numerous advantages for solid phase organic synthesis, including:

- Bound molecules are present in a solution-like environment
- High loading capacity
- Wide solvent compatibility, including water and polar protic solvents
- Excellent gel-phase NMR capability for qualitative analysis of resin bound molecules
- Low leachable impurities
- Excellent reaction kinetics due to rapid diffusion of reagents to reaction sites.
- Exceptional stability under the rigors of solid-phase organic reactions

FIGURE 1. Structure of ArgoGel



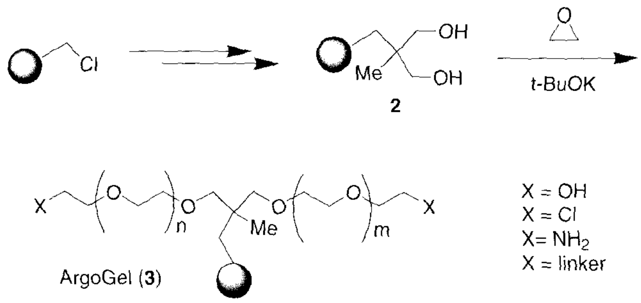
Development of ArgoGel Resins

Poly(styrene-oxyethylene) graft copolymers (PS-PEG), first reported by Bayer and Rapp,[1] have been commercially available for several years.[2,3] These conventional PS-PEG beads display relatively uniform swelling in a variety of solvents from medium to high polarity ranging from toluene to water and excellent reaction kinetics for peptide synthesis.[4] The polymers are produced by grafting ethylene oxide on to the polystyrene backbone creating long flexible chains that terminate with a reactive site spatially separated from the more rigid polystyrene backbone. These resins have the PEG graft linked to the polystyrene via a benzylic ether, a bond well known to be unstable to strongly acidic reagents. The average graft length of 68 units (3000 D) afforded a PEG composition of ~75% by weight and a loading of 0.2-0.3 mmol/g.[5]

The Argonaut approach to developing ArgoGel centered around improving the acid stability of the polystyrene-graft linkage and increasing the functional group loading per unit weight of resin (mmol functional group/g resin). We improved stability by replacing the benzylic ether linkage with an aliphatic linkage and increased loading through bifurcation prior to ethylene oxide grafting. In effect, ethylene oxide grafting to a bifurcated intermediate affords a bifunctional PEG chain that is attached to the PS backbone at its center. This approach allowed the preparation of ArgoGel resins with twice the loading capacity relative to conventional monofunctional PS-PEG graft copolymers, while maintaining equivalent PEG molecular weights (**Scheme 1**). The complete experimental details of this work have been published.[6]

In brief, a 1,3-diol functionalized polystyrene intermediate **2** was prepared as shown in **Scheme 1**. Graft copolymers were then prepared by anionic polymerization of ethylene oxide initiated by the alkoxide formed from **2**. Deprotonation of diol **2** with excess potassium t-butoxide followed by addition of a prescribed amount of ethylene oxide solution in THF led to facile polymerization as determined by weight gain of the isolated polymers (**3**) via FTIR and ^{13}C-NMR spectroscopy. Graft lengths (n and m) were varied from 29 to 58 repeat units (67-82 wt % PEG) and the solid state properties (crystallinity) characterized by differential scanning calorimetry. The optimum graft copolymer composition, determined by balancing the degree of functional group loading with resin crystallinity and swelling, was found to be in the 0.4 to 0.5

SCHEME 1. Structure of ArgoGel



mmol g^{-1} range. The hydroxyl substituted copolymer, ArgoGel-OH (AG-OH) was further elaborated to the chloro (AG-Cl) and amino (AG-NH_2) substituted base resins and ultimately on to other linker substituted materials.

Because the presence of residual linear PEG impurities was a major concern from the outset, a protocol for measuring the levels by extraction with TFA/water (95:5) was developed.[7] After extraction with 95:5 TFA/water for 4 hours followed by concentration of the filtrate, linear PEG levels of less than 0.5 % were routinely obtained.[8] AG-OH and AG-NH_2 displayed excellent chemical stability to the strongly acid cleavage conditions often employed in solid phase organic synthesis (e.g. TFA cleavage). The resins also displayed good swelling in a panel of solvents ranging from toluene to water. Thus, PS-PEG supports are an attractive choice for syntheses where polar solvents are required.

ArgoGel Characterization and Properties

ArgoGel resins are exceptionally stable under the rigors of solid phase organic synthesis. These support materials provide a high loading capacity and low levels of impurities due to the improved purification process. ArgoGel resins exhibit compatibility with a broad range of organic reagents and solvents due to their composition and structure. The relatively mobile environment allows the easy application of NMR for qualitative analysis of linked molecules.

High Loading Capacity for High Yields

ArgoGel resins provide compound yields approximately two fold higher than comparable grafted resins with similar polyethylene glycol (PEG) compositions. Traditional PEG-grafted polystyrene resins are prepared by ethylene oxide grafting to a monoalcohol immobilized on the polystyrene support providing a monofunctional PEG graft. The ArgoGel copolymer consists of a bifunctional PEG graft chain which is attached to the polystyrene backbone at its center. This provides twice the number of functional groups per backbone attachment site for a given graft length and translates to higher loading capacity per unit polymer weight without sacrificing the benefits conferred by long PEG grafts. ArgoGel-OH and -NH_2 have loading values in the range of 0.4-0.5 mmole per gram based on standard analytical techniques.

Low Levels of Impurities

Chemical Stability

ArgoGel resins enable production of high purity products. ArgoGel resins contain a chemically inert aliphatic spacer to link the graft to the poly(styrene/divinylbenzene) core matrix through a carbon-carbon bond rather than a benzylic ether present in other supports. This stable chemical linkage minimizes loss of loading through degradation of the PEG chains by aggressive reagents during synthesis and cleavage and results in the isolation of purer products in higher yields.

Low Leachable Impurities

PEG-grafted polystyrene supports often contain impurities that leach out during normal solid-phase organic synthesis. Of special concern are impurities which are released during the cleavage of desired products from the support and which become incorporated into the isolated material. Argonaut has developed advanced methods for producing resin with low impurity levels. This leads to advantages which include the following:

- Accurate product characterization (e.g., elemental analysis, NMR, mass spectra)
- Purification, if needed (e.g., crystallization), is more readily achieved
- Direct screening (activity/mg) may be performed

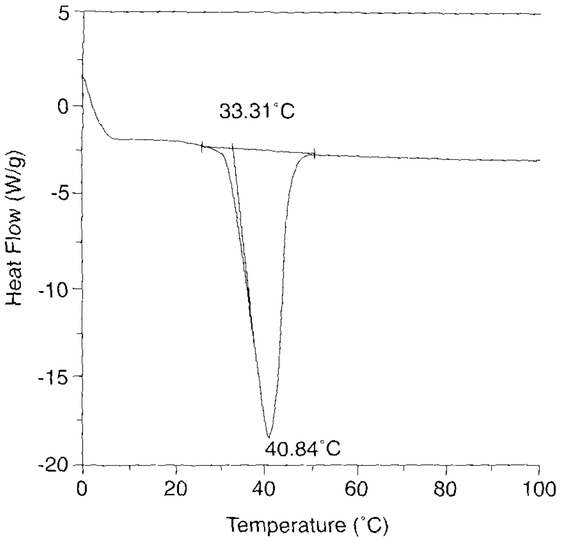
It is important to note that the PEG may preferentially bind low levels of certain reaction side products, e.g. ureas and amine salts. These can be efficiently removed by incorporating an acetic acid or acetic acid/DCM wash. Resins should be washed with acetic acid prior to cleavage to minimize release of low levels of bound impurities.

Enhanced Resin Properties

Uniform PEG Graft Chain Length

ArgoGel resins have been prepared so that the polyethylene grafts are of uniform length. This provides greater control and reproducibility over chemical transformations on the resin due to equivalent reactive sites. The DSC (Differential Scanning Calorimetry) endotherm shown in **Figure 2** documents the uniformity of the chain graft length. The endotherm is associated with a phase transition in which polyethylene glycol graft changes from the solid to the fluid state. The sharpness of the endotherm reflects the purity and uniformity of the polyethylene grafts.

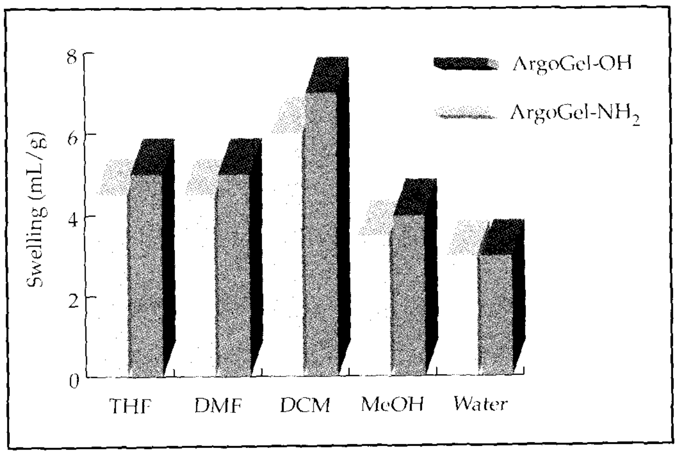
FIGURE 2.
DSC Showing Uniformity of Chain Graft Length



Optimum Swelling for Maximum Performance

As shown in **Figure 3**, ArgoGel resin exhibits excellent swelling properties in a range of solvents, from strongly polar protic solvents like water, to moderately polar aprotic solvents like toluene. A key advantage of ArgoGel is its ability to swell in aqueous solvent systems used in the typical workup, (e.g., saturated $NaHCO_3$, dilute HCl, etc.) which can be helpful in removing reagent-derived impurities.[9]

FIGURE 3.
ArgoGel Swelling in Solvents



Because the copolymers are composed of long, flexible PEG chains which terminate with a functional group spatially separated from the rigid polystyrene backbone, molecules attached to the ends of these chains are in a "solution-like" environment. This environment favorably impacts reaction kinetics by allowing rapid diffusion of reagents through the swollen gel to sites which are removed from the backbone. For example, it has been demonstrated that rate constants for the coupling of the active ester Boc-Gly-ONp to PS-PEG beads were of the same order of magnitude as in solution.[10] Large biomolecules, such as the 23.5 kDa enzyme trypsin, have been shown to readily penetrate PS-PEG beads providing further evidence of the mobile and bio-compatible environment within this matrix.[11]

Typical particle size and particle size distribution for ArgoGel resins

ArgoGel resins are composed of spherical beads with an average diameter of approximately 170 µm. The particle size distribution is 120-230 µm (95% within). For particle size distributions outside of these specifications please call (650) 598-1350 and ask to speak to the Product Marketing Manager for resins.

Temperature and Agitation

Four principal modes of agitation are recommended: (1) rocking in a shaker vessel; (2) tube rotation; (3) inert gas bubbling; or (4) overhead paddle stirring at low speed (< 60 rpm). Although magnetic stirring can be performed successfully under selective conditions (low rpm; pea or flea stir-bar; low temperature; short times), it is not recommended as a general procedure.

Chemistry on ArgoGel resin at a temperature of 130°C has been successfully conducted. Temperature stability will vary with reagents. In particular, ArgoGel is acid intolerant at high temperatures. In general, temperatures in the range of 130°C to 150°C can be used unless particularly harsh reagents are present.

Gel-Phase NMR Using ArgoGel

PS-PEG supports are particularly well-suited for on-bead analysis via NMR to gain structural information about compounds while they are attached to the beads. The relatively mobile environment created by grafting PEG chains on to the more rigid PS backbone facilitates the application of gel-phase ^{13}C-NMR in a standard spectrometer.[12] When swollen, good chain mobility results in high T_1 values and narrow linewidths comparable to those observed for small molecules in solution. A recent paper describes the use of ^{13}C-NMR to monitor an ether formation on ArgoGel-Wang-Cl.[13] The advent of the magic angle spinning technology also allows high quality ^{1}H-NMR data to be collected, however specialized equipment is required.[14]

Sample Preparation

A sample of dry ArgoGel resin (100-200 mg) is placed in a 5 mm NMR tube. The resin is scooped up with the tube and tapped gently to the bottom. Solvent is added (typically 500 µl of benzene-d_6). The resulting slurry is shaken or stirred to distribute the solvent, using enough to cover the resin. Resin sticking to the walls can often be coaxed down into the bulk sample by re-wetting with solvent and swinging the tube as though it were a medical thermometer. The sample should fill at least the normal NMR sample volume with wetted resin (about 30 mm for a 5 mm sample tube in our spectrometer). Small air bubbles do not seem to adversely affect the results. Care should be taken to avoid packing the resin in the bottom of the tube, as this will prolong the time it takes the resin to swell completely. An NMR tube spatula (Wilmad part no. 806) is very useful for distributing the solvent.

NMR Parameters

Standard ^{13}C parameters can be used to obtain gel-phase spectra. Proton decoupling aids in increasing the signal by NOE and decreases spectral complexity. A spectrum for purposes of characterization of a bound substrate may be obtained in as little as 30 minutes (1024 FIDs) at 300 MHz, and impurities down to the 5% level or better may be detected by running overnight (16384 FIDs). Typical spectra show large peaks due to polyoxyethylene (POE, 71 ppm) and solvent. Chemical shifts for the carbons in the terminal POE unit of ArgoGel resins are listed in **Table 3**. These values of ^{13}C chemical shifts in benzene d_6 are typical results. Line broadening of approximately 10-20 Hz is observed.

In an example of using gel phase ^{13}C NMR to monitor a simple transformation on the solid phase, we monitored the displacement of ArgoGel-Cl (C-1 carbon - 42.1 ppm) with a phenoxide anion to form a phenyl ether (**Figure 4**). In this case, only carbons for the phenyl ether attached to the resin, and the C-1 and C-2 terminal carbons of the POE chain are observable.

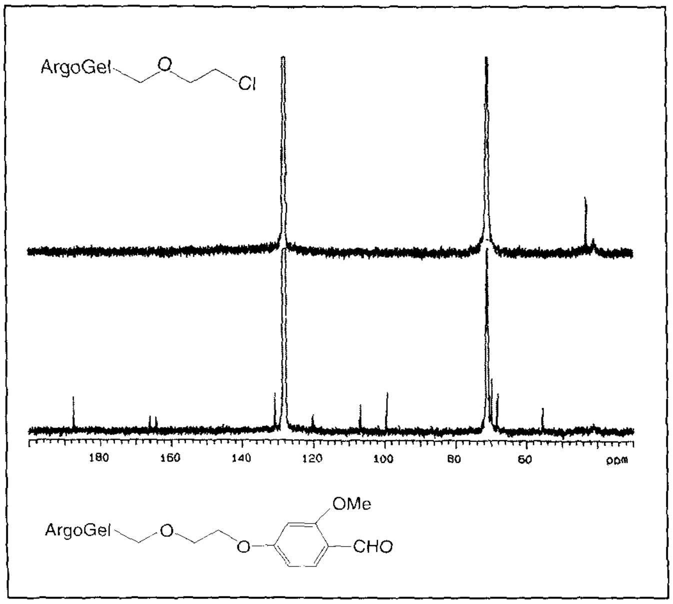
Table 3

Chemical Shifts for Carbons

Resin	C-1*	C-2
ArgoGel OH	61	72
ArgoGel Cl	42.1	70.6
ArgoGel NH_2	41.4	72.9

Figure 4

NMR



NMR Examples

Using ^{13}C NMR to Monitor and Evaluate the Efficiency of Esterifications

The benzylic carbon of ArgoGel-MB-OH shifts 2-3 ppm downfield upon formation of esters (cf. MB-OH NMR: 59.2 ppm (benzene D_6) for ArgoGel MB-OH and 61.6 ppm for ArgoGel MB-O-2-napthoate).

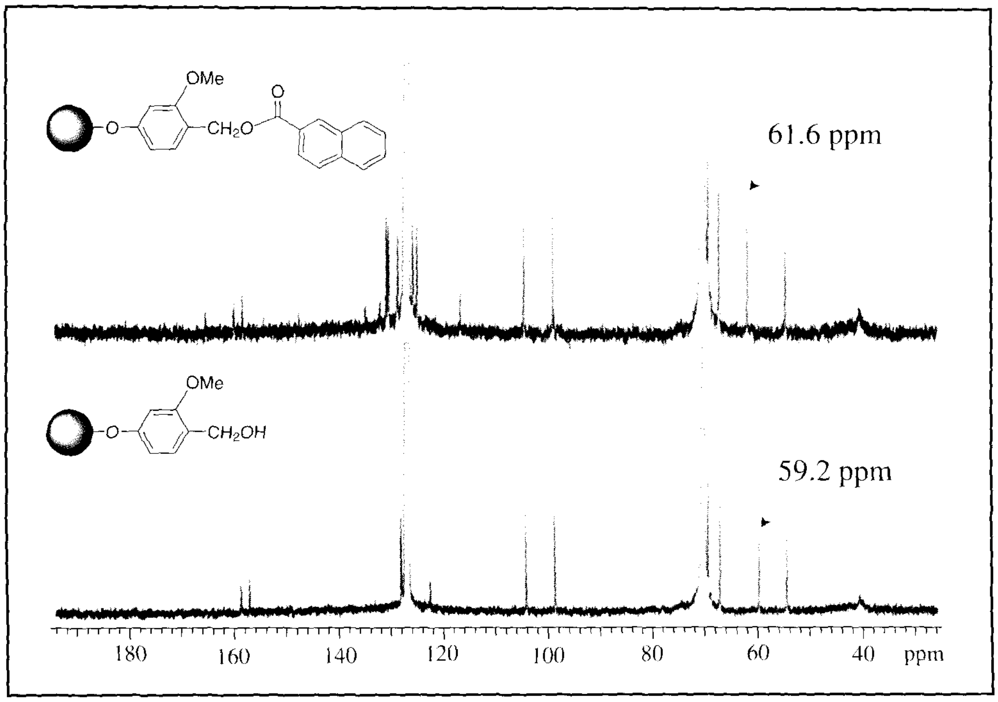


FIGURE 5.

Using ^{13}C NMR to Monitor Nucleophilic Displacements of ArgoGel-Cl

The displacement reaction of ArgoGel-Cl with phenols results in a shift of the C^1 carbon from 42.1 to 60-70 ppm allowing facile monitoring of the reaction (ArgoGel-Cl NMR).

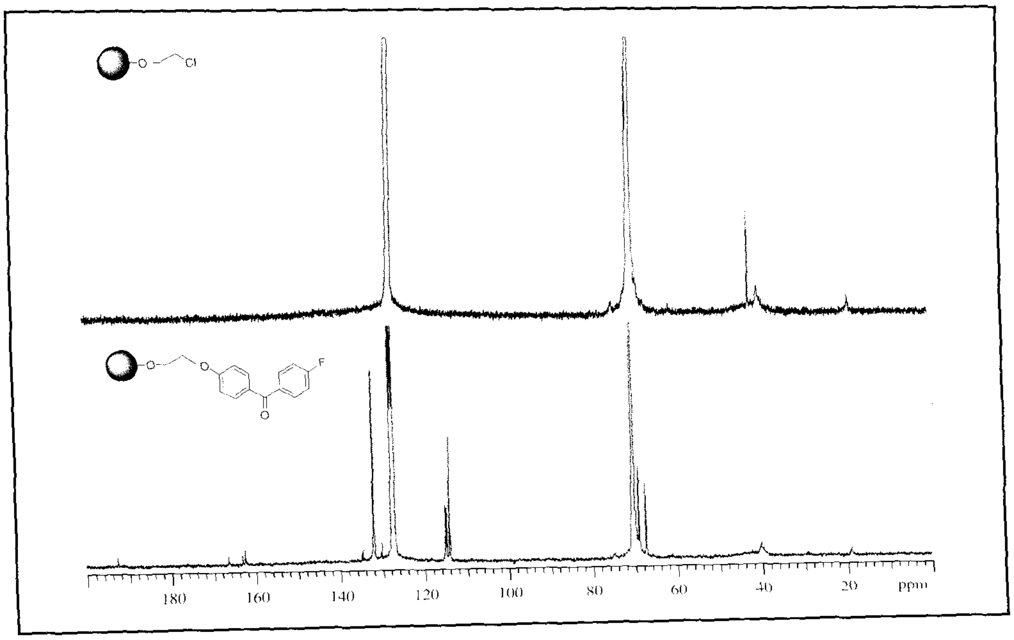


FIGURE 6.
Gel Phase ^{13}C NMR of ArgoGel-Cl and a representative phenyl ether resin (benzene-d_6).

Using ^{13}C NMR to Monitor Ether Formation of ArgoGel-Wang-Cl

Chloride displacement may be monitored by gel-phase ^{13}C NMR by observing the shift in the benzylic carbon (∂ 45.5 ppm) to the 60-70 ppm range.

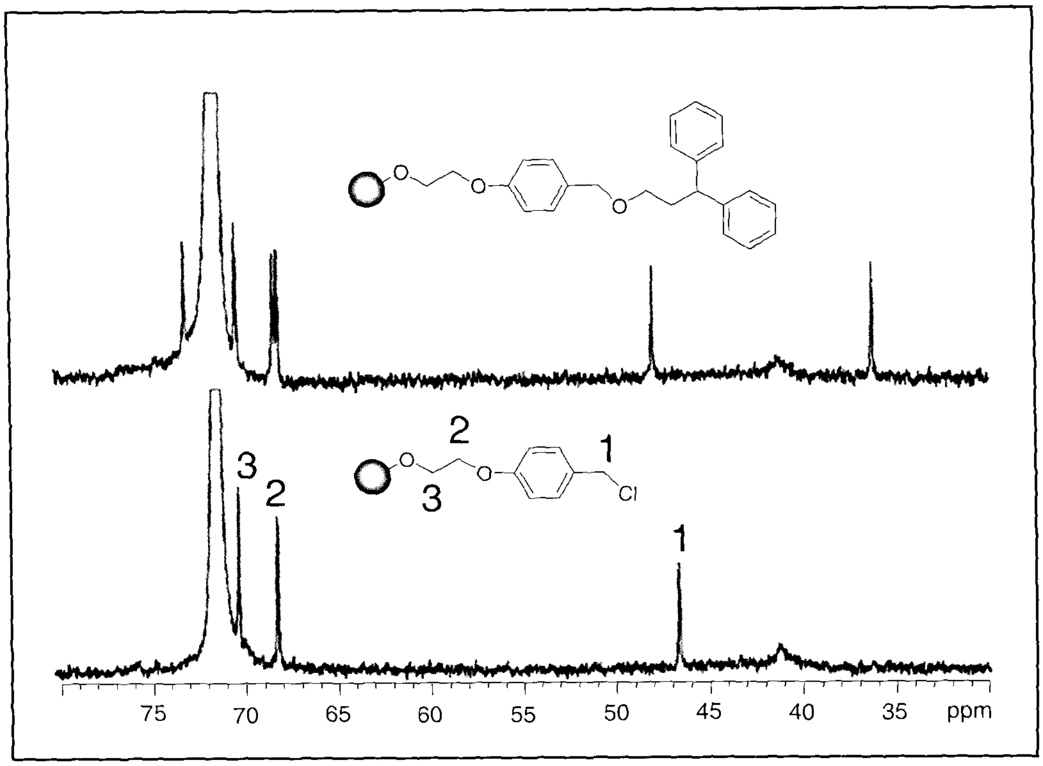


FIGURE 7

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Pre-Weighed Resin for Organic Synthesis
ArgoCaps®

Introduction

Argonaut offers the convenience of custom packaging in ArgoCaps.[1] ArgoCaps are a convenient and time saving method for delivery of fixed unit doses of resin to a reaction vessel, ensuring that resin weighing is no longer a tedious and time-consuming task. In addition, these convenient resin packages protect resins from moisture and are constructed from polycarbonate [2], which is easily dissolved with a wide range of organic solvents.

ArgoCaps filled with Argonaut's Resin Products

Any of Argonaut's resin products for solid phase synthesis can be custom packaged in ArgoCaps. The local Argonaut office will supply more information. ArgoCaps are available in two sizes.

ArgoGel Resins - Approximate quantity of ArgoGel per ArgoCap: 160 mg (#3 size) and 70 mg (#5 size).

ArgoPore Resins - Approximate quantity of ArgoPore per ArgoCap: 100 mg (#3 size) and 40 mg (#5 size).

1% Cross-linked Poly(styrene-co-divinylbenzene) Resins (PS) - Approximate quantity of resin per ArgoCap: 150mg (#3 size) and 65 mg (#5 size).

Custom Resin Filling of ArgoCaps

Argonaut Technologies also offers custom filling of ArgoCaps, with a customer's specific resin. Please contact us for further information on this unique service.

Capsule Resin Weight

ArgoCaps are filled volumetrically, and therefore, the fill weight is dependent on the resin density. The uniformity of resin weight per capsule is sufficient for them to be used without further quantitation in most cases. In those cases where more accuracy is required, the capsules can be individually weighed prior to use to determine a more exact resin weight for each ArgoCap. The tare weight of the #3 capsule is 60 + 1.5 mg, and the tare weight of the #5 capsule is 40 + 1.5 mg.

Capsule Dissolution

The polycarbonate polymer used for ArgoCaps is readily soluble in dichloromethane. To prepare the resin for synthesis, 4 mL of solvent are added to one or more ArgoCaps in a reaction vessel. After 10 minutes of agitation the solvent is drained and the washing process is repeated two more times. The resin is now free of polycarbonate and ready for use.This procedure has been shown by resin extraction, NMR, IR and DSC to remove all traces of the polymeric capsule material from the resin.

The effectiveness of capsule polymer removal through washing has been demonstrated by several analytical methods. Multiple capsules were serially washed with dichloromethane, and the polymer present in each filtrate measured. A representative set of results is shown in **Table 4**. Each ArgoCap contained 90 mg of ArgoPore-Wang. The ArgoCaps were exposed to 3 x 4 mL dichloromethane washes (10 min), followed by 2 x 4 mL rinses. A reaction vessel with 200 mg of ArgoPore-Wang (no capsule) was included as a control. The filtrate from each wash was collected, concentrated and the residue was measured gravimetrically. The results show that after three washes no further extraction of polycarbonate was observed.

The washed resin samples were analyzed by FT-IR, which showed no residual polycarbonate as indicated by the absence of the carbonate carbonyl stretch. The washed resins were also extracted with trifluoroacetic acid and the resultant extract was concentrated and analyzed by ^{1}H NMR. In each case the spectrum showed no polycarbonate present in the extract. These results are consistent with complete removal of the capsule material under the recommended washing protocol.

TABLE 4.
Quantitation of Polycarbonate Capsule

RV Contents	Wash 1 Extractable (mg)	Wash 2 Extractable (mg)	Wash 3 Extractable (mg)	Rinse 1 Extractable (mg)	Rinse 2 Extractable (mg)
2 ArgoCaps	131.2	13.8	0	0	0
3 ArgoCaps	167.1	43.8	2.6	0.1	0
ArgoPore-Wang	1.2	0	0	0	

Moisture Protection

In addition to providing a convenient means of quantitative resin delivery, ArgoCaps also protect the encapsulated resin from atmospheric moisture. The effectiveness of the capsule body as a barrier to water vapor was tested by exposing 4Å molecular sieves in both free and encapsulated forms to saturated water vapor. Molecular sieves were chosen to test as a "worst case" example. **Table 5** shows the molecular sieves in the ArgoCap displayed negligible moisture absorption in the first three hours relative to the unprotected sieves. The encapsulated molecular sieves did absorb moisture over a 24 hour period, indicating that the ArgoCaps should be stored in a dessicated environment when exposed to humid conditions over an extended period of time.

TABLE 5.
Comparison of % Weight Gain for Molecular Sieves in Encapsulated and Free Form

	Weight Gain %		
Sample	**1h**	**3h**	**24h**
Molecular Sieves	4	6.7	10.4
ArgoCap with Molecular Sieves	0.1	0.2	1.5
Empty Capsule Body	0.1	0.1	0.1

References

1. Patent pending
2. The polycarbonate is derived from bisphenol-A

Technical Information
for Polymer Resins and Reagents for Solution-Phase Synthesis and Purification

Introduction

To meet the increasing demands for reagents for parallel solution-phase synthesis, Argonaut Technologies has introduced a variety of polymer resins and reagents to facilitate a wide range of solution-phase reactions and purification strategies.

- Scavenger resins are added after a reaction is complete to quench and selectively react with excess reagents and reaction byproducts.

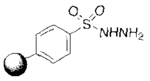
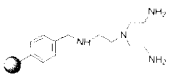
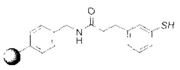
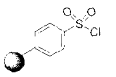
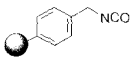
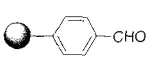
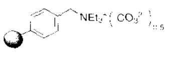
- Polymer-bound reagents are designed to be used in place of their small molecule equivalents and are particularly useful for multi-step reactions, saving time and solvents.

Two types of resin are used for these reagents, a lightly crosslinked polystyrene (PS) and a more highly crosslinked macroporous resin (MP). The PS resins require the use of solvents to swell the resin to permit reagents access to the functional groups. Functional groups in MP resins are already fully accessible without the addition of solvent.

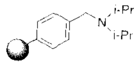
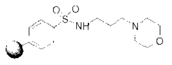
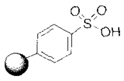
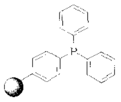
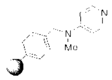
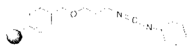
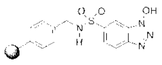
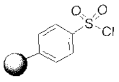
This section of the catalog contains additional information about Argonaut's polymer resins and reagents and includes reaction conditions for typical applications.

General information and product part numbers are found in the Solution Phase section of this catalog.

Scavengers

Product	Class	Structure	Function
PS-TsNHNH$_2$	Electrophile scavenger		Scavenges carbonyl compounds: aldehydes, ketones
PS-NH$_2$	Electrophile scavenger		Scavenges acid chlorides, sulfonyl chlorides, isocyanates, other electrophiles
PS-Trisamine	Electrophile scavenger		Scavenges acid chlorides, sulfonyl chlorides, isocyanates, other electrophiles
PS-Thiophenol	Electrophile scavenger		Scavenges alkylating agents: halides, mesylates, tosylates, α, ß-unsaturated carbonyls
PS-TsCl High Loading	Nucleophile scavenger		Scavenges alcohols, amines, other nucleophiles
PS-Isocyanate	Nucleophile scavenger		Scavenges nucleophiles, including amines, alkoxides, thiolos, organometallics
PS-Benzaldehyde	Nucleophile scavenger		Scavenges nucleophiles, including primary amines, hydrazines, reducing agents
MP-Carbonate			General base. Neutralizes ammonium salts, scavengers acids, acidic phenols

Polymer-Bound Reagents

Product	Class	Structure	Function
PS-DIEA	Polymer-bound base		Tertiary amine base, bound DIEA equivalent
PS-NMM	Polymer-bound base		Tertiary amine base, bound N-methymorpholine equilvalent
MP-TsOH	Polymer-bound acid		General acid, Scavenging and Catch and Release of amines
PS-Triphenylphosphine	Polymer-bound phosphine		Chlorination of acids and alcohols, Wittig and Mitsunobu reactions. Scavenges alkyl halides
PS-DMAP	Polymer-bound catalyst		Catalyst for acylation reactions, acid and sulfonyl halide Catch and Release
PS-Carbodiimide	Polymer-bound coupling agent		Coupling agent for amid and ester synthesis, pentafluorophenyl and other activated ester formaton
PS-HOBt	Polymer-bound coupling agent		Coupling of acids and amines, protecting group transfer
PS-TsC1	Electrophilic activation		Alcohol Catch and Release, scavenges nucleophiles

Polymer Reagents and Scavengers
For Parallel Solution Phase Syntheses & Purification

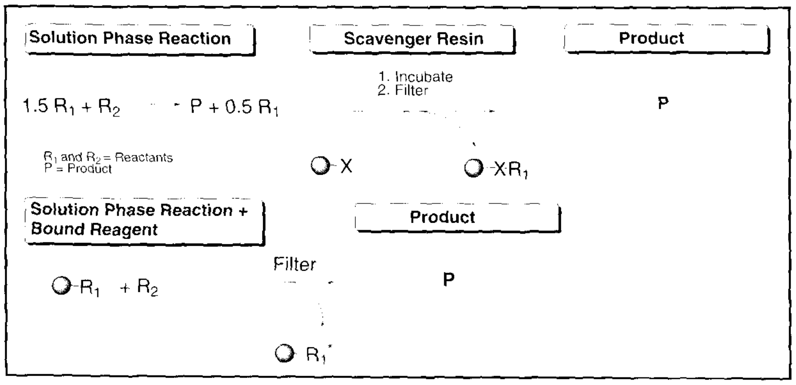
New methodologies that enable parallel solution phase synthesis of organic compounds are becoming an important complement to solid phase synthesis for the generation of compound libraries. The primary benefits relative to solid phase synthesis are:

- the ability to use known solution phase reaction conditions
- the ability to conveniently monitor reactions
- no need for linkage functionality

In order for parallel solution phase synthesis to be practical, improved methods of workup and purification must be developed as an alternative to individual aqueous extractions, crystallization and flash chromatography. The use of polymer-bound reagents and scavengers provides a simple and very effective means of purifying multiple solution phase reactions in parallel and has recently been the subject of intense investigation.[1-4]

In response, Argonaut Technologies has developed a variety of polymer scavengers and reagents to facilitate a wide range of reactions and workups. These products provide increased reaction throughput when used individually or in various combinations.

This section of the catalog includes background information for this methodology and provides specific product information, including scope of reactivity and detailed procedures for use in model applications.



Scheme 2

Background

The resins developed for parallel solution phase synthesis fall into two main categories:

- Scavenger Resins
- Bound Reagents

Scavenger resins provide a convenient means of effecting chemically-driven separations, allowing work up and purification of chemical reactions without the need for chromatography. A scavenger resin is added after the reaction is complete to quench and selectively react with excess reactants and/or reaction byproducts. The resulting resin bound reactants are removed by simple filtration. The removal of excess reactant is depicted in **Scheme 2**.
A bound reagent is present during the reaction and allows removal of both unreacted and spent reagent by filtration (**Scheme 2**). Properly designed bound reagents will often perform in a manner similar to their small molecule equivalents with minimal optimization for a given synthetic transformation.

Bound reagents and/or scavengers may be used individually or in concert to simplify reaction workups and avoid time consuming aqueous extraction and chromatography. It should be noted that polymer scavengers and reagents can also be quite useful for the purification of cleaved products from solid phase reactions. Cleavage strategies which allow for a diverse set of inputs, e.g. amines, are not restricted to volatile reagents when scavenging protocols are employed.

Terminology

The following terminology is used when describing resins in this technical paper.

Resin Type

The product name provides information regarding the resin type and the comparable small molecule reagent. PS designates lightly crosslinked polystyrene and MP a more highly crosslinked macroporous resin backbone. Lightly crosslinked polystyrenes typically require the use of solvents that will swell the resin to allow reagents to access the resin-bound functional groups. In cases where the solvent does not swell the resin, it may be necessary to add a cosolvent that is compatible with the resin, e.g. THF. Macroporous polystyrenes are porous resins; the resin functionality is accessed by reactants through the pore network which is typically not dependent on solvent.

Scavengers

Polymer scavengers are resins which are added after chemical reactions to remove excess reactants and byproducts. The functionality removed by each scavenger is given in the table on page 49 and the accompanying detailed product descriptions. The capacity of each resin has been determined by measurement of the uptake of a model substrate to better reflect the scavenging capability as compared to a loading based on elemental analysis. In addition, the effectiveness of each scavenger resin was measured for a series of substrates of varying reactivity to provide a guide for applications involving a range of substrate reactivities.

Since the reactive functionality of scavengers is polymer bound, mixtures of incompatible scavengers and reagents can be used together in the same vessel without limitations.[5] For example, a mixture of DDQ and DDQ-H was scavenged with a mixed-bed of a bound tetraalkylammonium ascorbate, to reduce unreacted DDQ, and bicarbonate resin, to sequester DDQ-H.[6] MP-Carbonate and MP-TsOH can also be used together as scavengers for acidic and basic compounds, respectively. The use of MP-TsOH and MP-Carbonate as a mixed-bed can be an effective means of removing a variety of weak Bronsted acid salts. The MP-TsOH acid protonates the anion, sequestering the cation, and the newly formed acid is subsequently sequestered on the MP-Carbonate resin. This method is useful for the removal of carboxylate and fluoride salts.

Bound Reagents

Bound reagents perform the same function as the small molecule analog. The tertiary amine resins, PS-DIEA and PS-NMM, are designed to behave similarly to diisopropylethylamine (DIEA) and N-methylmorpholine (NMM), respectively. In reactions where these serve as tertiary amine bases, they form bound amine hydrochloride salts which are readily removed by filtration. These may be used in conjunction with PS-DMAP where DMAP catalysis is required.

Catch and Release™ Resins

These are a subset of the polymer reagents which allow the "catching" of a small molecule as an activated polymer intermediate, analogous to resin capture.[7] The resin can be washed to remove soluble byproducts and then subjected to a second transformation to "release" the product. This has been applied using PS-TsCl to "catch" alcohols as polymer-bound tosylates. After a simple workup involving resin washing, the resin-bound tosylates can be reacted with secondary amines to "release" tertiary amine products.

Bound Acids and Bases

MP-TsOH and MP-Carbonate are quite useful in a number of capacities as a bound acid and base, respectively. These can be used to quench and purify reactions, analgous to an aqueous acid or base extraction. MP-Carbonate is used for neutralizing amine hydrochloride and carboxylate salts in reagent preparation, reaction workup or during reactions. In the case of insoluble amine hydrochlorides, a catalytic amount of a soluble base, e.g. DIEA, can be added as a "transfer base" to assist in the neutralization.

References

1. Kaldor, S. W.; Siegel, M. G. *Curr. Opin. Chem. Biol.* **1997**, 1, 101.
2. Flynn, D.; Krich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, 119, 4874.
3. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, 119, 4882.
4. Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.*, **1997**, 38, 513.

PS-TsNHNH$_2$

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 moderately loaded 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 acetic acid (5 - 10 %) may be required for ketones and hindered aldehydes. Acetic acid 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

TABLE 6. Comparative Scavenging Times in Dichloromethane

Carbonyl Substrates	PS-TsNHNH$_2$ (equiv)	Additive	Time (h)	% Scavenged
Benzaldehyde	3	-	1	100
Hexanal	3	-	1	100
2,6-Dimethoxybenzaldehyde	3	-	1	100
Cyclohexanone	3	Acetic Acid	1	100
Acetophenone	3	Acetic Acid	8	100
2,6-Dimethylcyclohexanone[1,2]	3	Acetic Acid (70 °C)	10	85

and ketone scavenging examples are presented in **Table 6.** 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 polymeric 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.[1-3]

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.

PS-Trisamine

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 a 3 - 6 equiv of PS-Trisamine and occurs with 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 7**). 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.

References

1. Booth, R. J.; Hodges J. C. *J. Am. Chem. Soc*, **1997**, 119, 4882.

TABLE 7 Comparative Scavenging of Electrophiles in Dichloromethane for 0.5 h

Electrophile	PS-Trisamine (equiv)[1]	% 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

1) Relative to electrophile, no additional base present

PS-Thiophenol

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 in the presence of diisopropylethylamine (DIEA) and MP-Carbonate. The solvent used for the scavenging reaction is critical for good scavenging rates. Both 1:1 THF/ethanol (THF/EtOH) mixtures and dimethylformamide (DMF) were found to be effective solvents for the scavenging reaction. Low levels of scavenging were observed in pure THF, indicating that removal of alkyl halides from a reaction carried out in THF would require the addition of ethanol to accelerate the reaction. It is likely that addition of ethanol may be necessary to accelerate the scavenging process in other solvents, by analogy to THF.

In the case of potassium trimethylsilanolate (TMSOK), two equivalents of base are incubated with the resin for 30 min in THF. The resin is then rinsed 3 x with THF to remove excess base. This can be carried out in bulk or individually 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 equiv of resin used may be required. Alternatively, DIEA (2 equiv) can be added to PS-Thiophenol in the presence of MP-Carbonate (2 equiv). The DIEA acts as a base for 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.

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 8.** PS-Thiophenol was effectively used as a scavenger in Williamson ether synthesis as shown in **Scheme 3.** High yields and purities were achieved using either the TMSOK or DIEA/MP-Carbonate scavenging method.

<u>Representative Procedure</u>: 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 110 µL of benzyl bromide (1.5 equiv, 0.90 mmol) was added and the solution was heated at 65 °C with stirring for 5 h.

Reaction Workup: (A)TMSOK Method: PS-Thiophenol (0.692 mg, 0.87 mmol/g, 0.60 mmol, 2 equiv) was treated with 7 mL of a deoxygenated 0.17 M TMSOK solution (154 mg, 1.20 mmol, 2 equiv) in THF:EtOH (1:1) and allowed to react for 30 min. The solution was removed by filtration and the resin was washed 3 x 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 2 x with THF:EtOH. The phenyl benzyl ether product was isolated in 94% yield after concentration. (B) DIEA/MP-Carbonate Method: The reaction solution was added to a mixture of 0.692 g of PS-Thiophenol and 0. 4 g of MP-Carbonate (2 equiv) and 3 mL of ethanol and 210 µL of DIEA was added. 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 5 x 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 equiv of PS-Thiophenol to afford phenyl octyl ether in 83% and 75% yield by Method A and B, respectively.

Ps-Thiophenol is stable when stored at 4°C. Stability studies have showed no loss in capacity over 18 months.

SCHEME 3

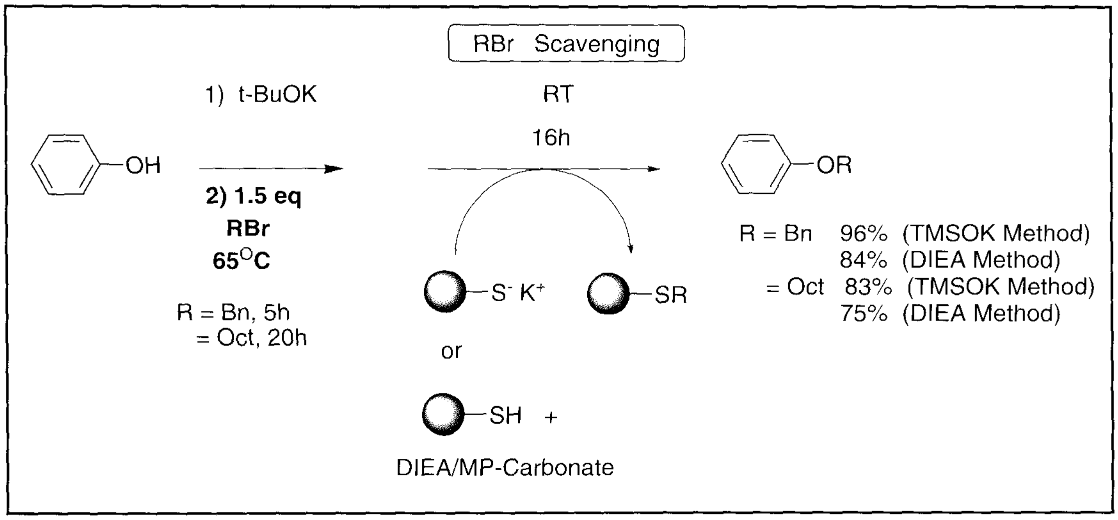


TABLE 8 Scavenging of Alkylating Agents with PS-Thiophenol

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

1) Conditions affording > 80% scavenging can typically be driven to completion with additional 1 - 2 equiv of resin. 2) Two equiv of DIEA and MP-Carbonate relative to PS-Thiophenol.

PS-TsCl High Loading (HL)

PS-TsCl-HL is the resin-bound equivalent of tosyl chloride. This high-loading resin is useful for the scavenging of various nucleophiles, including amines, hydrazines, alcohols and organometallics.

Scavenging reactions typically use 3 equivalents of resin per equivalent of substrate to be scavenged. Various solvents may be used, including 1,2-dichloroethane (DCE), dichloromethane (DCM), tetrahydrofuran (THF) and N,N-dimethylformamide (DMF), with a temperature range from 20 to 50 °C.

Representative Procedure

3-Phenylpropanol Scavenging:
PS-TsCl-HL (3 equivalents) is added to a solution of 3-phenylpropanol (1 equiv) in DCE/pyridine (20-50% pyridine, 10 mL/g resin added) and the reaction is stirred at room temperature for 5-6 h. Results by GC analysis indicate >90% scavenging after 3 hours and 96-99% scavenging after 5.5 h (heating for an additional 2 h at 50 °C achieved 100% scavenging). The pyridine-HCl generated was free-based by subsequent addition of MP-Carbonate resin (4 equiv) 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 to 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.

Scavenging of Nucleophiles with PS-TsCl-HL

Material Scavenged	Equiv.	Solvent	Base	Temp °C	% Scavenged	Time (h)
3-Phenylpropanol	1.0	THF	20% pyridine	20	90[1]	5.5
3-Phenylpropanol	1.0	DCE	20-50% pyridine	20	96-99[2]	5.5
Cyclohexanol	1.0	DCE	50 % pyridine	20	80[3]	5.5
3,5-Dimethylaniline	1.0	THF	6 equiv Et_3N or 20% pyridine	20	96-100	3
3,5-Dimethylaniline	1.0	DCE or DMF	6 equiv Et_3N or 20% pyridine	20	100	< 3
Acetophenone oxime	1.0	DCE	50% pyridine	20	87[2]	5.5
PhMgCl[4]	1.0	THF	-	20	100	1
Phenylhydrazine	1.0	DCE	1 equiv Et_3N	50	100	1

1. 97% scavenged after an additional 2 hours at 50 °C 2. 100% scavenged after an additional 2 hours at 50 °C 3. 90% scavenged after an additional 2 hours at 50 °C 4. Scavenging of PhMgCl was monitored by quenching of an aliquot of the reaction mixture with benzophenone, followed by TLC analysis and comparison to authentic triphenylmethanol.

PS-Isocyanate

PS-Isocyanate is a 1% crosslinked Polystyrene-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 8**). The resin can readily scavenge excess *nucelophiles from solution, which are often used to drive* reactions to completion thereby facilitating workup and purification.[1-5] The reaction of nucleophiles with the isocyanate moiety occurs without liberation of small molecule byproducts.

Removal of nucleophiles from solution generally requires a 2 - 3 equiv of PS-Isocyanate depending on substrate reactivity. Comparative scavenging of amines and alcohols (0.2 - 0.05 M) of varying reactivity was tested as a function of time and temperature (**Table 9**). Typical aliphatic amines are completely sequestered by three equiv of PS-Isocyanate within 1 h. Three equiv 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 diisopropylethylamine 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.

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. CH_2Cl_2, dichloroethane, THF and toluene are all good choices with CH_2Cl_2 being preferred.

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 base (**Scheme 4, Table 10**). Upon completion of the reaction, the excess benzylamine was scavenged using 3 equiv PS-Isocyanate resin. The product was then isolated by washing it free of the resin followed by concentration. The yields were determined gravimetri-

TABLE 9 Comparative Scavenging of Nucleophiles in Dichloromethane

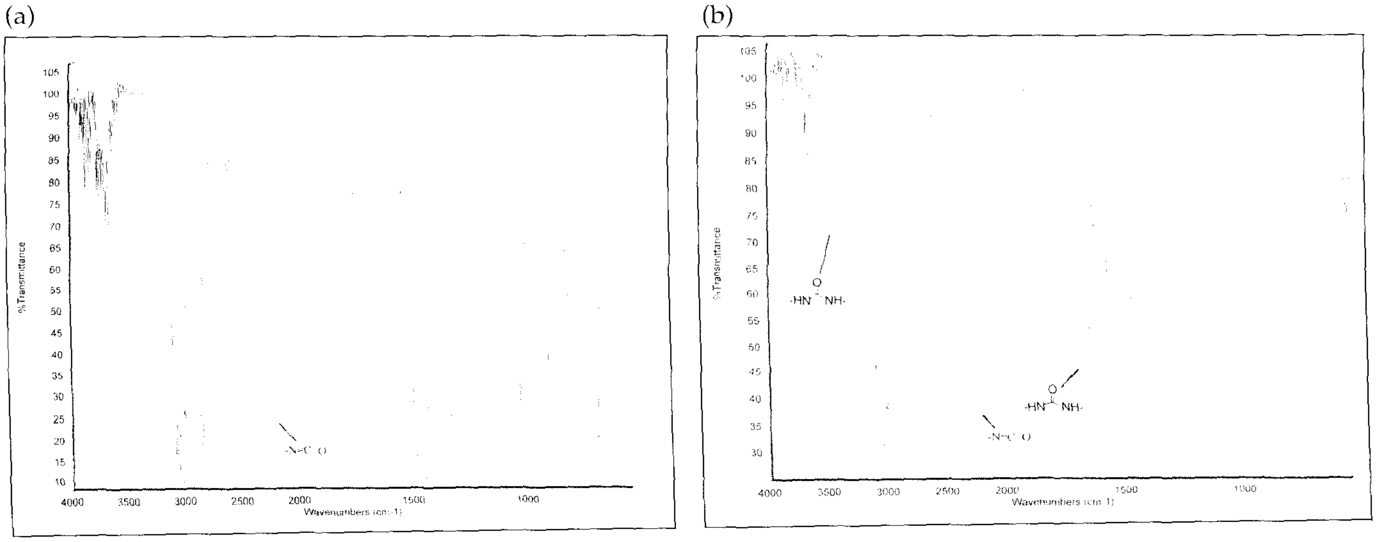
Nucleophile Scavenged	PS-Isocyanate (equiv)	Temp (°C)	% Scavenged 1 h	16 h
piperidine	3.0	20	100	-
benzyl amine	3.0	20	100	-
aniline	3.0	20	-	100
4-methoxyphenyl-1-butanol	2.0	20	0	68
4-methoxyphenyl-1-butanol	3.0	60[1]	0	29
2-aminobenzophenone	3.0	60[1]	-	81

1) Dichloroethane solvent

TABLE 10 Amide Bond Formation

Base	Scavenging Time	% Yield	% Purity
PS-DIEA	1 hr	87.0	96.7
PS-DIEA	3 hrs	87.4	94.5

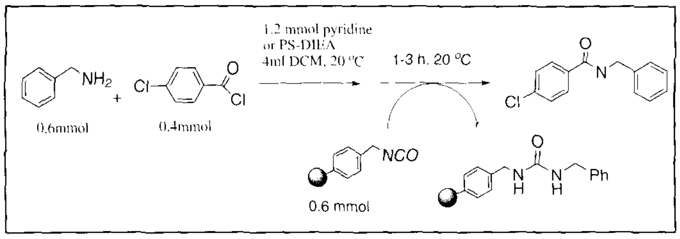
FIGURE 8 FT-IR Spectra of (a) PS-Isocyanate, 1.2 mmol/g; (b) polystyrene methylisocyanate, 0.9 mmol/g, prepared by the procedure described in reference 4.



(a)

(b)

Scheme 4



cally 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).

Representative Procedure: Amide Formation
Reaction: 4-chlorobenzoyl chloride was allowed to react for one hour with 1.5 equiv of benzylamine in CH_2Cl_2 with 3 equiv of PS-DIEA resin as the base.

Reaction Workup: The excess benzylamine was scavenged by adding PS-Isocyanate resin (3 equiv relative to excess amine). The beads were removed by filtration, washed 2 x with CH_2Cl_2 and the combined filtrate was concentrated to afford the benzyl 4-chlorobenzamide as the sole product in 87 % yield.

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.
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PS-Benzaldehyde

PS-Benzaldehyde[1,2] is the resin-bound equivalent of benzaldehyde. This resin is useful for the scavenging of various nucleophiles, including amines, hydrazines, and carbon-based nucleophiles such as Meldrum's acid and organometallics. The loading 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 1,2-dichloroethane (DCE), dichloromethane (DCM), and N,N-dimethylformamide (DMF), with a temperature range from 20 °C to 50 °C.

Representative Procedure
Phenylhydrazine Scavenging:
PS-Benzaldehyde resin (3 equiv) in 1,2-dichloroethane was allowed to react with phenylhydrazine (1 equiv) in the presence of a catalytic amount of glacial acetic acid. 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 acetic acid by heating for 1 h at 50 °C.

Scavenging Various Substrates:
PS-Benzaldehyde (3 equiv) was added to a solution of the substrate in 1,2-dichloroethane 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.

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.

Comparative Scavenging of Nucleophiles with PS-Benzaldehyde (3 equiv)

Material Scavenged	Equiv.	Solvent	Additive	Temp °C	% Scavenged[1]	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	Triethylamine	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 (Ref.1)	1.0	DCM	MeOH	20	100	18

1. 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 to an authentic triphenylmethanol sample.

MP-Carbonate

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 like carboxylic acids or acidic phenols.

Removal of excess carboxylic acids or acidic phenols, e.g. phenol or nitrophenol, from solution generally requires 3 - 4 equiv of MP-Carbonate. Removal of excess hindered phenol requires larger amounts of resin, typically up to 5-fold excess MP-Carbonate. Complete removal takes from 30 minutes to 2 hours. Upon completion of the scavenging, the resin is rinsed three times with a suitable solvent, including CH_2Cl_2, THF, or ethanol. Representative acids and phenol scavenging examples are presented in **Table 11.**

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. diisoproylethylamine (DIEA) or triethylamine, 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 equiv) can be added as a soluble transfer base.

References

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

TABLE 11. Comparative Scavenging Times in Dichloromethane

Substrates	MP-Carbonate (Equiv)	Time (h)	% scavenged
Benzoic acid	3	1	100
Hexanoic acid	4	1	100
Bromo-Benzoic acid	3	1	100
Phenol	4	1	100
Nitrophenol	2	1	100
2-allylphenol	6	1	93
2,6-Dimethylphenol	7	1	80

PS-DIEA

PS-DIEA is a high loading tertiary amine base which is a resin-bound equivalent of diisopropylethylamine. PS-DIEA is useful in applications requiring a tertiary amine base, where the resin-bound ammonium salt byproducts are 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 the benzylic position by analogy to 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 in the presence of reactive electrophiles like chloroformates.

The stability of polymeric tertiary amines towards electrophiles was studied as a function of amine structure. A methylene chloride solution of benzoyl chloride or methyl chloroformate 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 5**). The results showed good correlation between steric hindrance and amine stability (**Table 12**). Dimethylaminomethyl 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 cleavage. 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).

PS-DIEA was applied in the preparation of the mesylate of 3-phenylpropanol according to a literature procedure (**Scheme 6**).[4] The use of 3 equiv 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*, and hence, was greatly simplified over aqueous extractions when triethylamine was used as the base. Alternatively, the excess methanesulfonylchloride could have been removed by adding PS-Trisamine.

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 CH_2Cl_2 and 1 mmole of a primary alcohol and cooled in an ice bath. 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 3 x with CH_2Cl_2. The combined filtrate was concentrated on a rotary evaporator 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.

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.
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4. Gooding, O. W.; Bansal, R. P. *Synth. Comm.* **1995**, 25, 1155.

Scheme 5

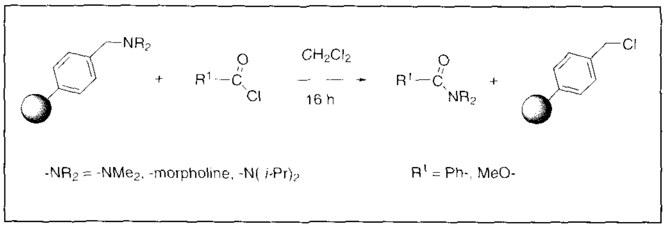
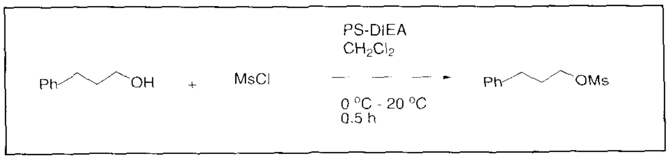


Table 12 Stability of Tertiary Amine Resins to Acid Chlorides and Chloroformates

Amine Resin (R)	Electrophile (R^1)	Cleavage Product (%)
Me	Ph	9
morpholine	Ph	0
morpholine	MeO	90
I-Pr	MeO	2.5

Scheme 6



PS-NMM

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 (CH_2Cl_2, 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 13**. The data shows 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 16.4 % when aniline was the reactant, even though the 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.

References

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TABLE 13 Formation of Amides, Sulfonamides, and Carbamates Using PS-NMM Resin

Electrophile	Amine	Resin	Yield (%)	Purity (% GC)
4-Cl benzoyl chloride	benzylamine	PS-NMM	94.2	100.0
tosyl chloride	benzylamine	PS-NMM	92.7	89.0
methyl chloroformate	benzylamine	PS-NMM	99.3	100.0
methyl chloroformate	benzylamine	P-morpholine[1]	76.5	95.8[2]
methyl chloroformate	aniline	PS-NMM	67.0	100.0
methyl chloroformate	aniline	P-morpholine[1]	67.0	83.6[3]

1) Morpholinomethyl polystyrene, 2) Contains 4.2 area % Methyl morpholine carbamate, 3) Contains 16.4 area % Methyl morpholine carbamate

MP-TsOH

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).[1-2, 6-7] However, 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 predominately restricted to the surface of the macroporous framework and 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.[8] Representative amine scavenging examples (batch mode) as a function of time are provided in **Table 14**. MP-TsOH is a useful alternative to quenching reactions with aqueous or soluble organic acids.

TABLE 14 Amine Removal by MP-TsOH (Batch Mode)

Amine	MP-TsOH (equiv)	% Scavenged	
		20 min	1 h
diisopropylamine	2.0	100	100
aniline	1.5	96	99.6
2-aminobenzophenone	1.6	63	71
benzylamine	1.9	100	100
N-benzyldiethylamine	1.8	99	100

TABLE 15 Amine Removal by MP-TsOH (Cartridge Mode)

Amine Scavenged	MP-TsOH (equiv)	% (10 min)
benzylamine	4.67	97
N-benzyldiethylamine	4.67	95

MP-TsOH may also be used in cartridge applications to perform Catch and Release of amine derivatives in analogy to silica-derived SCX columns.[3-5] MP-TsOH (1.4 mmol/g) has approximately double the sulfonic acid capacity of SCX media (approx. 0.7 mmol/g). In addition, MP-TsOH circumvents the contamination of amine products with particulates that sometimes occurs with silica-derived SCX columns. This is presumably due to dissolution of silica by methanol used to elute amine products from the media. Representative amine scavenging examples (cartridge mode) as a function of time are provided in **Table 15.**

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.
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PS-Triphenylphosphine

PS-Triphenylphosphine is a phosphinated polystyrene resin that is a resin-bound equivalent of triphenylphosphine. The active loading capacity of PS-Triphenylphosphine is determined by the quantitation of benzyl bromide uptake in DMF (GC, internal standard method). This resin can readily convert acids or alcohols to the corresponding acyl or alkyl chlorides in CCl_4 (**Scheme 7**).[2-4] The conditions are mild and products are formed in high purity (**Table 16**). PS-Triphenylphosphine may also be utilized for Mitsunobu reactions to prepare aryl ethers in high purity (**Scheme 8, Table 18**).[5] Removal of hydrazide byproducts is readily accomplished using a silica SPE cartridge. PS-Triphenylphosphine resin can be utilized to synthesize olefins via the Wittig reaction (**Scheme 9, Table 19**).[1,6] The resin gave superior results for Wittig reactions when compared to polymer-bound Triphenylphosphine (Fluka, 2 % DVB), in which case starting materials were recovered. PS-Triphenylphosphine may also be used as a scavenger for alkyl halides (**Table 17**).

Representative Procedure for Chlorination (Entry 1, Table 16):

A 2.2 mL solution of benzyl alcohol (15.4 mg, 0.14 mmol) in CCl_4 was added under nitrogen to a reaction vessel containing 214.2 mg of PS-Triphenylphosphine resin (1.35 mmol/g, 0.29 mmol). The mixture was stirred and heated under reflux for 2 h at 80 °C. The product was filtered and the resin was washed with CH_2Cl_2 (3 x 3 mL). GC quantitation (using biphenyl as internal standard) showed that benzyl chloride was produced from the resin in 100% yield and 98% purity (GC).

Representative Procedure for Mitsunobu Reactions (Entry 3, Table 18):

To a reaction vessel containing 1 mL CH_2Cl_2 was added a solution of p-methoxy phenol (0.35 mL, 0.175 mmol) in 2 mL CH_2Cl_2, a solution of benzyl alcohol (0.35 mL, 0.175 mmol) in 2 mL CH_2Cl_2, and 130 mg of PS-Triphenylphosphine resin (1.35 mmol/g, 0.175 mmol). The reaction mixture was stirred for 0.5 h at room temperature and cooled to 0 °C. A solution of DEAD (0.35 mL, 0.175 mmol) in 2 mL CH_2Cl_2 was added to the reaction mixture at 0 °C and then stirred for 16 h at room temperature. The reaction mixture was washed with aq. KOH solution (5 %, 4 mL), followed by 5 % aq. HCl (4 mL). The methylene chloride extract was filtered into a vial and the resin was washed further with CH_2Cl_2 (2 x 4 mL). The solvent was concentrated and the product was purified by filtration through a SPE cartridge (6 mL/ 2 g silica gel, Alltech, Part No. 209202) with 10:1 of hexane/ether. The solvent was concentrated to provide *p*-methoxy-phenyl benzyl ether in 88 % yield (GC purity 96 %). 1H NMR ($CDCl_3$, 300 MHz): δ 7.45- 7.30 (m, 5H, Ar-H), 6.95- 6.83 (m, 4H, Ar-H), 5.03 (s, 2H, CH_2), 3.78 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.01, 152.98, 128.49, 127.82, 127.41, 115.88, 114.65, 70.73, 55.68 ppm

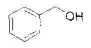
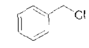
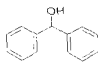
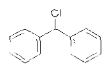
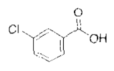
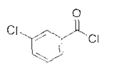
SCHEME 7

$$\text{ROH or RCOOH} \xrightarrow[\text{CCl}_4,\ 80\,^{\circ}\text{C}]{\text{PS-triphenylphosphine (2 equiv)}} \text{RCl or RCOCl}$$

Representative Procedure for Wittig Reactions (Entry 5, Table 19):

1-Iodobutane (0.53 mL, 8.52 mmol) was added to a suspension of PS-Triphenylphosphine (1.42 mmol/g, 3.0 g) in 30 mL DMF and the reaction was stirred for 48 h at 65 °C. The phosphonium resin was washed with DMF (4 x 40 mL), toluene (4 x 40 mL), CH_2Cl_2 (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 addition of 2 mL THF. 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 mixture was 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 2 mL anhydrous THF was added a solution of *p*-methoxy-benzaldehyde (0.2

TABLE 16 Chlorination of Acids and Alcohols using PS-Triphenylphosphine Resin

Entry	ROH or RCOOH	RCl or RCOCl	Yield	GC Purity[1]
1			100%	98%
2			98%	95%
3			100%	100%
4			73%	98%

[1] GC analysis: HP-5 phenylmethylsilicone column 100-280 °C, 15 °C/min, 1 min hold

mL, 0.1 mmol) in 2 mL THF and stirred for 16 h. The reaction mixture was directly diluted with 2 mL hexane and directly applied to a silica SPE cartridge (6 mL/ 1 g silica gel, e.g. Varian Mega Bond Elut Part. No. 12256008), followed by washing twice with 4 mL of 2:1 hexane/ether. The solvent was concentrated to provide the olefin in 94% yield (GC purity 91%).

Representative Procedure for Alkyl Halide Scavenging. (Entry 1, Table 17):

PS-Triphenylphosphine (3.0 equiv) was added to a solution of benzyl bromide (1.0 equiv) in DMF (10 mL/g resin added) and the reaction was stirred at room temperature for 5-16 h. Results by GC analysis indicate > 80% scavenging after 6 h and 100 % scavenging after 16 h. Scavenging reactions may be performed in THF or a THF/DMF mixture (1:1). In these cases, THF was found to give lower scavenging efficiency.

References

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2. Relles, H. M.; Schluenz, R. W. *J. Am. Chem. Soc.* **1974**, 96, 6469.
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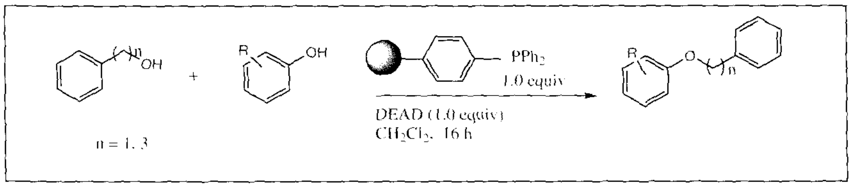
6. Bolli, M. H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1.* **1998**, 15, 2243.

SCHEME 8 Mitsunobu Reaction using PS-Triphenylphosphine Resin



SCHEME 9 Wittig Reaction using PS-Triphenylphosphine Resin

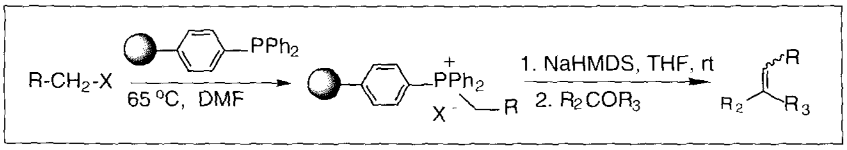
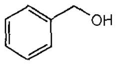
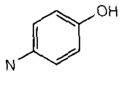
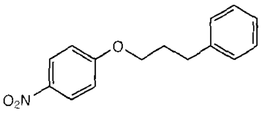
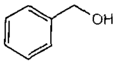
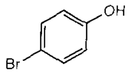
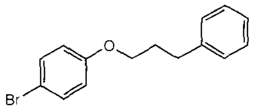
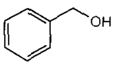
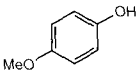
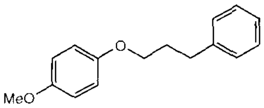
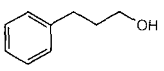
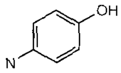
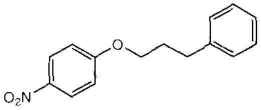
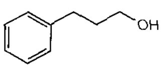
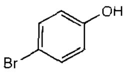
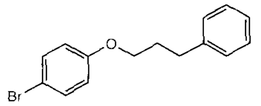
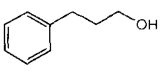
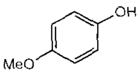
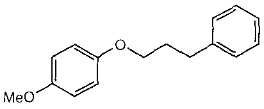


TABLE 17 Comparative Scavenging of Alkyl Halides with PS-Triphenylphosphine Resin (3.0 equiv)

Entry	Material Scavenged	Equiv	Solvent	Temp °C	% Scavenged[1]	Time (h)
1	Ethyl bromoacetate	1.0	DMF	20	100	6 h
2	Benzyl bromide	1.0	DMF	20	100	16 h
3	Cinnamyl chloride	1.0	THF: DMF	50	68	10 h
4	Cinnamyl bromide	1.0	DMF	20	100	16 h

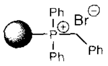
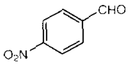
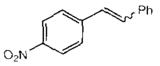
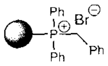
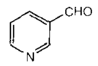
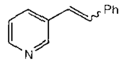
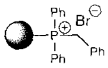
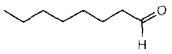
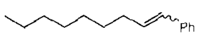
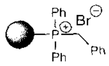
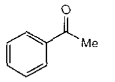
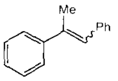
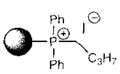
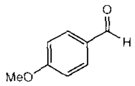
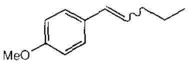
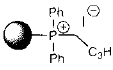
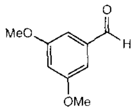
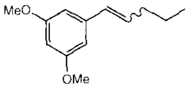
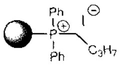
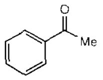
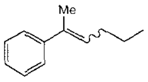
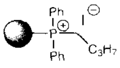
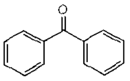
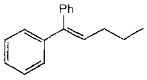
[1] GC analysis: HP-5 phenylmethylsilicone column 100-250 °C, 15 °C/min, 10 min hold.

TABLE 18 Mitsunobu Reaction using PS-Triphenylphosphine Resin

Entry	Alcohol	Phenol	Aryl ether	% Yield (isolated)	GC Purity[1]
1				79	98%
2				80	92%
3				88	98%
4				62	100%
5				68	96%
6				75	100%

[1] GC analysis : HP-5 phenylmethylsilicone column 100-250 °C, 15 °C/min, 10 min hold

TABLE 19 Wittig Reaction using PS-Triphenylphosphine Resin

Entry	Phosphonium resin	Carbonyl compound	Olefin	% Isolated Yield (cis:trans) [1]	GC Purity [2]
1				98% (3:1)	96%
2				81% (5:1)	95%
3				96% (1:1)	81%
4				88% (2:1)	87%
5				94% (2:3)	91%
6				87% (1:3)	98%
7				88% (2:1)	94%
8				82%	99%

[1] Ratio determined by ^{1}H NMR analysis. [2] GC analysis: HP-5 phenylmethylsilicone column 100-250 °C, 15 °C/min, 10 min hold.

PS-DMAP

PS-DMAP is a polymer-bound equivalent of dimethylaminopyridine (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.

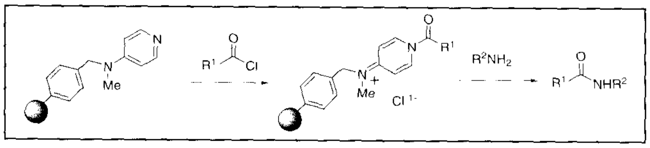
The application PS-DMAP as a catalyst for the esterification of tertiary alcohols was investigated using 1-methylcyclohexanol.[1,2] A 0.5 M solution of cyclohexanol (1 equiv) in toluene was acylated with acetic anhydride (1.64 equiv) in the presence of triethylamine (1.5 equiv) and PS-DMAP (0.1 equiv). The reaction mixture was heated at the reflux temperature overnight. 1-Methylcyclohexane acetate was isolated by filtration, followed by an aqueous workup. Alternatively, MP-Carbonate was added at the completion of the reaction, followed by concentration to remove triethylamine. The results of this reaction are given in **Table 20.** The results indicate the PS-DMAP reaction was 95% complete relative to the 98% complete with DMAP.

TABLE 20

Synthesis of 1-Methylcyclohexyl Acetate

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

SCHEME 10



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.[3,4] Catch and Release involves the reaction of the electrophilic partner 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.[5] The Catch and Release of an acid chloride by an amine is shown in **Scheme 10**. 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 functions with a loading of approximately 0.35 mmole/g for Catch and Release applications.

In Catch and Release applications, PS-DMAP is typically allowed to react with 2 equiv of acyl or sulfonyl halide in dichloromethane for 1 h at room temperature. The resin is then washed with dichloromethane followed by the addition of 0.7 equivalents of amine. After 16 h the product is isolated by filtration and concentration. **Table 21** 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 remained, scavenging may be accomplished with PS-Isocyanate.

Representative Procedure

Alcohol Acylation: One equiv of alcohol (e.g. 3° alcohol) was reacted with acetic anhydride (1.64 equiv), triethylamine (1.5 equiv), and 0.1 equiv PS-DMAP in toluene (17.5 ml/g of resin) and heated at the reflux temperature overnight. After cooling, MP-Carbonate (6 equiv) was added and the mixture was agitated for 4 h. The resin was removed by filtration and washed 2 - 3 x with CH_2Cl_2. 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 equiv) and MP-Carbonate (4 equiv) can be used to work up the reaction.

Catch and Release Amide/Sulfonamide Formation: 1 equiv of PS-DMAP (approximately 0.35 mmol/g capacity) was quaternized with an acid or sulfonyl chloride (2 equiv) in dichloromethane (5

TABLE 21 Amide and Sulfonamide Formation by Catch and Release Using PS-DMAP[1]

R-COCl/$R-SO_2Cl$	Amine[1]	Product Purity (% GC)	% Yield
Benzoyl Cl	Cyclohexylamine	100	82.7
Benzoyl Cl	2,2-Diphenylethylamine	100	82.3
Benzoyl Cl	Piperonylamine	100	80.9
Tosyl Cl	Cyclohexylamine	100	81.9
Tosyl Cl	Benzylamine	100	88.1
Tosyl Cl	Piperonylamine	100	88.5
p-Anisoyl Cl	Benzylamine	100	77.1
p-Anisoyl Cl	Piperonylamine	100	79.8
2-Naphthalene Sulfonyl	Cyclohexylamine	86	68.0
2-Naphthalene Sulfonyl	Benzylamine	100	66.2

mL/g of resin) and mixed at room temperature for 1 h. The resin was washed 5 x with CH_2Cl_2 to remove excess acid and/or sulfonyl chloride. 0.7 equiv of an amine in CH_2Cl_2 (5 mL/g of resin) was added and the reaction mixed at room temperature for 16 h. The product was filtered and the resin washed 3 x with CH_2Cl_2, and the filtrate concentrated to afford the amide or sulfonamide product. This procedure was used to prepare cyclohexyl benzamide and cyclohexyl toluenesulfonamide in 83% and 82% yield, respectively.

References

1. Keay, J. G.; Scriven , E. F. V. *Chem. Ind.*, **1994**, 53, 339.
2. Guendouz, F.; Jacquier, R.; Verducci, J. *Tetrahedron*, **1988**, 44, 7095.
3. Tomoi, M.; Akada, Y.; Kakiuchi, H. *Makromol. Chem., Rapid Commun.*, **1982**, 3,537.
4. Shai, Y.; Jacobson, K. A.; Patchornik, A. *J. Am.Chem. Soc.*, **1985**, 107, 4249.
5. Patchornik, A. *Chemtech*, **1987**, 58.
6. 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.

PS-Carbodiimide

PS-Carbodiimide is a neutral, tethered carbodiimide that may be used for the synthesis of amides, esters, and activated 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)(**Table 22 and 23**). Excess HOBt may be scavenged post reaction using PS-Trisamine resin.[2] PS-Carbodiimide has been found to give superior results relative to a commercial N-Cyclohexylcarbodiimide-N'-Me PS resin[3] (**Figure 9, Table 22**) and the quaternary carbodiimide resin P-EDC.[4] In general, PS-Carbodiimide was found to synthesize amides in high yield and purity without evidence of residual amine or carboxylic acid. The carboxylic acid, normally used in excess relative to the amine, remains bound to the resin during work-up. PS-Carbodiimide may also be used for the synthesis of pentafluorophenyl (PFP) activated esters (**Table 24**) and N-hydroxysuccinimidyl esters.[5] The shelf stability of PS-Carbodiimide at room temperature was found to be superior to the charged P-EDC resin (**Figure 10**), which makes PS-Carbodiimide a reliable and shelf-stable reagent for coupling reactions.

Representative Procedures for Amide Synthesis:

Method A:

PS-Carbodiimide resin (2.0 equiv) was added to a dry reaction vessel. The acid (1.5 equiv) in CH_2Cl_2 (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 equiv) in CH_2Cl_2 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.

Method B:

Amine (1.0 equiv) and acid (1.5 equiv) in CH_2Cl_2 (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 equiv) with a reaction solvent volume of 10 mL/g resin. The reaction was then stirred overnight.

Method C:

PS-Carbodiimide (2.0 equiv), acid (1.5 equiv) and HOBt (1.7 equiv) were dissolved in CH_2Cl_2 and added to a dry reaction vessel and stirred for 5-10 min prior to addition of amine (1.0 equiv). The reaction was stirred at room temperature overnight. After the reaction, the HOBt was scavenged using PS-Trisamine resin (5 equiv) for 2 h at room temperature prior to filtration.

General Procedure for Reaction Workup:

The reaction mixture is filtered and the amide product is collected in the filtrate. The resin is further washed an additional two times with the reaction solvent (CH_2Cl_2 or CH_2Cl_2/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 generally 85+% yield.

FIGURE 9 Structures of Carbodiimide Resins

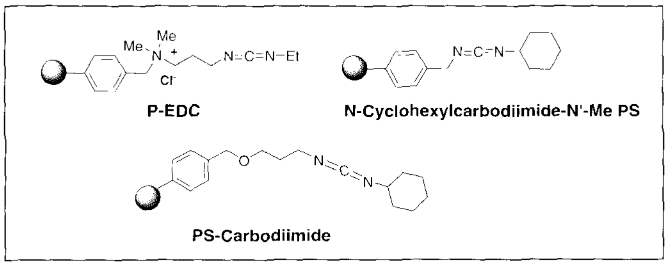
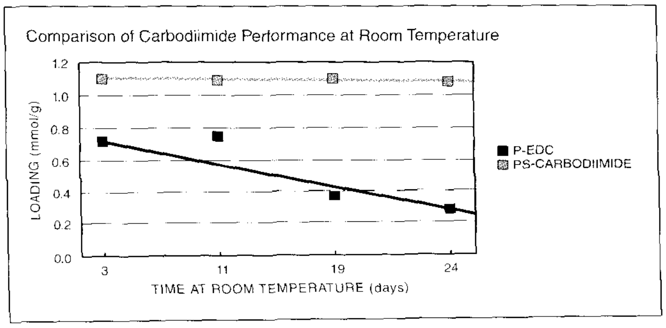


FIGURE 10 Stability of PS-Carbodiimide Relative to P-EDC



*Loading measured by ^1H NMR consumption of AcOH compared to Ac_2O produced.

Representative Procedure for (Pentafluorophenol) PFP Ester Formation:

To a dry reaction vessel PS-Carbodiimide resin (1.6 equiv) was added. The acid (1.3 equiv) in DMF or CH_2Cl_2 was added to the dry resin and the mixture stirred at room temperature for 5 min, followed by addition of PFP (1.0 equiv). After 18 h at room temperature the activated ester product was filtered away from the resin and the resin washed twice with CH_2Cl_2 or DMF. HPLC analysis shows purities for activated esters ranging from 89-98%.

References

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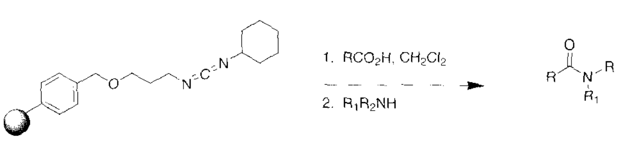
5. Adamczyk, M.; Fishpaugh, J.R.; Mattingly, P.G. *Tetrahedron Lett.* **1995**, 36, 8345.

SCHEME 11 Synthesis of Amides Using PS-Carbodiimide Resin



SCHEME 12 Synthesis of Activated PFP Esters Using PS-Carbodiimide Resin

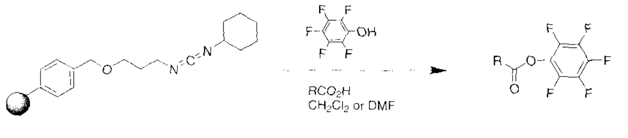


TABLE 22 Amide Formation Results (Method A) for Three Different Carbodiimide Resins

Entry	Resin	Acid	Amine	HPLC Purity[1]	GC Amine[2] 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	PS-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	96	18	75
12	P-EDC	3-Iodobenzoic acid	1,2,3,4-tetrahydroisoquinoline	97	10	73
13	**PS-Carbodiimide**	**Boc-Phe**	**3,5-dimethylaniline**	**100**	**0**	**89**
14	N-Cyclohexyl-N'Me	Boc-Phe	3,5-dimethylaniline	98	0	83
15	P-EDC	Boc-Phe	3,5-dimethylaniline	96	0	76

[1] HPLC analysis: Microsorb C18 3 μ (100 A°) column. $CH_3CN:H_2O$ with 0.1% TFA, 10-100%, 10 min

[2] GC analysis: HP-5 phenylmethylsilicone column 120-300 °C, 20 °C/min, 10 min hold

TABLE 23 Amide Formation Using PS-Carbodiimide (Methods B and C)

Entry	Method	Acid	Amine	HPLC Purity[1]	GC Amine[2] 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

[1] HPLC analysis: Microsorb C18 3 µ (100 A^{0}) column. $CH_3CN:H_2O$ with 0.1% TFA, 10-100%, 10 min

[2] GC analysis: HP-5 phenylmethylsilicone column 120-300 ^{0}C, 20 ^{0}C/min, 10 min hold

TABLE 24 PFP Ester Formation Using PS-Carbodiimide

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

[1] HPLC analysis: Microsorb C18 3 µ (100 A^{0}) column. $CH_3CN:H_2O$ with 0.1% TFA, 10-100%, 10 min

PS-HOBt

PS-HOBt is a resin-bound equivalent of 1-hydroxybenzotriazole (HOBt) which is attached via a sulfonamide linkage.[1] The loading capacity of PS-HOBt is determined by quantitation of N-benzylbenzamide generated by coupling benzoic acid and excess benzylamine (GC, internal standard method). The resin reacts readily with carboxylic acids in the presence of PyBrOP and DIEA to give a variety of functionalized polymers which can be used as acylation reagents for amines in organic synthesis (**Scheme 13**).[1-5] We have found that in the cleavage of resin-bound activated esters with amines the use of DIEA improves the overall reaction yield. In most cases, amides are formed in high purity and no further purification is needed (**Table 25**). PS-HOBt may also be used for the protection of amines (**Scheme 14**). This resin is an effective activating reagent for transfer of protecting groups, e.g. Fmoc and Cbz, to amines (**Table 26**).[6] Resin-bound activated esters and protecting groups can be stored at 0-5 °C for extended periods. PS-HOBt is stable and recyclable which makes it attractive for use in automated synthesis. The resin is ready for re-use after washing to remove any remaining reagents (**Table 27**).

Representative Procedure: Synthesis of Amides

(Entry 1, Table 25)

A solution of 2,2-diphenylpropionic acid (102 mg, 0.45 mmol), PyBrOP (201 mg, 0.43 mmol) and DIEA (207 mμL, 1.2 mmol) in 1.5 mL DMF was added under nitrogen to a reaction vessel containing 230 mg of PS-HOBt resin (0.9 mmol/g, 0.2 mmol). The mixture was stirred for 5 h at 25 °C. The reaction mixture was drained and the resin washed with DMF (3 x). A further 1.5 mL solution of 2,2-diphenylpropionic acid (102 mg, 0.45 mmol), PyBrOP (201 mg, 0.43 mmol) and DIEA (207 mμL, 1.2 mmol) in DMF was added, and the mixture was stirred for 5 h at 25 °C. The resin was then washed with DMF (5 x). A solution of benzylamine (17 mg, 0.16 mmol) and DIEA (144 μL, 0.83 mmol) in 1.7 mL CH_2Cl_2 was added, and the mixture was stirred for 20 h at 25 °C. Finally, the solution was filtered into a pre-weighed vial (three CH_2Cl_2 washes to rinse product from the resin). The solvent was then concentrated to give benzyl-2,2-diphenylpropionylamide in 100% yield (GC purity 100%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.10 (m, 15 H, Ar-H), 5.75 (s, 1 H, N-H), 4.45 (d, 2 H, CH_2), 2.05 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.95, 144.94, 138.22, 128.61, 128.50, 128.14, 127.38, 127.33, 126.97, 57.07, 43.90, 27.19 ppm.

Representative Procedure: Protection of Amines as Fmoc Derivatives

(Entry 1, Table 26)

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 CH_2Cl_2 were added to a reaction vessel. A solution of pyridine (65 mg, 0.82 mmol) in 1.2 mL CH_2Cl_2 was then added. The mixture was stirred for 1 h at 25 °C. The reaction mixture was drained and the resin washed with CH_2Cl_2 (3 x), DMF (3 x), CH_2Cl_2 (3 x) and diethyl ether (3 x). A solution of benzylamine (14 mg, 0.13 mmol) in 3.2 mL CH_2Cl_2 was added, and the mixture was stirred for 20 h at 25 °C. Finally, the solution was filtered into a pre-weighed vial (washed with CH_2Cl_2 (3 x) to rinse product from the resin). The solvent was then concentrated to give Fmoc-benzylamine in 78% yield (HPLC purity 99%). ^1H NMR ($CDCl_3$, 300 MHz): δ 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, CH_2), 4.40 (d, 2 H, CH_2), 4.25 (t, 1 H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 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.

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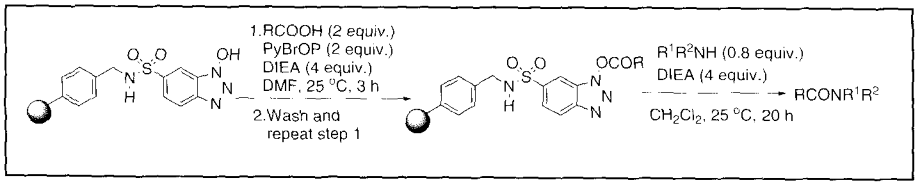
6. Dendrinos, K. G.; Kalivretenos, A. G., *J. Chem. Soc.*, Perkin Trans 1 **1998**, 1463.

SCHEME 13



SCHEME 14

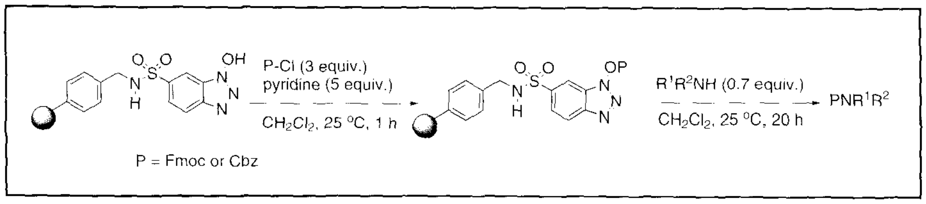


TABLE 25 Synthesis of Amides using PS-HOBt Resin

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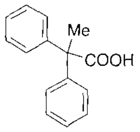
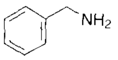
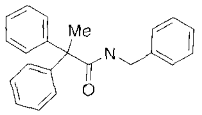
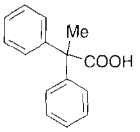
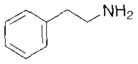
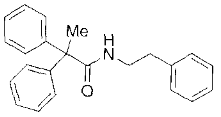
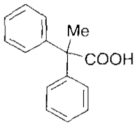
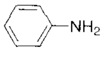
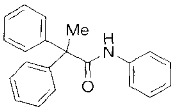
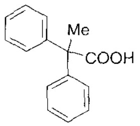
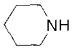
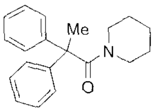
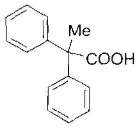
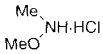
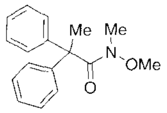
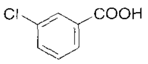
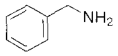
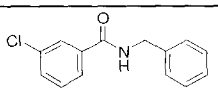
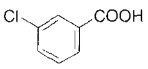
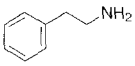
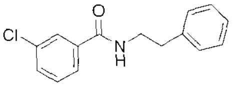
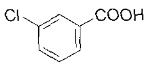
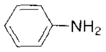
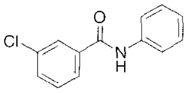
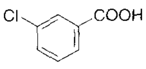
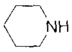
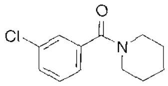
1				100%	100%
2				100%	99%
3				92%	98%
4				100%	99%
5				51%[a]	87%
6				89%	95%
7				82%	98%
8				68%	100%
9				88%	100%

[a] The combined filtrate and washings were treated with 0.5 g of (3.18 mmol/g) MP-Carbonate in CH_2Cl_2 for 1 h at room temperature to remove the DIEA•HCl complex. The mixture was then filtered and concentrated.

TABLE 26 Protection of Amines using PS-HOBt Resin

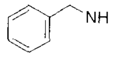
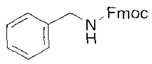
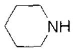
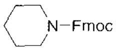
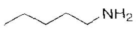
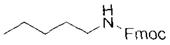
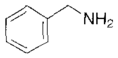
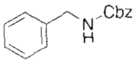
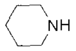
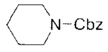
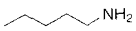
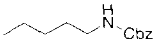
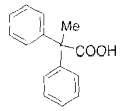
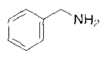
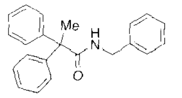
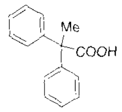
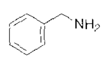
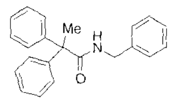
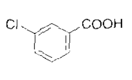
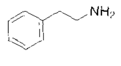
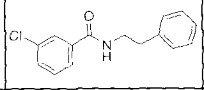
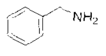
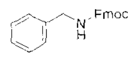
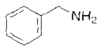
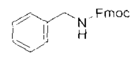
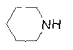
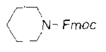
Entry	Protecting Group P-Cl	Amine R^1R^2NH	Protected Amine PNR^1R^2	Yield	HPLC Purity
1	Fmoc-Cl			78%	99%
2	Fmoc-Cl			75%	100%
3	Fmoc-Cl			76%	100%
4	Cbz-Cl			87%	97%
5	Cbz-Cl			42%	95%
6	Cbz-Cl			70%	95%

TABLE 27 Recycling PS-HOBt Resin

Resin	Cycle	Acid RCOOH or Protecting Group P-C1	Amine R^1R^2NH	Amide $RCONR^1R^2$ or Protected Amide PNR^1R^2	Yield	Purity
A	1				86%	100%[c]
A[a]	2				100%	100%[c]
A[b]	3				80%	98%[c]
B	1	Fmoc-C1			77%	93%[d]
B[a]	2	Fmoc-C1			100%	100%[d]
B[a]	3	Fmoc-C1			81%	97%[d]

[a] Washed with CH_2Cl_2 (3 x) before use. [b] Treated with excess isopropylamine in CH_2Cl_2 and then washed with CH_2Cl_2 (3 x), MeOH (3 x), DMF (3 x), NMP (3 x), MeOH (3 x), CH_2Cl_2 (3 x) and Et_2O (3 x) before use (ref. 5). [c] GC purity. [d] HPLC purity.

PS-TsCl

PS-TsCl is a chlorosulfonated polystyrene resin that is a resin-bound equivalent of tosyl chloride and has a loading 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.[1-6]

PS-TsCl can be employed in Catch and Release applications, where soluble substrates are reacted with PS-TsCl to form an activated polymer intermediate, e.g. a tosylate. After purification by washing, the polymeric intermediate is subjected to a second transformation that releases a new product from the resin. This has been applied to synthesis of tertiary amines as described below.

Loading of primary alcohols to PS-TsCl resin typically requires reaction with a 3 - 5 equiv of alcohol for 5 h at room temperature in CH_2Cl_2/pyridine solvent mixture (1:1, 100 mg resin/mL) under an inert atmosphere. The resin is washed with DCM (3 x), DMF (5 x), DMF/H_2O (3:1, 5 x), THF (3 x), DCM (3 x), and dried under vacuum.

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 (3 x), DMF (3 x), DMF/H_2O (3:1, 3 x), THF (3 x). 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 (3 x, DCM (3 x), THF (3 x), then stained with a few drops of bromophenol blue (1% in dimethylacetamide). The beads are further washed with DMF (5 x). 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 equiv of secondary amine in the presence of 6 equiv of diisopropylethylamine in CH_3CN at 70 °C for 18 h, or 80 °C for 8 h. Alternatively, cleavage using volatile secondary amines may be performed using 6 equiv 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 15)**, with the results for representative examples given in **Table 28**. 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 Experimental Procedures

(**Entry 1, Table 28**): To a reaction vessel containing 75 mg of PS-TsCl resin, (1.47 mmol/g, 0.11 mmol) under argon, 3 mL of a 4-methoxyphenyl-1-butanol (178 µL, 1.05 mmol) was added in DCM/pyridine (1:1). The mixture was stirred for 5 h. The resin was then washed with DCM (3 x), DMF (5 x), DMF/H_2O (3:1, 5 x), THF (3 x), DCM (3 x) and dried under vacuum. A solution of 1-phenylpiperazine (31 µL, 0.21 mmol) and N,N-diisopropylethylamine

(107 µL, 0.63 mmol) in 3 mL acetonitrile, was added and the mixture was heated at 70 °C for 18 h. Finally, 255 mg of PS-Isocyanate resin (1.21 mmol/g, 0.31 mmol) was added, with 2 mL of THF. After 3 h, the solution was filtered into a pre-weighed vial (three THF washes to rinse product from the resin). The solvent was then concentrated to give 1-phenyl-4-(4-methoxyphenyl)butylpiperazine in 98% yield (GC purity 100%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33-6.81 (m, 9 H, Ar-H), 3.79 (s, 3 H, CH_3O), 3.27 (m, 4 H), 2.72-2.41 (m, 8 H), 1.63 (m, 4 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.69, 150.88, 134.12, 129.12, 129.02, 119.90, 116.11, 113.61, 58.05, 55.00, 52.66, 48.37, 34.45, 29.11, 25.39 ppm.

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2. Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, 39, 979.
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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.

SCHEME 15

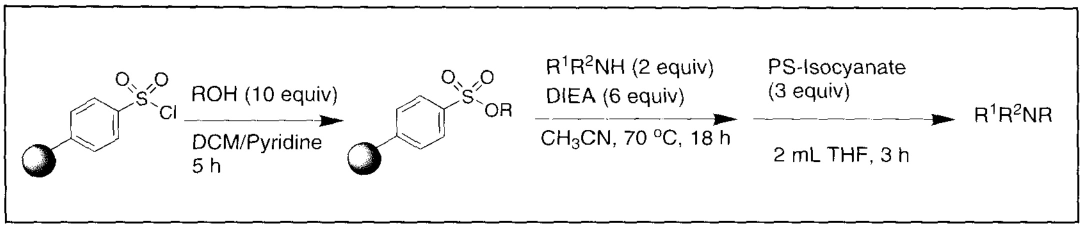
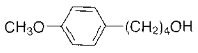
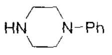
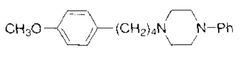
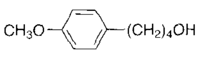
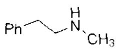
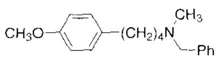
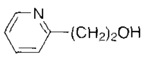
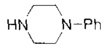
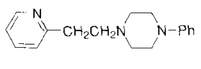
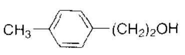
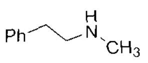
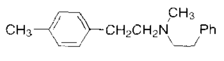


TABLE 28 Synthesis of Tertiary Amines from Alcohols using PS-TsCl

Entry	ROH	R¹R²NH	R¹R²NR	Yield	GC Purity
1				98%	100%
2				99%	100%
3				99%	100%
4				97%	100%