POLYMER REAGENTS AND SCAVENGERS
FOR PARALLEL SOLUTION PHASE SYNTHESIS & PURIFICATION

INTRODUCTION

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.

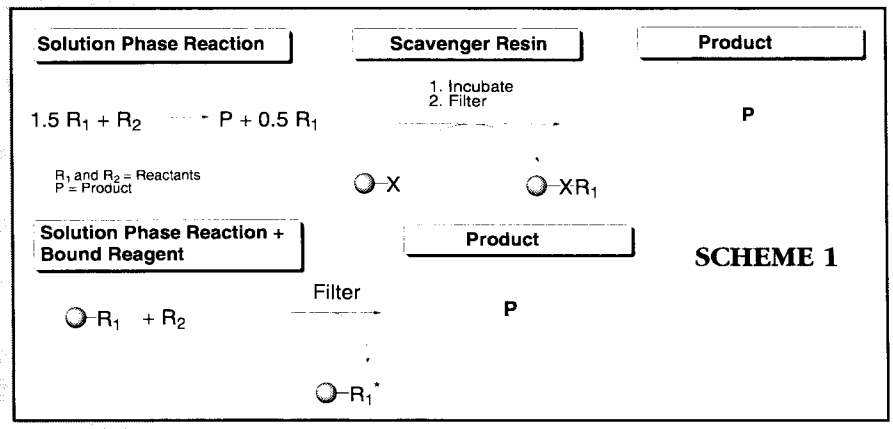
This technical paper includes background information for this methodology and provides specific product information, including scope of reactivity and detailed procedures for use in model applications.

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 1**.



SCHEME 1

A bound reagent is present during the reaction and allows removal of both unreacted and spent reagent by filtration (**Scheme 1**). Properly designed bound reagents will often perform in a manner similar to their small molecule equivalents with minimal optimization for a given synthetic transformation.

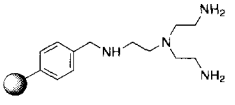
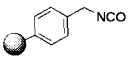
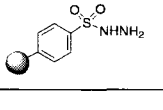
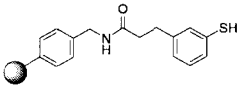
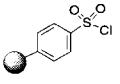
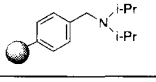
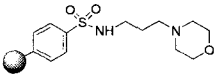
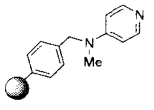
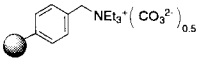
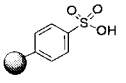
Bound reagents and/or scavengers may be used individually or in concert to simplify reaction workups and

ARGONAUT TECHNOLOGIES

Overview of Argonaut's Chemistry Products for Parallel Solution Phase Synthesis and Purification

To meet the growing demand from chemists seeking to increase their use of parallel chemistry, Argonaut Technologies has introduced the set of polymer scavengers and reagents shown in **Table 1**. These products enable parallel solution phase reactions in the medicinal chemistry laboratory. Detailed product information, including specific product descriptions, scope of reactivity and procedures for use are provided in the following sections. A brief overview of the products is provided below.

TABLE 1. Chemistry Products for Parallel Solution Phase Synthesis and Purification

Product Name[1]	Structure	Function
PS-Trisamine		Scavenge electrophiles: acid chlorides, sulfonyl chlorides, isocyanates
PS-Isocyanate		Scavenge nucleophiles: amines, thiols, alkoxides, organometallics
PS-TSNHNH$_2$		Scavenge carbonyl compounds: aldehydes, ketones
PS-Thiophenol		Scavenge alkylating agents: halides, mesylates, tosylates, α,β-unsaturated carbonyls
PS-TsCl		Bound tosyl chloride equivalent: "catch and release" of alcohols
PS-DIEA		Tertiary amine base: bound DIEA equivalent
PS-NMM		Tertiary amine base: bound N-methylmorpholine equivalent (non-benzylic)
PS-DMAP		Bound dimethylaminopyridine: acylation catalyst, acid and sulfonyl halide "catch and release"
MP-Carbonate		General base: quenching reagent, neutralization of amine hydrochlorides, scavenging acids and acidic phenols
MP-TsOH		General acid: quenching reagent, amine scavenger, amine "catch and release"

1. The product name designates the resin type and the comparable small molecule reagent (PS: lightly crosslinked polystyrene, MP: macroporous polystyrene).

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 **Table 1** and the accompanying detailed product descriptions. The capacity of each resin has bee determined by measurement of the uptake of a model substrate to better reflect the scav-

enging 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

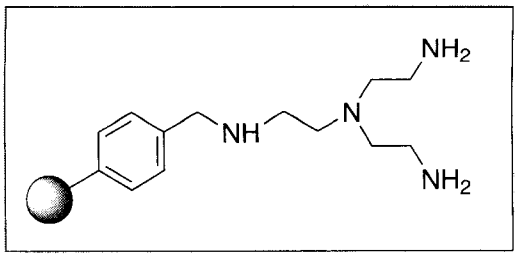
MP-TsOH and MP-Carbonate are quite useful in a number of capacities as a bound acid and base, respectively. These can be used to quench and purify reactions, analgous to an aqueous acid or base extraction. MP-Carbonate is quite useful for neutralizing amine hydrochloride and carboxylate salts in reagent 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.
5. Parlow, J. J. *Tetrahedron Lett.* **1995**, 1395.
6. Deegan, T. L.; Gooding, O.W.; Baudart, S.; Porco, J. A., Jr. *Tetrahedron Lett.* **1997**, *38*, 4973.
7. Brown, S. D.; Armstrong, R.W. *J.Am. Chem. Soc.* **1996**, *118*, 6331.

PRODUCT INFORMATION

Product: PS-Trisamine



Chemical Name: Tris-(2-aminoethyl)amine polystyrene
Capacity: 3 - 4 mmol/g (based on benzoyl chloride uptake)
Resin Type: 1% crosslinked Poly(styrene-*co*-divinylbenzene)
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
Recommended Agitation: Gentle magnetic stirring, swirling or overhead stirring for large resin quantities (>5g)

Part #	Quantity
800228	10 g
800229	25 g
800230	100 g

Representative Procedure:
Acid Chloride Scavenging

Reaction: The application of PS-Trisamine in amide synthesis was tested by reacting an acid chloride (1.5 equiv, 0.60 mmol) with benzylamine (44 µL, 0.40 mmol) in the presence of pyridine (97 µL, 1.2 mmol) in 2 mL of CH_2Cl_2 for 1 h at RT.

Reaction Workup: 6 equiv of PS-Trisamine, relative to excess acid chloride, was added to the reaction mixture and agitated for 3 h. The resin was removed by filtration and washed 3 × with CH_2Cl_2 .The filtrate was concentrated to afford the desired amide. This procedure was used to prepare benzyl 2,6-dimethoxybenzamide as the sole product in 97% yield.

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 2**).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.

TABLE 2. 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

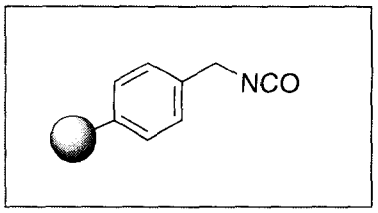
1) Relative to electrophile, no additional base present

References

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

PRODUCT INFORMATION

Product: PS-Isocyanate



Chemical Name: Polystyrene methylisocyanate
Capacity: 1.0 - 1.7 mmol/g (based on benzylamine uptake)
Resin Type: 1% crosslinked Poly(styrene-*co*-divinylbenzene)
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
Recommended Agitation: Gentle magnetic stirring, swirling or overhead stirring for large resin quantities (>5 g)

Part #	Quantity
800260	10 g
800261	25 g
800262	100 g

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 1**, on next page). 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 3**). Typical aliphatic amines are completely sequestered by two equiv of PS-Isocyanate within 1 h. Two equiv of PS-Isocyanate sequestered 89% and 99% aniline at room temperature and 60 °C for 16 h, respectively. Complete removal of aniline would likely occur at room temperature with 3 - 4 equiv of PS-Isocyanate. 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

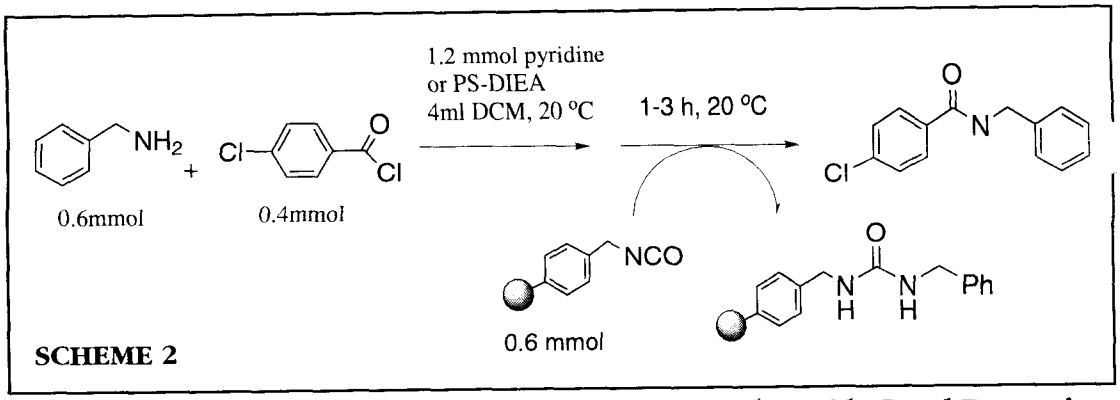
TABLE 3. Comparative Scavenging of Nucleophiles in Dichloromethane

Nucleophile Scavenged	PS-Isocyanate (equiv)	Temp (°C)	% Scavenged 1 h	16 h
piperidine	3.0	20	100	-
benzyl amine	3.0	20	100	-
aniline	2.0	20	19	89
aniline	3.0	60[1]	-	99
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

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 benzyl amine in the presence of PS-DIEA resin as base (**Scheme 2, Table 4**). 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 gravimetrically and the purities by GC. PS-Isocyanate was also used to sequester excess secondary amines in the preparation of tertiary amines using PS-TsCl (see PS-TsCl product information).

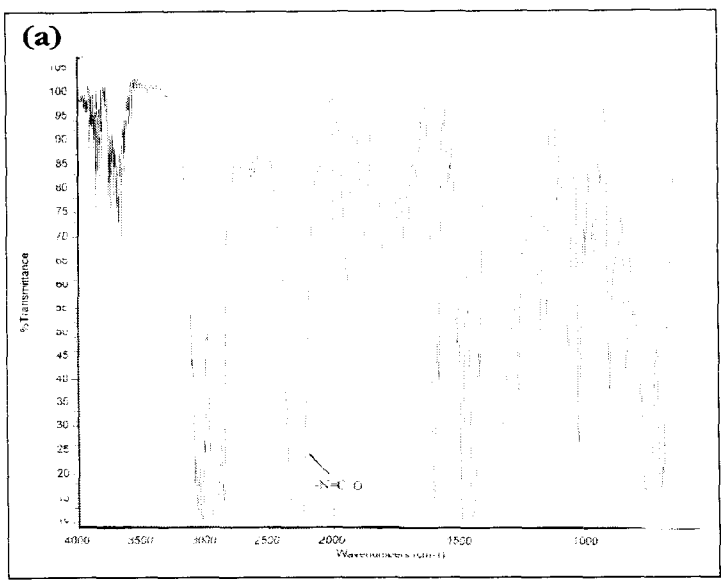


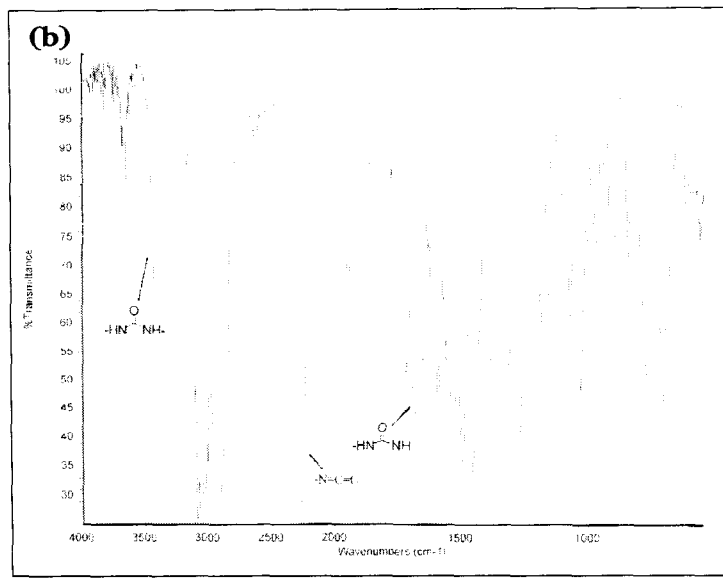
SCHEME 2

TABLE 4. 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 1. 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.





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.

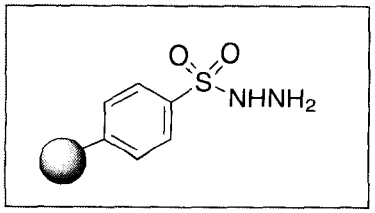
Reaction Workup: The excess benzylamine was scavenged by adding PS-Isocyanate resin (3 equiv relative to excess amine). The beads were removed by filtration, washed 2 × with CH_2Cl_2 and the combined filtrate was concentrated to afford the benzyl 4-chlorobenzamide as the sole product in 87 % yield.

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.
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.

PRODUCT INFORMATION

Product: PS-TsNHNH$_2$



Product: Polystyrene sulfonyl hydrazide
Capacity: 1.8 - 3.2 mmol/g (based on benzaldehyde uptake)
Resin Type: 1% crosslinked Poly(styrene-*co*-divinylbenzene)
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
Recommended Agitation: Gentle magnetic stirring, swirling or overhead stirring for large resin quantities (>5 g)

Part #	Quantity
800270	10 g
800271	25 g
800272	100 g

Representative Procedure: Alcohol Formation by Addition of Butyl Grignard to Hexanal

Reaction: Butylmagnesium chloride (1 equiv) in THF was added to excess hexanal (2 equiv).

Reaction Workup: To the reaction was added 1 equiv of acetic acid, relative to butylmagnesium chloride, and 3 equiv of PS-TsNHNH$_2$, relative to excess hexanal. The mixture was agitated for 2 h, filtered and the resin was washed 2 × with THF. The combined filtrates were concentrated to afford 5-decanol as the sole product in 97% yield. For less reactive carbonyl compounds, acetic acid was added to bring the concentration to 10% for scavenging. Excess acetic acid can be removed *in vacuo* or by the addition of MP-Carbonate.

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 and ketone scavenging examples are presented in **Table 5**. PS-TsNHNH$_2$ was successfully used to workup 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]

TABLE 5. Comparative Scavenging Times in Dichloromethane

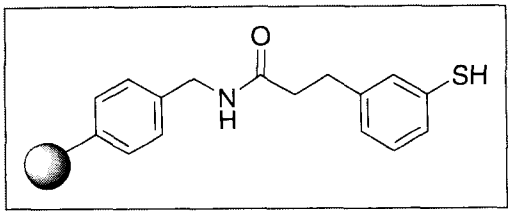
Carbonyl Substrates	PS-TsNHNH$_2$ (equiv)	Additive	Time (h)	% Scavenged
Benzaldehyde	3	-	1	100
Hexanal	3	-	1	100
2,6-Dimethoxybenzaldehyde	3	-	1	100
Cyclohexanone	3	Acetic Acid	1	100
Acetophenone	3	Acetic Acid	8	100
2,6-Dimethylcyclohexanone[1,2]	3	Acetic Acid (70 °C)	10	85

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.

Product Information

Product: PS-Thiophenol



Chemical Name: 3-(3-mercaptophenyl)propanamidomethylpolystyrene
Capacity: 1.0 - 1.5 mmol/g (based on benzyl bromide uptake)
Resin Type: 1% crosslinked poly(styrene-*co*-divinylbenzene)
Application: Scavenging alkylating agents
Disulfide Reduction: The resin is treated with a 0.7 M tributylphosphine solution (95:5 THF/water) for 0.5 - 1 h, followed by washing with 3 × THF (deoxygenated) to reduce sulfides.
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. The ethanol is added for the scavenging process and may provide benefit in solvents other than THF.
Compatible Solvents: DMF (7.0 mL/g), THF (7.0 mL/g) , CH_2Cl_2 (7.0 mL/g), and other swelling solvents
Recommended Agitation: Gentle magnetic stirring, swirling or overhead stirring for large resin quantities (>5 g)

Part #	Quantity
800273	10 g
800274	25 g
800275	100 g

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

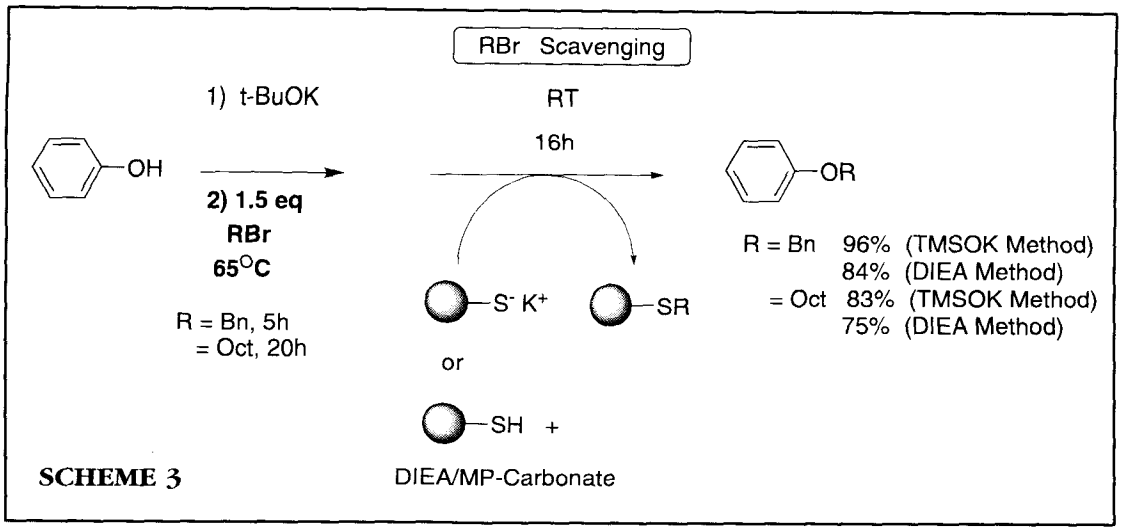
As a precautionary measure, PS-Thiophenol is typically prepared for use by reduction with a 0.7 M tributylphospine solution (95:5, THF/water) to cleave disulfide linkages that may be present. PS-Thiophenol treated in this fashion has been found to be unchanged for several weeks (longer term stability studies in progress).

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 × 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.

PS-Thiophenol continued.....

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 6**.



SCHEME 3

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.

TABLE 6. 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.

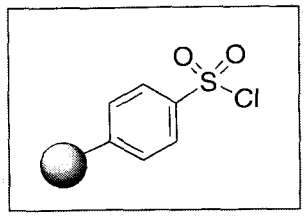
Representative Procedure: Scavenging Excess Electrophiles from Williamson Ether Synthesis

Reaction: To a 0.2 M solution of phenol (57 mg, 0.60 mmol) in THF was added 0.41 mL of 1.61 M potassium t-butoxide (0.66 mmol). After 0.5 h 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 × 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 × 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 × 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.

Product Information

Product: PS-TsCl



Chemical Name: Polystyrene sulfonyl chloride
Capacity: 1.0 - 2.0 mmol/g (based on sulfur analysis)
Resin Type: 1% crosslinked Poly(styrene-*co*-divinylbenzene)
Application: Loading of alcohols and 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
Recommended Agitation: Gentle magnetic stirring, swirling or overhead stirring for large resin quantities (>5 g)

Part #	Quantity
800276	10 g
800277	25 g
800278	100 g

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 ×), DMF (5 ×), DMF/H_2O (3:1, 5 ×), THF (3 ×), DCM (3 ×), and dried under vacuum.

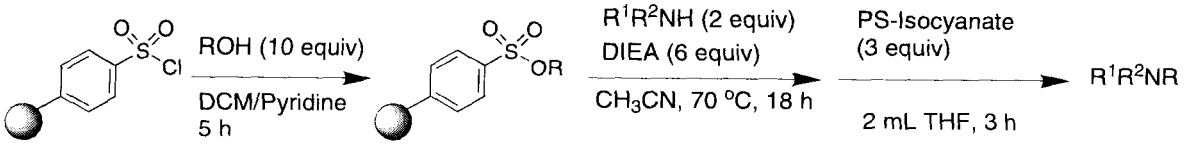
The sulfonate formation may be monitored using a simple bead staining test. To check for residual sulfonyl chloride groups on the resin, a few beads may be sampled from the alcohol loading reaction, and the beads washed with DCM (3 ×), DMF (3 ×), DMF/H_2O (3:1, 3 ×), THF (3 ×). The resin is then treated 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 ×), DCM (3 ×), THF (3 ×), then stained with a few drops of bromophenol blue (1% in dimethylacetamide). The beads are further washed with DMF (5 ×). 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 4**), with the results for representative examples given in **Table 7**. PS-Isocyanate was used to sequester excess secondary amine from the sulfonate

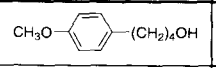
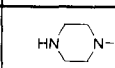
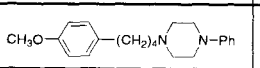
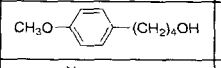
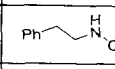
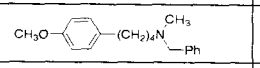
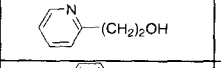
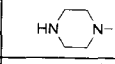
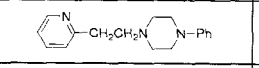
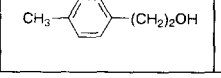
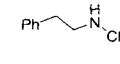
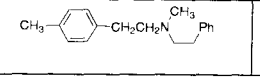
PS-TsCl continued.....

SCHEME 4



displacement reaction. This expedited approach afforded tertiary amine products in high yield and purity while circumventing extractions and chromatography in product isolation and purification.

TABLE 7. Synthesis of Tertiary Amines from Alcohols using PS-TsCl

Entry	ROH	R^1R^2NH	R^1R^2NR	Yield	GC Purity
1				98%	100%
2				99%	100%
3				99%	100%
4				97%	100%

Representative Experimental Procedures (entry 1, Table 7): 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 ×), DMF (5 ×), DMF/H_2O (3:1, 5 ×), THF (3 ×), DCM (3 ×) 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)butyl-piperazine in 98% yield (GC purity 100%). 1H 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.

References

1. Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 975.
2. Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 979.
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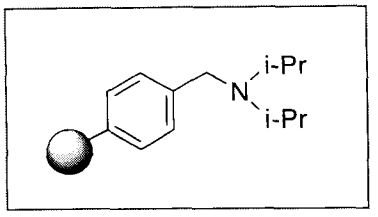
6. Takahashi, T.; Ebata, S.; Doi, T. *Tetrahedron Lett.* **1998**, *39*, 1369.

PRODUCT INFORMATION

Product: PS-DIEA



Chemical Name: N,N-(Diisopropyl)aminomethylpolystyrene (1% inorganic antistatic agent)
Capacity: 3 - 4 mmol/g (based on nitrogen analysis)
Resin Type: 2% crosslinked Poly(styrene-*co*-divinylbenzene)
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)
Recommended Agitation: Gentle magnetic stirring, swirling or overhead stirring for large resin quantities (>5 g)

Part #	Quantity
800279	10 g
800280	25 g
800281	100 g

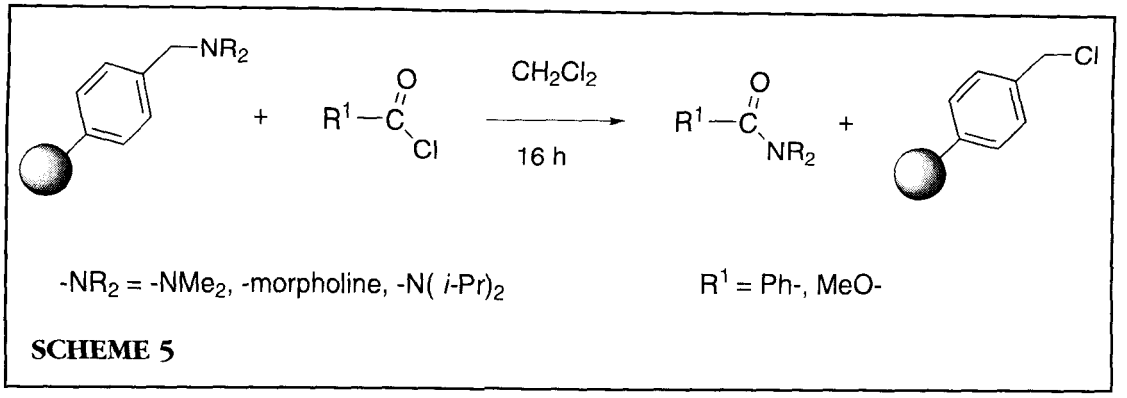
PS-DIEA is a high loading tertiary amine base which is a resin-bound equivalent of diisopropylethylamine. PS-DIEA is useful in applications requiring a tertiary amine base, where the resin-bound ammonium salt byproducts are readily separated by filtration.[1] Synthesis of amides, sulfonamides and carbamates 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 on next page**). The results showed good correlation between steric hindrance and amine stability (**Table 8 on next page**). 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 on next page**).[4] The use of 3 equiv of PS-DIEA afforded complete conversion to the desired mesylate in 95 % isolated yield. Reaction workup

PS-DIEA continued..... 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.



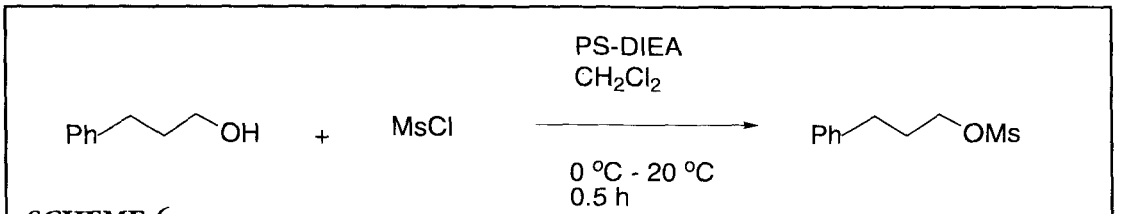
SCHEME 5

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 × 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.

TABLE 8. 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

References

1. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.
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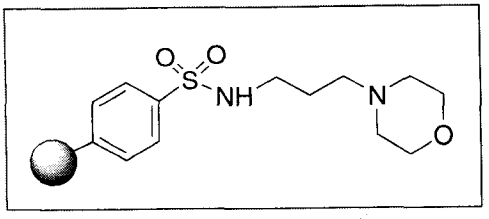
3. Yang, B. V.; OíRoarke, D.; Li J. *Synlett.* **1993**, 195.
4. Gooding, O. W.; Bansal, R. P. *Synth. Comm.* **1995**, *25*, 1155.

PRODUCT INFORMATION

Product: PS-NMM



Chemical Name: 3-(Morpholino)propyl polystyrenesulfonamide
Capacity: 1.5 - 2.5 mmol/g based on nitrogen analysis.
Resin-Type: 1% crosslinked poly(styrene-*co*-divinylbenzene)
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)
Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

Part #	Quantity
800282	10 g
800283	25 g
800284	100 g

Representative procedure
Amide Formation: A reaction vessel was charged with 0.66 g (1.2 mmol, 3 equiv) of PS-NMM resin, followed by 6 mL of CH_2Cl_2. Benzylamine (66 µL, 0.6 mmol, 1.5 equiv) and 4-chlorobenzoyl chloride (51 µL, 0.4 mmol, 1.0 equiv) were added sequentially and the reaction was agitated for 2 h at RT. 0.3 g (0.4 mmol, 2 equiv) of PS-Isocyanate was then added and the reaction mixed for a further 2 h. The product was filtered, the resin washed 2 × CH_2Cl_2 and 1 × THF, and the combined filtrates concentrated to afford to N-benzyl-4-chlorophenyl carboxamide (94.2%, 100% purity by GC).

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 morpholinomethyl 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 9**. 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.

TABLE 9. 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]

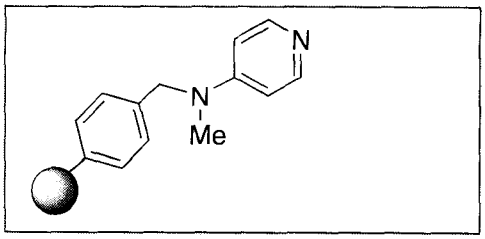
1) Morpholinomethyl polystyrene, 2) Contains 4.2 area % Methyl morpholine carbamate, 3) Contains 16.4 area % Methyl morpholine carbamate

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.; OíRoarke, D.; Li J. *Synlett* **1993**, 195.

PRODUCT INFORMATION

Product: PS-DMAP



Chemical Name: N-(Methylpolystyrene)-4-(methylamino)pyridine

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.

Resin Type: 4% crosslinked Poly(styrene-*co*-divinylbenzene)

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 magnetic stirring, swirling or overhead stirring for large resin quantities (>5 g)

Part #	Quantity
800288	10 g
800289	25 g
800290	100 g

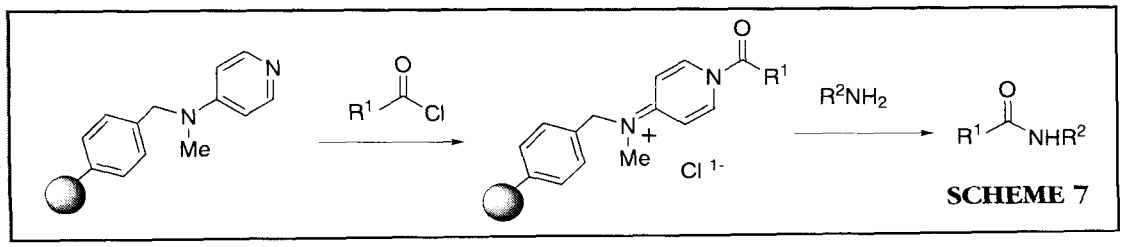
PS-DMAP is a polymer-bound equivalent of dimethylaminopyridine (DMAP) which may be used as a catalyst for acylation and related reactions. Typical catalysis conditions require 10 - 20 mol% relative to the nucleophile. Catalytic PS-DMAP accelerates the acylation of sluggish nucleophiles, *e.g.* tertiary 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 10**. The results indicate the PS-DMAP reaction was 95% complete relative to the 98% complete with DMAP.

TABLE 10. Synthesis of 1-Methylcyclohexyl Acetate

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

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 electrophillic 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 7**. 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.



SCHEME 7

PS-DMAP continued.....

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 11** 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.

TABLE 11. 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

1) Catch: PS-DMAP = 0.35 mmol/g, 2 equiv R-COCl/R-SO_2Cl, dichloromethane 1 h. Release: 0.7 equiv amine, dichloromethane, 16 h, room temperature.

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 × 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:

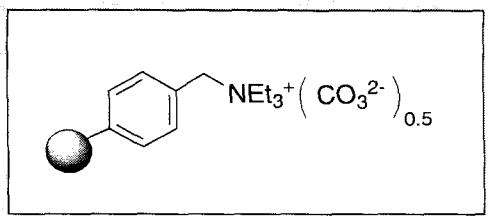
1 equiv of PS-DMAP (approximately 0.35 mmol/g capacity) was quaternized with an acid or sulfonyl chloride (2 equiv) in (5 mL/g of resin) and mixed at room temperature for 1 h. The resin was washed 5 × with CH_2Cl_2 to remove excess acid and/or sulfonyl chloride. 0.7 equiv of an amine in CH_2Cl_2 (5 mL/g of resin) was added and the reaction mixed at room temperature for 16 h. The product was filtered and the resin washed 3 × 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.

PRODUCT INFORMATION

Product: MP-Carbonate



Product: Macroporous triethylammonium methylpolystyrene carbonate (1% inorganic antistatic agent)

Capacity: 2.5 - 3.5 mmol/g (based on nitrogen elemental analysis)

Resin Type: Macroporous poly(styrene-*co*-divinylbenzene)

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 (2.9mL/g)

Recommended Agitation: Strong 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 the Quest 210. Optimal mixing may be achieved with MP-Carbonate in cartridges or filter plates using rotatory or orbital mixing.

Part #	Quantity
800267	10 g
800268	25 g
800269	100 g

Representative Procedure: Neutralization of Amine Hydrochloride Salt of Ephedrine.

Reaction: Ephedrine hydrochloride salt (1 equiv) was converted to the free amine with MP-Carbonate (4 equiv) in CH_2Cl_2 or Methanol for one hour. Since ephedrine hydrochloride is not soluble in CH_2Cl_2, a catalytic amount of DIEA (0.05 equiv) was added as a transfer base and was removed during sample concentration.

Reaction Workup: The resin was removed by filtration and washed 2 × with CH_2Cl_2. The filtrate was concentrated to give ephedrine in 100% yield (MeOH) and 82% yield (CH_2Cl_2) (NMR purity: 100%).

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 12**.

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 later 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.

TABLE 12. 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

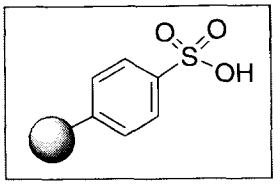
References

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

MP-TsOH resin is a sulfonated macroporous polystyrene resin that is a resin-bound equivalent of *p*-toluenesulfon-

PRODUCT INFORMATION

Product: MP-TsOH



Chemical Name: Macroporous polystyrene sulfonic acid (1% inorganic antistatic agent)
Capacity: 1.1 - 1.6 mmol/g based on uptake of benzylamine
Resin-Type: Macroporous poly(styrene-*co*-divinylbenzene)
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)
Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

Part #	Quantity
800285	10 g
800286	25 g
800287	100 g

References

1. Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J J.; South, M. S.; Woodard, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 4874.
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4. Shuker, A. J.; Siegel, M. G.; Matthews, D. P.; Weigel, L. O. *Tetrahedron Lett.* **1997**, *38*, 6149.
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ic 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 resi 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 13**. 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 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 14**.

TABLE 13. Amine Removal by MP-TsOH (*Batch Mode*)

Amine	MP-TsOH (equiv)	% Scavenged 20 min	1h
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 14. Amine Removal by MP-TsOH (*Cartridge Mode*)

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

Chemistry Solutions for Parallel Synthesis and Purification

In order to facilitate a wide range of solution phase reactions and workups, Argonaut offers a complete Solution Phase Toolbox and convenient solution kits to meet specific application needs.

Solution Phase Toolbox

- 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™ (pre-calibrated scoop for convenient resin measuring)

Part # 800266

Scavenger Kit

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

Part # 800368

Coupling Kit

- 10 gram quantities of each: PS-HOBt, PS-Isocyanate, PS-DMAP, PS-Carbodiimide

Part # 800377

Polymer Tosyl Kit

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

Part # 800293

Base Kit

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

Part # 800294

About Argonaut Technologies

Argonaut Technologies enables chemists to realize the productivity gains promised by parallel synthesis. Argonaut's products are currently used for chemistry development, library synthesis, lead optimization and process development in pharmaceutical, agrochemical and biotechnology research laboratories worldwide.

Our products include organic synthesizers, software and chemical resins and reagents that facilitate solution and solid phase chemistry. Our worldwide staff of experienced organic chemists are dedicated to providing technical support on all aspects of parallel organic synthesis.

Argonaut has assembled a world-class team of chemists, systems engineers and software programmers who work together to design systems optimized for parallel synthesis based on a wide range of chemistries.

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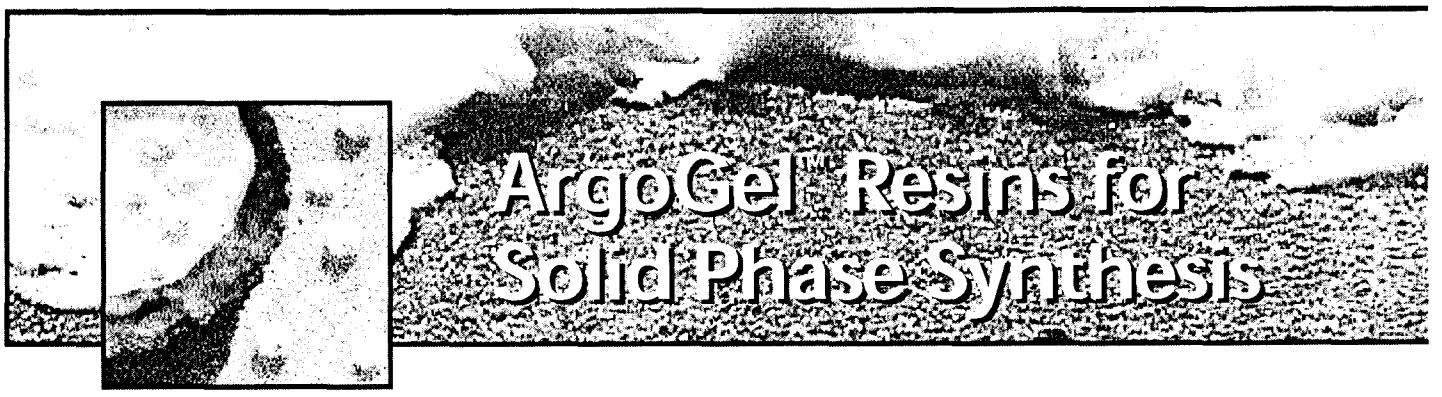
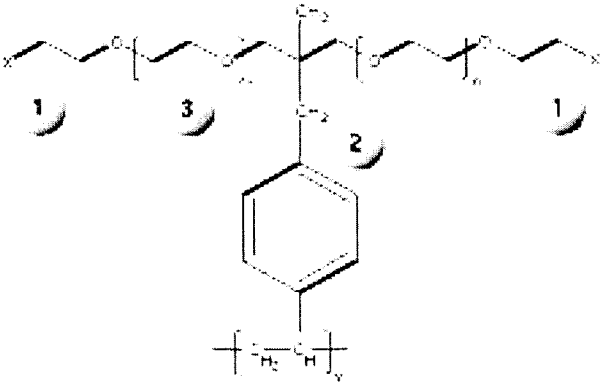
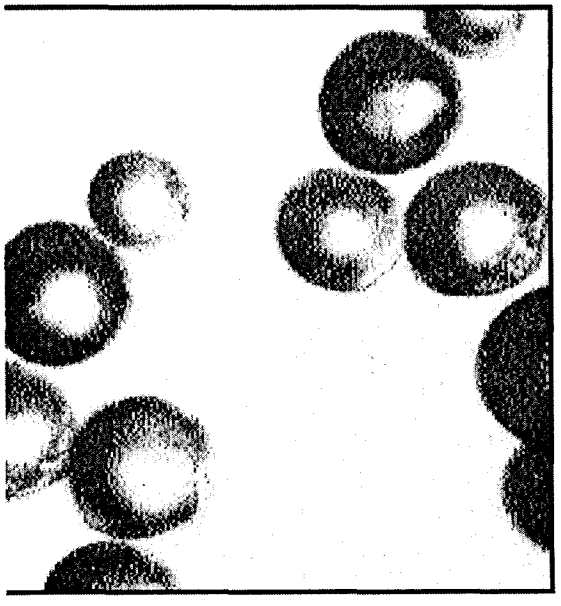


ArgoGel™ Resins for Solid Phase Synthesis

- **High Yield**
- **Low levels of impurities**
- **Enhanced Resin Properties**

Argonaut Technologies has developed ArgoGel® resin -- a family of products based on a new polyethylene glycol-polystyrene graft (PEG/PS) co-polymer. These support materials are exceptionally stable under the rigors of solid phase organic synthesis. ArgoGel resins provide a high loading capacity, low levels of impurities and exhibit compatibility with a broad range of organic reagents and solvents due to their unique structure and improved purification process.





Solvent-swollen ArgoGel beads provide a solution-like environment for solid-phase synthesis.

1 High Loading Capacity for High Yields

ArgoGel resins provide yields approximately two-fold higher than comparable resins. The copolymer is built on a novel framework consisting of twice the number of groups per backbone attachment site. This results in higher loading capacity per unit weight without sacrificing the benefits conferred by the polyethylene glycol graft. ArgoGel-OH and -NH_2 have loading values in the range of 0.4-0.5 mmole per gram based on standard analytical techniques.

2 Low levels of impurities

Chemical Stability

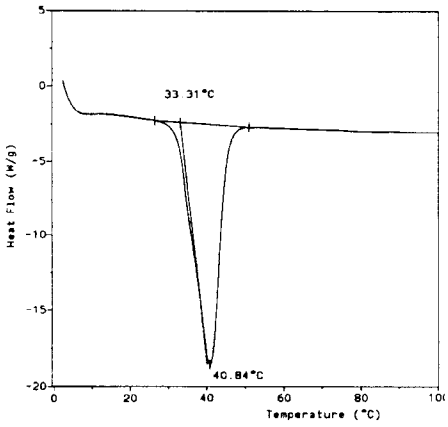
ArgoGel supports enable production of higher purity products. ArgoGel employs an inert 1,3 diol construct which is linked directly to the poly(styrene/divinylbenzene) core matrix through a carbon-carbon bond. This chemical linkage minimizes degradation of the PEG chain and loss of loading by aggressive reagents used during cleavage. The result is more pure product per gram of resin.

Low leachable impurities

Polyethylene-glycol-grafted supports contain impurities that often leach out during normal solid-phase organic chemistry steps. Of special concern are impurities which are released during the cleavage of the desired product from the support and incorporated into the final product. 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 is minimized
- Purification, if needed (e.g., crystallization), is more readily achieved
- Screening (activity/mg) is easily achieved

Fig. 1

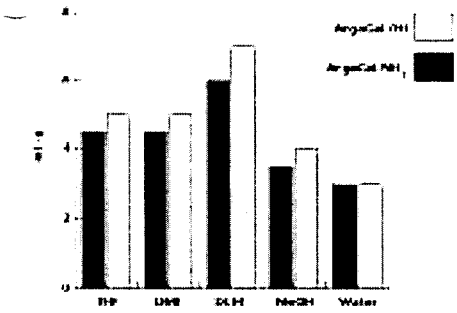


3 Enhanced resin properties

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. The DSC (Differential Scanning Calorimetry) endotherm shown in Figure 1 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 graft.

Fig. 2



Optimum swelling for maximum performance

As shown in Figure 2, ArgoGel resin exhibits excellent swelling properties in a range of solvents, from strongly polar protic to moderately polar aprotic. Rapid reaction rates are achieved with ArgoGel because core polystyrene material is made to an exacting specification, and through construction of the polyethylene glycol graft, the user enjoys solution-like reaction conditions.

Particle Size Distribution

ArgoGel is a white to cream colored crystalline material composed of spherical beads approximately 170 µm in diameter. The particle size distribution is 120-230 µm (95% within). For particle size distributions outside of these specifications, please contact Argonaut's Marketing Department.

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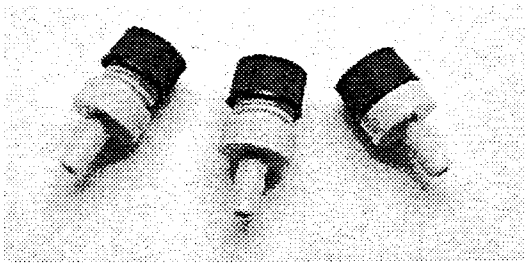
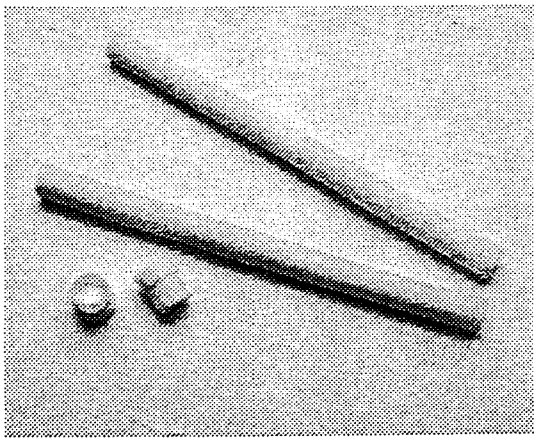
Quest™ 210 Accessories

Part Number	Description
900098	**Quest 210 Collection Rack for Liquid Scintillation Vials.** Collection rack for 20 scintillation vials.
900110	**Quest 210 Collection Rack for 20 mm x 125 mm Test Tubes** Collection rack for twenty 20 mm x 125 mm test tubes.
900111	**Quest 210 Collection rack for 13 mm x 100 mm Test Tubes** Collection rack for twenty 13 mm x 100 mm test tubes.
900123	**Quest 210/205 Chiller Interface Kit (Quest's with 1/4 in. male pipe fittings).** Contains the fittings necessary to interface a Quest 210 or 205 reaction bank to a Julabo F83-MW Refrigerated Recirculating Chiller.
900125	**Bubbler Kit.** Bubbler allows the visualization of the inert gas flow rate through the Quest 210 or 205. Includes 6 ft of 1/8 in. Teflon® tubing and 1/8 in. Peek fitting and Tefzel ferrule.
900137	**Quest 210 Chiller Interface Kit (Quest 210's with barbed fittings).** Contains the fittings necessary to interface a Quest 210 with barbed fittings to a Julabo F83-MW Refrigerated Recirculating Chiller.



900145 **Septum Luer Plugs (10/pkg).**
Septum Luer Plugs allow the quick and efficient delivery of reagents while maintaining a closed reaction environment. They are used in place of the standard upper manifold luer plugs on the Quest 210/205.

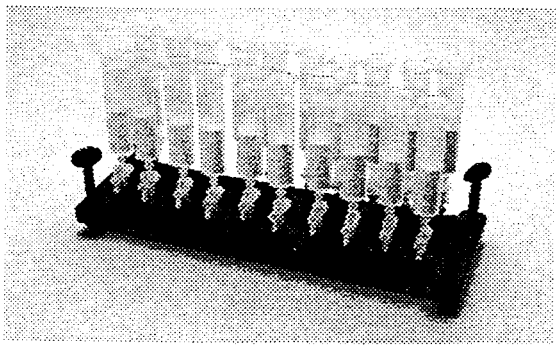


900146 **Quest 210 5 mL Blank Reaction Vessels (5/pkg).**
Blank reaction vessels occupy the unused reaction vessels positions and allow syntheses with less than 10 reaction vessels in a reaction bank.

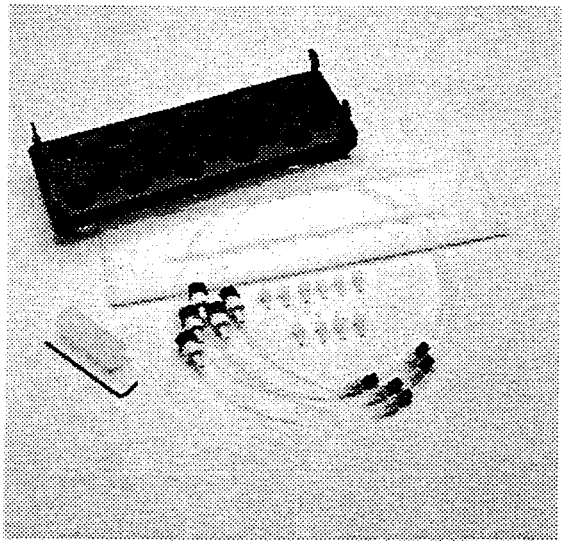
900147 **Quest 210 10 mL Blank Reaction Vessels (5/pkg).**
Blank reaction vessels occupy the unused reaction vessels positions and allow syntheses with less than 10 reaction vessels in a reaction bank.

900158 **Microfunnels (20/pkg).**
Microfunnels facilitate the addition of dry reagents of slurry to the Quest 210 reaction vessels.

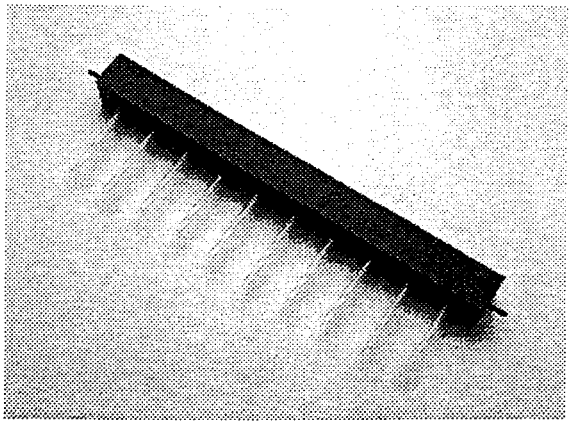
900181 **Quest 210 Accessory Bundle.**
Includes the following Quest 210 accessories: 900125, 900145, 900146, 900147, 900158 and 900182.



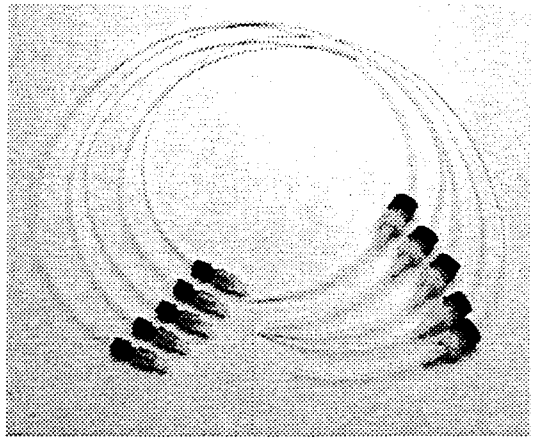
900182 **Quest 210 Solid Phase Extraction Rack.**
Rack that holds up to 20 solid phase extraction cartridges for on-line purification directly on the Quest 210. The rack conveniently fits on the Quest Waste Tray simplifying product collection.



900186 **Quest 210 Lower Manifold Luer Upgrade.**
This kit upgrades a Quest 210 with standard Teflon reaction vessel outlet lines to having male luer fittings. This kit allows the direct attachment of SPE cartridges with female luer connections for on-line purification. Also enables the use of bank-to-bank transfer cannulas for multi-step reactions on the Quest 210. Kit is user installable and includes ten bank-to-bank transfer cannulas. All parts and tools necessary to perform the upgrade are included.



900243 **Quest 210 Funnel Manifold.**
This manifold has ten integrated funnels for solid reagent addition to a bank of Quest 210 reaction vessels



900245 **Quest 210 Transfer Cannulas (10/pkg).**
Cannulas used for bank-to-bank transfer of reaction solutions.

900248 **Quest 210 Adjustable Height Scintillation Vial Rack.**
Scintillation vial rack with adjustable legs for use with SPE cartridges. Holds up to 20 scintillation vials. This rack is included with 900186 Quest 210 Lower Luer Manifold Update.

ARGONAUT TECHNOLOGIES
San Carlos, California USA • Phone: (888) 598-1350 • Fax: (650) 598-1350
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The following literature references are for papers authored by Argonaut chemists, customers and affiliates.

1999

Glycosidation of Solid-Supported Glycosyl Donors Tethered by a Trialkylsilane Linker
Doi, T.; Sugiki, M.; Yamada, H.; Takahashi, T.; Porco Jr., J.A.; *Tetrahedron Letters*, **1999**, *40*, 2141-2144.

Related Argonaut Products: PS-DES

Cross-Coupling of Aryl Halides and Allyl Acetates with Arylboron Reagents in Water Using an Amphiphilic Resin-Supported Palladium Catalyst
Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.*, **1999**, 3384-3386.

Related Argonaut Products: ArgoGel-NH_2

Polymer-bound N-Hydroxysuccinimide Esters: A Column-Free Fluorescent-Labeling Method
Katoh, M.; Sodeoka, M. *Bioorg. & Med. Chem. Letters*, **1999**,*9*, 881-884.

Related Argonaut Products: PS-Thiophenol

A polymer-supported silyl triflate and subsequent functionalization: synthesis and solid-phase Diels-Alder reactions of silyloxydienes
Smith, E. M. *Tetrahedron Lett.*, **1999**, *40*, 3285-3288.

Related Argonaut Products: PS-DES

Ester enolate Claisen rearrangement using a polymer-supported silyl triflate
Hu, Y.; Porco, J. A. *Tetrahedron Lett.*, **1999**, *40*, 3289-329.

Related Argonaut Products: PS-DES

Solid-supported reagents in organic synthesis
Drewry, D.H.; Coe D.M.; Poon, S.; *Med Res. Rev.* **1999**, *19*(2), 97-148.

The current interest in solid-phase organic synthesis has led to a renewed interest in a complementary technique in which solid supported reagents are used in solution-phase chemistry. This technique obviates the need for attachment of the substrate to a solid-support, and enables the chemist to monitor the reactions using familiar analytical techniques. The purpose of this review is to increase awareness of the wide range of useful transformations which can be accomplished using solid-supported reagents.

On the Development of New Poly(styrene-oxyethylene) Graft

Copolymer Resin Supports for Solid-Phase Organic Synthesis
Gooding, O.W.; Baudart, S.; Deegan, T.L.; Heisler, K.; Labadie, J.W.; Newcomb, W.S.; Porco, J.A.,Jr; van Eikeren, P., *Journal of Combinatorial Chemistry* **1999**, *1*,113.

Argonaut Related Product: **ArgoGel resin**

Parallel Synthesis of 1,2,3-Thiadiazoles Employing a "Catch and Release" Strategy
Hu, Y.; Baudart, S.; Porco, J. A., Jr., *J. Org. Chem.*, **1999**, *64* (3), 1049-1051

1,2,3-Thiadiazoles were synthesized in parallel on the Quest 210 using a polymer sulfonylhydrazide resin (PS-TsNHNH$_2$) employing a "catch and release" synthesis strategy. "Resin capture" of ketones synthesized from Weinreb amides and Grignard reagents (quenched using MP-TsOH resin) afforded resin-bound sulfonylhydrazones. Cyclative cleavage of support-bound sulfonylhydrazones with thionyl chloride afforded 1,2,3-thiadiazoles. Excess thionyl chloride was neutralized using liquid-liquid extraction cartridges. Further functionalization reactions (Stille coupling) on resin-bound sulfonylhydrazones are also described.

Related Argonaut Products: **Quest 210, PS-TsNHNH, MP-TsOH**

Parallel Synthesis of 1,2,4-Oxadiazoles Using CDI Activation
Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Pufko, D. E.; Porco, J. A. , *Bioorganic and Medicinal Chemistry Letters*,9 (2) 209-212 , **1999**

1,2,4-Oxadiazoles were prepared in parallel on the Quest 210 using 1,1'-carbonyldiimidazole (CDI) as a reagent for both formation and cyclodehydration of O-acyl benzamidoximes. The use of CDI facilitates parallel purification of the oxadiazole products by simple liquid-liquid extraction and filtration.

Related Argonaut Product: **Quest 210**

1998

Polymer-assisted solution phase (PASP) chemical library synthesis
Flynn et. al. *Med. Chem. Res.* **1998**, 8:4/5 219-243.

Solution-Phase Library Generation: Methods and Applications in Drug Discovery
Gayo, L.M. *Biotechnology and Bioengineering* (Combinatorial Chemistry), **1998**, *61*, 2, p. 95.

Gel phase MAS 1-H NMR as a probe for supramolecular interactions at the solid-liquid interface
de Miguel, R.Y.;Bampos, N.; Nalin de Silva, K.M.; Richards, S.A.; Sanders, J.K.M., *Chem. Commun.*, **1998**, 2267.

Argonaut Related Product: ArgoGel resin

"Polymeric Supports for Solid Phase Synthesis"
Labadie, J., *Current Opinion in Chemical Biology* 2, 346, **1998**.

Related Argonaut Product: General Resins for Solid Phase Synthesis

---

"Applications of N-Boc-Diamines for the Solution Phase Synthesis of Ketopiperazine Libraries Utilizing a Ugi/De-Boc/Cyclization (UDC) Strategy"
Hulme, C. , Peng, J. ,Louridas, B., Menard, P., Krolikowski, P., Kumar, N.V., *Tetrahedron Lett.*, 39, 8047, **1998**.

Related Argonaut Product: PS-DIEA Resin

"Phosgenated p-Nitrophenyl(polystyrene)ketoxime or Phoxime Resin. A New Resin for the Solid-Phase Synthesis of Ureas via Thermolytic Cleavage of Oxime-Carbamates"
Scialdone, M.A., Shuey, S.W., Soper, P., Hamuro, Y., Burns, D.M., *J. Org. Chem.*, *63*, 4802-4807, **1998**.

Related Argonaut Product: Nautilus 2400

"Chameleon Catches in Combinatorial Chemistry: Tebbe Olefination of Polymer Supported Esters and the Synthesis of Amines, Cyclohexanones, Enones, Methyl Ketones and Thiazoles"
Ball, C.P., Barrett, A.G.M., Commercon, A., Compere, D., Kuhn, C., Roberts, R.S., Smith, M.L., Venier, O., *Chem. Commun.*, 2019-2020, **1998**.

"Solid Phase Synthesis of Substituted 1-Phenyl-2-aminomethyl-benzimidazoles and 1-Phenyl-2-thiomethyl-benzimidazoles"
Tumelty, D. , Schwarz,M., Needels, M.C., *Tetrahedron Letters*, *39*, 7467-7470, **1998**.

Related Argonaut Product: ArgoGel-Rink-Fmoc

"Solid Phase Synthesis of Hydroxamic Acids"
Dankwardt, S.M., *Synlett*, 761, **1998.**

Related Argonaut Product: ArgoGel-OH

"Novel Polymer-Supported Trialkylsilanes and Their Use in Solid-Phase Organic Synthesis"
Hu, Y.; Porco, J.A. Jr.; Labadie, J.; Gooding; Trost, B.M., O., *J. Org. Chem.*, *63*, 4518-4521, **1998**.

Polymer-supported trialkylsilanes were prepared and evaluated as linkers for solid-phase organic synthesis. Various silanes were prepared by hydrosilylation of the corresponding polymer-bound terminal olefin. Loading of substrate molecules was accomplished by either direct reaction with the silane (Si-H) or the more reactive silyl chloride derived from chlorination of the silane. The loading and cleavage of several alcohols and aromatic derivatives are described.

Related Argonaut Product: PS-DES

Complimentary reprints available by contacting Argonaut Technologies.

"Solid-Supported Synthesis of Imidazoles: A Strategy for Direct Resin-Attachment to the Imidazole Core"
Bilodeau, M.T.; Cunningham, A.M., *J. Org. Chem.*, *63*, 2800-2801, **1998.**

Related Argonaut Product: **ArgoGel-MB-CHO**

"Alcoholysis and Carbonyl Hydrosilylation Reactions using a Polymer-Supported Trialkylsilane"
Hu, Y.; Porco, J.A., Jr., *Tetrahedron Letters*, *39*, 2711-2714, **1998**

Polystyrene-diethylsilane (PS-DES) resin may be reacted with alcohols (alcoholysis) and carbonyl compounds (hydrosilylation) in 1-methyl-2-pyrrolidinone (NMP) using Wilkinson's catalyst (RhCl(PPh3)3) to afford the corresponding resin-bound silyl ethers. The silyl ethers formed were effectively cleaved using HF/pyridine solution in THF. Methoxytrimethylsilane was employed to scavenge excess HF from product solutions.

Related Argonaut Product: **PS-DES**

Complimentary reprints available by contacting Argonaut Technologies.

"Analysis of 9-Fluorenylmethoxycarbonyl (FMOC) Loading of Solid-Phase Synthesis Resins by Gas Chromatography"
Newcomb, W.S., Deegan T.L., Miller, W. and Porco, J.A. , Biotechnology and Bioengineering (Combinatorial Chemistry), *vol. 61*, No. 1, Winter, **1998**.

This technical article compares several sample manual and automated preparation methods using the Nautilus 2400 and finds that the Nautilus can be used to reduce operation time and increase throughput of sample analysis.

"Automated Chemical Synthesis: Chemistry Development on the Nautilus™ 2400"
Porco, J.A. Jr.; Deegan, T.L.; Devonport, W.; Gooding, O.; Labadie, J.W.; MacDonald, A.A.; Newcomb, W.S.; van Eikeren, P. *Drugs of the Future*, 23 (1), pp. 71-78, **1998**.

The automation of the organic synthesis of small molecules is now a major focus in the pharmaceutical industry. Over the last few years, commercially available instrumentation for automated organic synthesis has steadily increased, concomittant with the need for increased throughput for chemistry development and library synthesis. However, it is apparent that further development of robust and inert instrumentation is required to facilitate the automation of a broad range of synthetic organic chemistries, either on solid-support or using conventional solution-phase methods. In this chapter, we will describe the Nautilus 2400, a chemistry development workstation, and demonstrate examples of its ability 1) to handle air- and moisture-sensitive reagents 2) to exhibit precise control over reaction time, and 3) to perform individual temperature control in segregated reaction vessels. The result is a useful tool for drug discovery which allows chemists to increase efficiency in chemistry development, lead optimization, and library synthesis.

Related Argonaut Product: **Nautilus 2400**

"Solid-Phase Synthesis of 2-Aminothiazoles"
Kearney, P.C.; Fernandez, M.; Flygare, J.A., *J. Org. Chem.*, *63*, 196-200, **1998**.

Related Argonaut Product: **ArgoGel MB-CHO**

1997

Combinatorial chemistry using polymer-supported reagents

Kaldor, S.W.; Siegel, M.G.,*Current Opinion in Chemical Biology*, **1997**, 1:101-106.

"Non-Acidic Cleavage of Wang-Derived Ethers From Solid Support: Utilization of a Mixed-Bed Scavenger for DDQ"
Deegan, T.; Gooding, O.; Baudart, S.; Porco, J.A. , Jr., *Tetrahedron Letters, Vol. 38, No. 28*, pp. 4973-4976, **1997**.

Ethers derived from ArgoGel Wang Chloride resin have been prepared and evaluated in both trifluoroacetic acid and DDQ-mediated cleavage protocols. DDQ cleavage of resin bound p-alkoxy benzyl ethers has been found to circumvent problems associated with trifluoroacetylation of alcohol products during TFA treatment. In order to facilitate the removal of excess DDQ and DDQH from cleaved products, a mixed bed ion exchange scavenger has been developed.

Related Argonaut Product: **ArgoGel Wang-Cl**

"Tandem UPS: Sequential Mono- and Dialkylation of Resin-Bound Glycine via Automated Synthesis"
Griffith, D.; O'Donnell, M.; Pottorf, R.; Scott, W.; Porco, J.A.,Jr., *Tetrahedron Letters, Vol. 38*, No. 51, pp. 8821-882, **1997**.

A method has been developed for the synthesis of racemic a,a-disubstituted amino acids by a tandem alkylation process ("Tandem UPS") on solid support. Consecutive alkylations of Wang resin-bound benzophenone imines of glycine afforded unnatural, disubstituted amino acid derivatives. Automated chemical synthesis was used to efficiently optimize conditions for both formation and hydrolysis of resin bound disubstituted benzophenone imines and to generate a matrix of disubstituted amino acid derivatives.

"The Solid Phase Synthesis of Trisubstituted 1,4-Diazabicyclo (4.3.0)nonan-2-one Scaffolds: On Bead Monitoring of Heterocycle Forming Reactions Using ^{15}N NMR"
Swayze, E., *Tetrahedron Letters, Vol. 38*, No 50, pp. 8643-8646, **1997**.

Several representative 3,4,8-trisubstituted 1,4-diazabicyclo(3,4,0)nonan-2-ones have been prepared employing solid phase smethodologies. Elaboration of a 4-hydroxyproline derivative with an ^{15}N-amino acid derivative allowed convenient monitoring of the reaction sequence on solid support by gel-phase ^{15}N NMR. An intramolecular Mitsunobu cyclization provided the desired heterocycle, which could be further functionalized at the 4-position. This synthetic method is facile, general and suitable for the construction of large libraries of compounds for biological assays.

Related Argonaut Product: **ArgoGel-OH**

"Secondary Amide-based Linkers for Solid Phase Organic Synthesis"
Swayze, E., *Tetrahedron Letters, Vol. 38*, No. 49, pp. 8465-8468, **1997**.

The electron rich benzaldehyde derivatives 4-hydroxybenzaldehyde and 2-methoxy-4-hydroxybenzaldehyde have been investigated for use as linkers for solid phase organic synthesis. Reductive amination of these aldehydes attached to ArgoGel resins with a model primary amine ggave the corresponding benzylic secondary amines. These compounds were then converted to the corresponding ureas, sulfonamides, aryl amides, and alkyl amides by derivatization with an appropriate electrophile. The desired secondary amide derivative was then cleaved from the support by treatment with trifluoroacetic acid to provide essentially quantitative yields of products in high purity.

Related Argonaut Product: **ArgoGel MB-CHO**

"Parallel Synthesis of Tamoxifen and Derivatives on Solid Support via Resin Capture"
Brown, S.D.; Armstrong, R.W., *J. Org Chem.*, *62*, 7076-7077, **1997**.

Related Argonaut Product: **ArgoGel NH_2**

"Solid-Phase Synthesis of4-Arylazetidin-2-ones via Suzuki and Heck Cross-Coupling Reactions"
Ruhland, B.; Bombrun, A.; Gallop, M., *J. Org. Chem*, *62*, 7820-7826, **1997**

Related Argonaut Product: **ArgoGel MB-OH**

"Synthesis of Benzofuran Derivatives on Solid Support via SmI_2-Mediated Radical Cyclization"
Du, X.; Armstrong, R.W., *J. Org. Chem*, *62*, 5678-5679, **1997**.

Related Argonaut Product: **ArgoGel Rink-NH-FMOC**

"Solid Phase Synthesis of N-Alkyl Sulfonamides"
Dankwardt, S.M.; Smith, D.B.; Porco Jr., J.A.; Nguyen, C.H., *Synlett*, 854, **1997**.

Polymer-supported sulfonamides were alkylated using alkyl halides in the presence of DBU or with alcohols via the Mitsunobu reaction.

Related Argonaut Product: **ArgoGel Wang**

1996

"Automated Chemical Synthesis: From Resins to Instruments"
Porco, J.A. Jr.; Deegan, T.; Devonport, W.; Gooding, O.; Heisler, K.; Labadie, J.; Newcomb B.; Nguyen, C.; van Eikeren, P.; Wong, J.; Wright, P., *Molecular Diversity*, *2*, 197-206, **1996**.

Related Argonaut Product: **Nautilus 2400**; **ArgoGel Resins**

"Automated Solid Phase Synthesis of Small Organic Molecules: A New Instrument promises to Automate a Broad Range of Chemical Synthetic Procedures"
Hoeprich Jr., P., *Nature Biotechnology*, *Volume 14*, October **1996**.

Related Argonaut Product: **Nautilus 2400**

"Boosting the Productivity of Medicinal Chemistry Through Automation Tools: Novel Technological Developments Enable a Wide Range of Automated Synthetic Procedures"
Gooding, O.; Hoeprich Jr., P.; Labadie, J.; Porco Jr., J.; van Eikeren, P.; Wright, P., *Molecular Diversity and Combinatorial Chemistry*, Irwin M. Chaiken and Kim D. Janda, Editors, **1996**.

The authors describe novel approaches to automating solid phase organic chemistry through the use of an instrument, the Nautilus, and a resin, ArgoGel. The Nautilus synthesizer automates organic reactions through the use of a computer controlled fluid delivery system which is composed of glass and polytetrafluoroethylene and which is isolated from the outside atmosphere. ArgoGel resin is a novel polyethylene glycol grafted polystyrene polymer that provides higher loading and higher acid stability than existing gel phase resins.

ArgoPore®
A New Macroporous Polystyrene Resin For Solid Phase Organic Synthesis

Introduction

The ArgoPore family of products is based on a highly-crosslinked, rigid macroporous polystyrene framework. ArgoPore resin has a high internal surface area with reaction sites at the surface of the internal pore structure. These reaction sites are accessible without the need for swelling by solvent as with lightly crosslinked poly(styrene-co-divinylbenzene) resins, referred to as gel-type resins. Therefore, ArgoPore can be used with any solvent, including water.

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

With ArgoPore, byproducts and impurities may be removed in fewer washes - with shorter wash times and using virtually any solvent, even aqueous acids and bases.

ArgoPore resins are available as aminomethyl, hydroxymethyl and chloromethyl base resins. Loading values for these base resins range from 0.6-1.1 mmole per gram. In addition, high load and low load aminomethyl resins are available with capacities of 1.1-1.6 and 0.2-0.6 mmole per gram respectively. ArgoPore linker products include Rink, Wang, arylsulfonamide and 2-methoxy-4-alkoxy benzaldehyde.

Benefits of ArgoPore As A Support For Solid Phase Organic Synthesis

The internal structure of ArgoPore offers numerous advantages for solid phase organic synthesis including:

- Rapid diffusional access of reagents to the reaction sites
- Improved reaction rates at low temperatures
- Access to polymer-supported intermediates that are soluble only under reaction conditions which cause collapse of swollen gel-type resins
- Excellent resistance to cracking due to rapid swelling (osmotic shock)
- Rapid solvent removal in vacuo between synthesis steps
- Low and predictable swelling in all solvents; ideal for small volume reaction vessels and 96-well plate applications

ArgoPore Characterization & Properties

The internal pore structure of ArgoPore has been specifically designed for synthesis of organic molecules, and has been characterized by nitrogen adsorption measurements. Pore profile data for ArgoPore-NH_2, ArgoPore-Cl, and ArgoPore-Wang is given in **Table 1**. The smaller average pore diameter and high total surface area distinguish ArgoPore resins from macroporous resins designed for biopolymer synthesis and allows ArgoPore to be functionalized to significantly higher levels.

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	90	0.75	500

TABLE 1. Representative Pore Profile Data For ArgoPore Resins

It is important to note that the pore data presented in **Table 1** is measured on polymer in the dry state and that 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.

ArgoPore resins do not swell appreciably in the presence of solvents due to their highly crosslinked nature. The resins undergo an approximately 1X volume expansion upon addition of organic solvent due to solvent regain into the pore structure. In **Figure 1** the volume per gram of ArgoPore-NH_2 is compared to a gel aminomethyl polystyrene for a series of solvents.

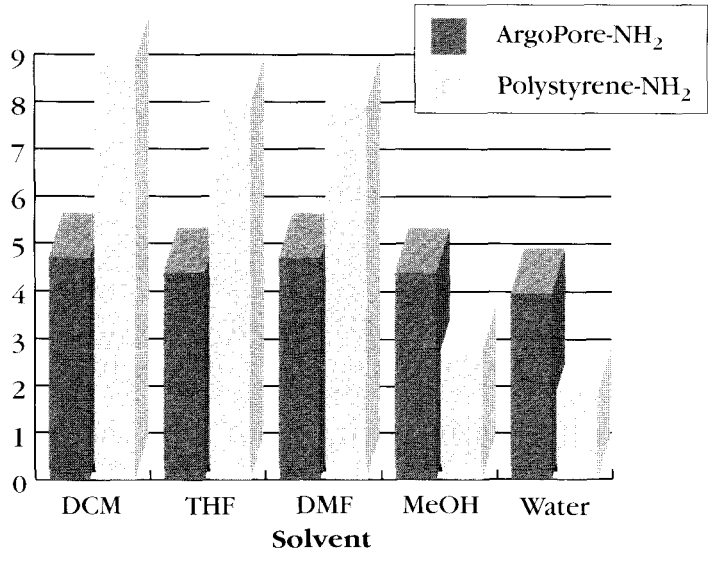


FIGURE 1. Swelling of ArgoPore-NH_2 versus 1% Crosslinked Aminomethyl Polystyrene

The swelling data shows that the ArgoPore occupies a volume of 4-4.5 mL/g in organic solvents, with a slightly lower value of 3.5 mL/g in water. Solvent uptake is very uniform as a function of solvent. In contrast, th gel-type resin swells to 9 mL/g in solvents of medium polarity and is not swollen at all in polar, protic solvents.

The removal of reaction byproducts from ArgoPore is readily achieved with solvent washes. **Table 2** shows the comparative retention of an impurity in ArgoPore-Wang and polystyrene-Wang when impregnated with a solution of biphenyl in dichloromethane.[1] The data shows that the majority of the biphenyl was removed more rapidly from ArgoPore than gel-type polystyrene, and that the biphenyl was totally removed with fewer washes for ArgoPore than the gel-type resin. This profile was repeated with other impurities, such as nitrobenzaldehyde and phenanthrene, with similar results. Equilibration of impurities between the pore phase and the bulk solution occurred more rapidly than with gel-type resin, after which time the solvent was drained and replenished, resulting in shorter wash times.

	BIPHENYL REMOVED (%)			
Resin	Wash 1	Wash 2	Wash 3	Wash
ArgoPore-Wang	91.20	8.00	0.01	0
Polystyrene-Wang	81.85	14.98	2.62	0.01

TABLE 2. Comparative Impurity Removal of ArgoPore-and Polystyrene-Wang

During the course of synthesis applications on ArgoPore, it was observed that removal of colored impurities and reactant neutralizations were more rapid 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. 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.

CHEMISTRY ON ARGOPORE RESINS

The utility of ArgoPore for solid phase organic synthesis was tested in a number of synthetic transformations. These reactions included examples that were known to proceed well on gel-type polystyrene, *e.g.* Suzuki couplings, to more challenging organometallic-based alkylations and those which require protic solvents and aqueous chemistry, hence, do not proceed well on gel-type polystyrene resins.

Suzuki Biaryl Synthesis

The Suzuki couplings of aryl halides and boronic acids[2,3] were evaluated on a Rink amide modified ArgoPore resin (ArgoPore-Rink-NH-Fmoc) in a comparative study with polystyrene-Rink resin, the latter of which was known to be an effective support for these transformations. Several sterically hindered biaryl products were included as target compounds to test the effect of ArgoPore relative to polystyrene in sterically demanding couplings. The synthetic approach involved the reaction of polymer supported *o*- and *p*-iodobenzoic acids (**1a** and **1b**, respectively) or 2-bromonaphthoic acids (**2**) with *o*-tolyl, *p*-methoxyphenyl and naphthalene boronic acids, in the presence of a palladium (II) catalyst (**Scheme 1, Table 3**). In the coupling of halides **1a** and **1b**, the reactions were shown to proceed efficiently to high purity products (entries **1-8, Table 3**).[4] The results revealed ArgoPore-Rink to perform equivalently in most cases. The couplings with *p*-methoxyphenyl boronic acid occurred with significantly higher yields on ArgoPore than on the gel-type analogs (entries **7** and **8, Table 3**). Couplings between the highly hindered 2-bromonaphthoic acid with naphthalene boronic acid showed low conversion, however, the ArgoPore resin gave somewhat higher conversion than the gel-type resin (entries **9** and **10, Table 3**). The post-reaction resins were quickly and easily washed and shown to retain negligible amounts of palladium, boron and phosphorus as determined by elemental analysis. The results demonstrate that ArgoPore is effective in palladium catalyzed cross-coupling reactions.

SCHEME 1

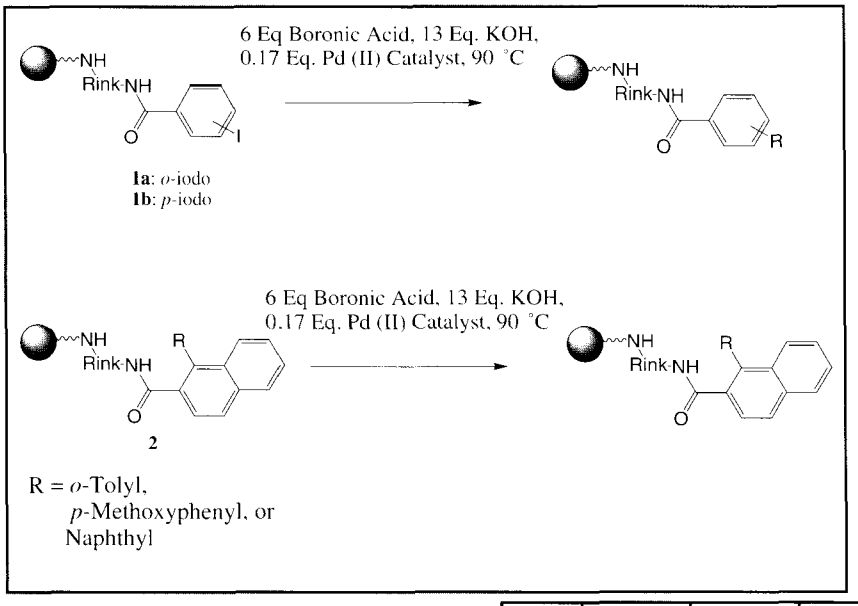


TABLE 3. Suzuki Biaryl Synthesis

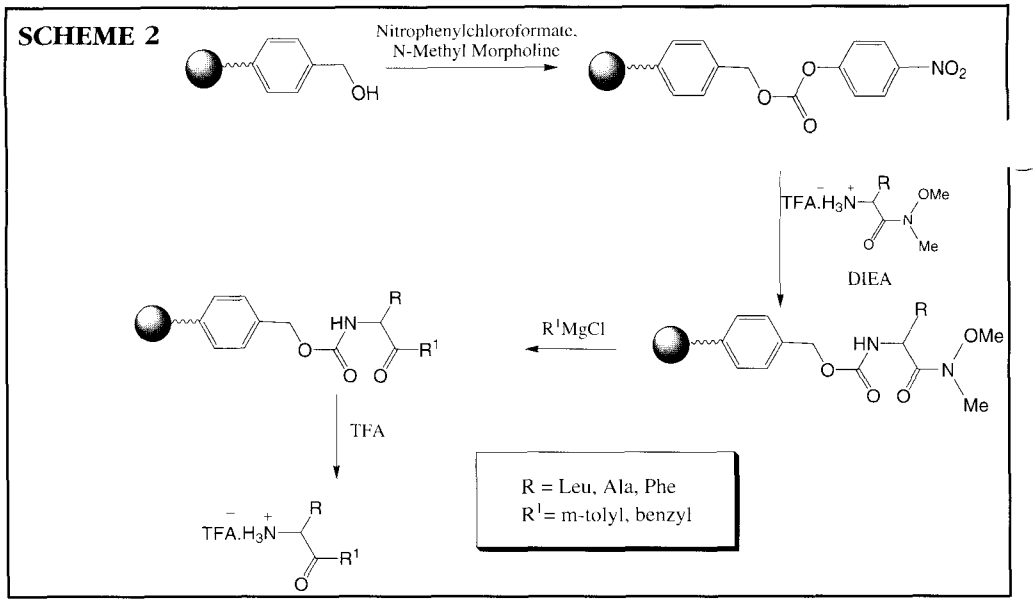
Entry	Resin Type	Loading[a]	Boronic Acid	Halide	% Yield (% Purity)	% Conversion
1	AP-Rink	0.45	*o*-Tolyl	**1a**	76(100)	91
2	PS-Rink	0.52	*o*-Tolyl	**1a**	78(100)	89
3	AP-Rink	0.45	*o*-Tolyl	**1a**	77(100)	92
4	PS-Rink	0.52	*o*-Tolyl	**1a**	86(100)	90
5	AP-Rink	0.45	*o*-Tolyl	**1b**	93(100)	91
6	PS-Rink	0.46	*o*-Tolyl	**1b**	89(100)	100
7	AP-Rink	0.45	*p*-Methoxyphenyl	**1b**	97(100)	97
8	PS-Rink	0.43	*p*-Methoxyphenyl	**1b**	78(100)	96
9	AP-Rink	0.33	Naphthyl	**2**	77(76)	34.1
10	PS-Rink	0.35	Naphthyl	**2**	72(76)	27.6

[a]Determined by loading and cleavage of the relevant halobenzoic acid
AP=ArgoPore, PS = 1% Crosslinked poly(styrene-co-divinylbenzene)

Synthesis of Aminoketones Using Polymer-Supported Weinreb Amides

Another test of established chemistry[5] was performed utilizing ArgoPore-Wang in the synthesis of aminoketones by reaction of polymer-supported Weinreb amides with Grignard reagents (**Scheme 2, Table 4**).[6] Various Weinreb amide derivatives of amino acids were loaded quantitatively on the nitrophenyl carbonate derivative of ArgoPore-Wang.[7]

SCHEME 2



Aminoketone formation was effected by reaction of the resin bound Weinreb amides with a series of Grignard reagents at 25 °C for 4 h. It was found that ArgoPore-Wang performed comparably with polystyrene resins, however it was necessary to increase the concentration of Grignard reagent from 0.5 M to 1.0M in order to achieve complete conversion (entries **1** and **2, Table 4**), which was not the case with gel-type polystyrene. ArgoPore showed higher yield in the case of alkylation of the alanine derivative, and comparable conversion and yield relative to polystyrene for entries **3-6 (Table 4)**. Phenylalanine derivatives showed conversions in the 80% range and comparable yields to gel-type polystyrene (entries **7-10, Table 4**).

TABLE 4. Synthesis of Aminoketones Using Polymer-Supported Weinreb Amides

Entry	Resin Type	Loading[a] mmol/g	Weinreb Amide	Grignard[b] Reagent	% Yield (% Purity)	% Conversion
1	AP-Wang	0.73	Leu	*m*-Tolyl[c]	-	61
2	AP-Wang	0.73	Leu	*m*-Tolyl	66	88
3	AP-Wang	0.63	Ala	*m*-Tolyl	87(100)	96
4	PS-Wang	0.914	Ala	*m*-Tolyl	70(100)	100
5	AP-Wang	0.63	Ala	Benzyl	85(100)	96
6	PS-Wang	0.914	Ala	Benzyl	69(100)	100
7	AP-Wang	0.63	Phe	*m*-Tolyl	85(100)	87
8	PS-Wang	0.914	Phe	*m*-Tolyl	88(100)	100
9	AP-Wang	0.63	Phe	Benzyl	83(100)	81
10	PS-Wang	0.914	Phe	Benzyl	79(100)	100

[a]Loadings determined by loading and cleavage of nitrophenylcarbonate, and subsequent UV analysis

[b]Grignard concentration = 1.0 M in THF

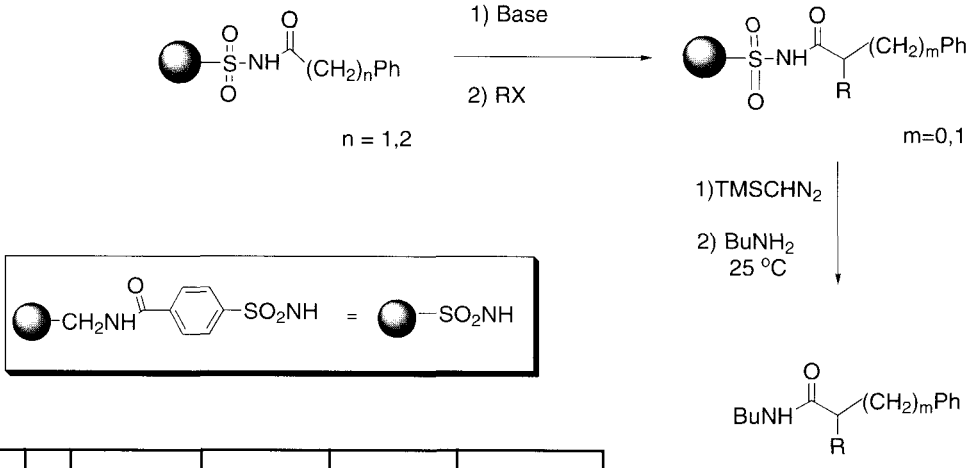
[c]Grignard concentration = 0.5 M in THF

AP = ArgoPore, PS = 1% Crosslinked poly(styrene-co-divinylbenzene)

Alkylation of Acylsulfonamides

The rigid nature of ArgoPore offers advantages in chemical reactions where insoluble intermediates are formed on resin. This is exemplified for alkylation of acylsulfonamides using Ellman's variant of Kenner's "safety-catch" linker.[8,9] Ellman's work was carried out using a macroporous resin, Rohm and Haas's XE-305[10], and this study sought to repeat the synthesis using ArgoPore modified with the same arylsulfonamide linker. The reaction sequence **Scheme 3** involved deprotonation of the acylsulfonamide with 3.3 equivalents of base, followed by quenching with an electrophile.[11,12] Cleavage of the product acylsulfonamide resin was achieved by activation of the linker with trimethylsilyldiazomethane followed by addition of butylamine to afford the alkylated amide product. When a 1% crosslinked polystyrene resin was utilized in this reaction sequence the resin collapsed (deswelled) during the addition of base, this was attributed to aggregation of a polyionic species. After electrophile quench and cleavage, a low conversion to products was observed, presumably due to incomplete trianion formation due to aggregation (entry **1, Table 5**). When ArgoPore modified with the arylsulfonamide linker, ArgoPore-AS-SO_2NH_2, was used, high conversion of the acylsulfonamide was observed and alkylated amides were recovered in high purity (Entries **2-8, Table 5**). Both lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LiHMDS) were found to be effective bases for the reaction. Notably, the reaction was effective for ArgoPore-AS-SO_2NH_2 when the deprotonation was carried out at -78 °C, whereas the 1% crosslinked polystyrene resin showed no reaction (Entry **6, Table 5**). This result was attributed to the facility to which the base can reach the reaction sites in ArgoPore by diffusion through the pore structure, as compared to the poor diffusion of base through the polymer gel at low temperature in the case of 1% crosslinked polystyrene. This example highlights advantages offered by ArgoPore over gel-type polystyrene for certain reactions involving anion chemistry.

SCHEME 3



Entry	Resin Type[a]	Loading[b] mmol/g	n	Base[c]/Temp (°C)	RX[d]	% Yield (% Purity)	% Conversion
1	PS-AS-SO_2-NH_2	0.69	1	LDA/0	BnBr	98(100)	42
2	AP-AS-SO_2-NH_2	0.57	1	LDA/0	BnBr	65(97)	99
3	AP-AS-SO_2-NH_2	0.57	1	LiHMDS/0	BnBr	66(97)	99
4	AP-AS-SO_2-NH_2	0.57	1	LiHMDS/0	EtI	67(97)	97
5	AP-AS-SO_2-NH_2	0.57	1	LiHMDS/0	MeI	66(94)	92
6	AP-AS-SO_2-NH_2	0.57	2	LDA/0	BnBr	57(95)	97
7	AP-AS-SO_2-NH_2	0.57	2	LiHMDS/0	BnBr	65(96)	97
8	AP-AS-SO_2-NH_2	0.49	1	LDA/-78	BnBr	93(100)	92
9	PS-AS-SO_2-NH_2	0.69	1	LDA/-78	BnBr	93(100)	0

TABLE 5. Enolate Alkylation of Acylsulfonamides

[a]AP-AS-SO_2NH_2 = ArgoPore-Arylsulfonamide

[b]Determined by sulfur elemental analysis

[c]3.3 eq, 1h

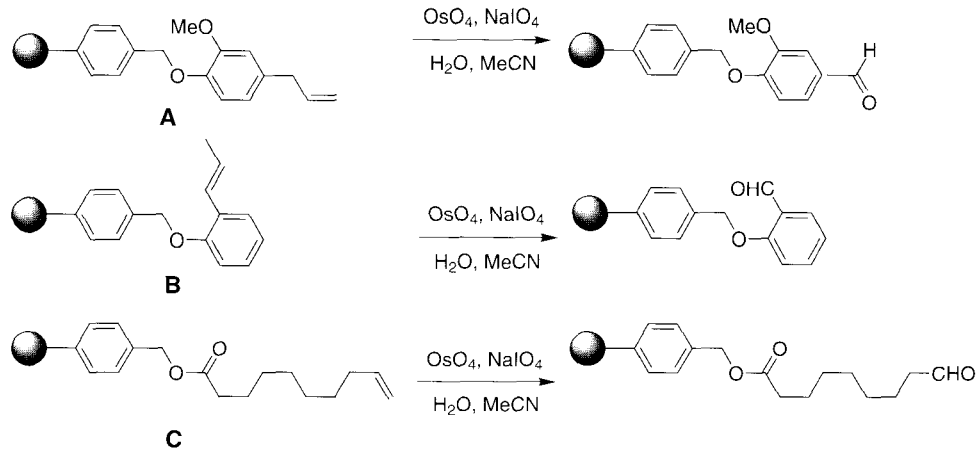
[c]5 eq, 6-16h

AP = ArgoPore, PS = 1% Crosslinked poly(styrene-co-divinylbenzene)

Osmium Tetroxide Mediated Olefin Oxidations

A drawback of solid phase organic synthesis on gel-type polystyrene resin has been limitation of reaction solvent, generally excluding reactions which require protic, non-swelling solvents. In contrast, these reactions are possible on ArgoPore and have been demonstrated for osmium tetroxide mediated oxidation of olefins to aldehydes in aqueous media (**Scheme 4**).[13] The reaction of vinyl substrates on ArgoPore resin proceeded in high efficiency and yield. (**Table 6**).[14] The oxidation of polymer-supported eugenol (**Scheme 4**) occurred with over-oxidation to the aryl aldehyde. Oxidation reactions did not proceed on gel-type resins, yielding starting material and unidentified byproducts.

SCHEME 4



Substrate	Resin	% Yield (% Purity)	% Conversion
Eugenol (A)	ArgoPore-Wang	89 (100)	100
Eugenol (A)	Polystyrene	Recovered Starting Material	0
2-propenylphenol (B)	ArgoPore-Wang	79 (100)	100
9-decenoic acid (C)	ArgoPore-Wang	93 (91)	84

TABLE 6. Osmium-Mediated Olefin Oxidations

The excellent compatibility of ArgoPore resins with a wide variety of reaction conditions facilitates the direct transfer of solution phase synthesis conditions to solid phase. Particularly, reagents and solvents from a solution phase procedure can be successfully transferred directly to solid phase synthesis on ArgoPore without concern of swelling properties. In general, higher temperatures and longer reaction times are often required relative to solution chemistry. Other examples of where solution phase reagent/solvent combinations and concentrations were used without modification include, osmium tetroxide mediated olefin oxidation, titanium (III) chloride reduction of nitro groups, and sodium borohydride reduction of aldehydes.[15] In optimizing these reactions on ArgoPore, only the reaction time and temperature were varied relative to the successful solution phase conditions.

Other Argonaut References for ArgoPore Resins

"Consumables for Organic Synthesis," 1998 Catalog

"Chemistry Products for Parallel Organic Synthesis and Purification," PL-006 Price List

1. Resins were incubated with a solution of biphenyl (4mL, 32mg/mL in DCM) for 1h. The biphenyl solution was drained and the filtrate collected. DCM (4mL) was added and the resin agitated for 5min. The DCM wash was drained and the filtrate collected as a separate fraction. This was repeated a further 5 times. Each fraction was analyzed by capillary gas chromatography using naphthalene as an internal standard.
2. In a typical experiment, 4-iodobenzoic acid (0.45mmol) was coupled to ArgoPore-Rink resin (0.58 mmol/g, 200mg, 0.116 mmol) in the presence of 4-hydroxybenzoletriazole (0.75 mmol), diisopropylcarbodiimide (0.75 mmol), DMF (2 mL), and agitated at 25 °C for 18h. Washing was conducted with DMF, THF, DCM and MeOH. Suzuki biaryl coupling of the resulting benzamide to o-tolylboronic acid (0.9 mmol) was conducted in the presence of $PdCl_2(PPh_3)_2$ (0.0255 mmol), aq. KOH (1.95 mmol, 2M), DME (1.6 mL) and agitated at 90°C for 3h. Washing was conducted with DME, DME/H_2O, 0.2M HCl, and MeOH.
3. T. Watanabe, N. Miyaura, A. Suzuki, *Synlett*, **1992**, 207.
4. % Yield determined gravimetrically; % Conversion was determined by comparison of HPLC area% of the starting material to that of all other products; %purity was determined by comparison of HPLC area% of the desired product to all non-starting material products. These determinations were used in all chemistries described in this document.
5. T. Deegan, J. Porco, Jr., *Argonaut Technologies Application Note #005.*
6. a) J.A. Ferentz, M. Paris, A. Heitz, J. Velek, C.-F. Lui, F. Winternitz, J. Martinez, *Tetrahedron Lett.*, **1995**, *36*, 7871; b) T.Q. Dihn, R.W. Armstrong, *Tetrahedron Lett.*, **1996**, *37*, 1161.
7. In a typical experiment, 4-nitrophenylchloroformate (0.75 mmol) was coupled to ArgoPore-Wang resin (0.15 mmol, 0.75 mmol/g) in the presence of N-methylmorpholine (1.5 mmol) and DCM (2 mL) for at 25 °C for 4h. Washing was conducted with MeOH, MeOH/H_2O, THF and MeOH. To nitrophenylcarbonate resin in NMP (2 mL), was added the TFA salt of Boc-Leu-Nme(OMe) (1.0M, 1.5 mmol), DIEA (2.25 mmol) and agitated at 25 °C for 18h. Washing was conducted with NMP, DMF, THF, DCM and MeOH. The carbamate functionalized resin was rinsed with dry THF (2 mL) before addition of benzylmagnesiumchloride (3.0 mmol). The solution was agitated at 25 °C for 4h. Washing was conducted with DMF, DMF/H_2O, THF, IPA, DCM and MeOH.
8. B.J. Backes, J.A. Ellman, *J. Am. Chem. Soc.*, **1994**, *116*, 11171.
9. G.W. Kenner, J.R. McDermott, Jr., *J. Am. Chem. Soc.*, **1971**, 636.
10. Rohm & Haas's XE-305 resin is a low cross-linked macroporous resin which is no longer commercially available.
11. In a typical experiment, phenylacetic acid was loaded on the arylsulfonamide using the symmetric anhydride as described in reference 7. The resulting acylsulfonamide resin (0.13 mmol) in 1.3 mL of THF at 0 °C was treated with 0.65 mL of LDA (2 M, 1.3 mmol) to afford dark green colored beads (LHMDS afforded orange colored beads). After 1 h at 0 °C, benzyl bromide (2 mmol) was added and the reaction was stirred overnight. The reaction was quenched with 3:1 methanol /acetic acid and the resin washed with DMF/water, TFA/THF, THF, MeOH, and dried *in vacuo*. The acylsulfonamide was activated for cleavage by adding 1 mL THF, followed by trimethylsilyldiazomethane in hexane (1.6 mmol) which resulted in mild gas evolution. After 2 h, the solution was drained and the resin washed THF, MeOH, and THF. To the resin in THF was added 0.2 mL of butylamine and the mixture was agitated overnight. The contents of the cartridge were drained into a collection flask and the resin was rinsed DCM and THF. The combined filtrate was concentrated to afford the amide product.
12. Macroporous resins have been reported to be effective in ester enolate acylations and alkylations. *c.f.* Y.H. Chang and W. T. Ford, *J. Org. Chem.* **1981**, *46*, 5364; b)Patchornik, A.; Kraus, M.A., *J.A. Chem. Soc.* **1970**, *92*, 7889.
13. R. Pappo, D.S. Allen, Jr., R.U. Lemieux, W.S. Johnson, *J. Org. Chem.*, **1956**, *21*, 478.
14. In a typical experiment, eugenol (0.75 mmol) was reacted with Wang resin (0.75 mmol/g, 0.15 mmol) in the presence of tributylphosphine (0.75 mmol), 1,1'-azobis(N,N-dimethylformamide) (0.75 mmol), DCM (1 mL) and toluene (1 mL) at 25 °C for 4h. The resins were washed with DMF, THF, DCM and MeOH. The olefin functionalized resin was rinsed with acetonitrile. Water (2 mL), sodium periodate (0.75 mmol), osmium tetroxide (0.0075 mmol, 4 wt% in water) were added and the solution heated at 70 °C for 14h. The resins were washed with DMF, THF, DCM and MeOH.
15. Reduction of 3- and 4-nitrobenzoate esters on ArgoPore reductions were carried with six equivalents of a 2:1 mixture of 20% $TiCl_3$ and acetonitrile at 60 °C for 3 h. Aldehyde reductions on 3- and 4-formyl benzoate with five equivalents of sodium borohydride in MeOH at 45 °C for 16 h. Methoxide mediated cleavage afforded high purity amino and hydroxymethyl substituted methyl benzoates in 70-90% yield.

About Argonaut Technologies

Argonaut Technologies enables chemists to realize the productivity gains promised by parallel synthesis. Argonaut's products are currently used for chemistry development, library synthesis, lead optimization and process development in pharmaceutical, agrochemical and biotechnology research laboratories worldwide.

Our products include organic synthesizers, software and chemical resins and reagents that facilitate solution and solid phase chemistry. Our worldwide staff of experienced organic chemists are dedicated to providing technical support on all aspects of parallel organic synthesis.

Argonaut has assembled a world-class team of chemists, systems engineers and software programmers who work together to design systems optimized for parallel synthesis based on a wide range of chemistries.

From personal synthesizers that are suitable for every laboratory to fully automated library synthesizers designed to support multiple users efficiently, Argonaut provides tools that are appropriate for chemists throughout the discovery process.

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12/98 REV3

1% Crosslinked Poly(styrene-co-divinylbenzene) Resins
For Solid Phase Organic Synthesis

Background

1% crosslinked poly(styrene-co-divinylbenzene) resin, commonly referred to as simply polystyrene, is a widely used solid support for organic synthesis. The many references for polystyrene in the literature provide a rich source of information for chemists planning solid phase chemistry. Some aspects of polystyrene resin that contribute to its wide use are:

- stability
- high loading capacity
- good swelling characteristics
- compatibility with a variety of non-protic solvents
- low cost

In order to provide a full line of resins for solid phase organic synthesis, Argonaut Technologies offers three resin types: polystyrene, ArgoPore® and ArgoGel® - each with distinctive characteristics.

For a wide range of reactions, standard polystyrene resins provide a cost-effective option. But due to the hydrophobicity of polystyrene divinylbenzene, aqueous or other protic solvents do not result in the resin swelling necessary to enable reagents to reach the reaction sites inside the polymer bead. For chemistry in protic solvents, ArgoPore resin, based on a highly-crosslinked macroporous polystyrene framework, or ArgoGel resin, based on a polyethylene glycol (PEG) grafted polystyrene, are good alternatives.

Linkers provide attachment sites for different functional groups and are subject to different cleavage conditions. It is important to have a variety of linkers available in order to allow for flexibility in the selection of reaction conditions and reagents.

Argonaut's polystyrene-based resins offer high purity and high loading capacities. Total extractables are typically less than 0.2%. Chloromethyl and aminomethyl base resins are available with a loading range of 1.2-1.7 mmol/g. Linker products include Rink, Wang, arylsulfonamide, 2-methoxy-4-alkoxy benzaldehyde and butyl diethylsilane (DES). Argonaut's resin products based on 1% crosslinked poly(styrene-co-divinylbenzene) are denoted by PS in the product name.

Argonaut's novel PS-DES resin is similar to a TES (triethylsilyl) group in terms of chemical stability, and is generally useful as a linker for solid phase synthesis, for the attachment of alcohols, carbonyls, acetylenes and aromatics.

In addition to the standard quantities listed in this document, Argonaut's polystyrene resins are also available in larger bulk quantities and pre-weighed in ArgoCaps.™ These capsules are a time-saving, convenient way to deliver fixed units of resins to a reaction vessel. ArgoCaps protect resins from moisture but are constructed of a polymer which is easily dissolved with dichloromethane.

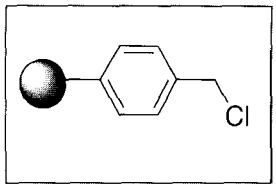
- #3 size ArgoCaps each contain approximately 150 mg of polystyrene resin.
- #5 size ArgoCaps each contain approximately 65 mg of polystyrene resin.

Custom resin filling of ArgoCaps is available; please contact Argonaut for more information.

ARGONAUT TECHNOLOGIES

Product Information

Product: PS-Cl



Chemical Name: Chloromethyl polystyrene

Capacity: 1.3 - 1.7 mmol/g (determined by Volhard titration)

Bead Size: 100 - 200 mesh (75 - 150 microns)

Resin Swelling: CH_2Cl_2 (8.7 mL/g), THF (8.3 mL/g), DMF (6.0 mL/g)

Linker Functionality: Acids, secondary amines

Reaction Conditions Tolerated: Acidic, neutral, mildly basic

Typical Cleavage Conditions: Alkoxide in alcohol or alcohol/THF

Products: Esters, amines

Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

Part #	Qty
800257	10 g
800258	25 g
800259	100 g

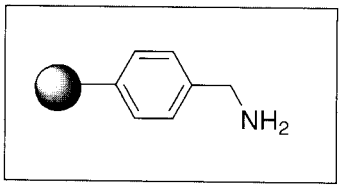
This chloromethyl polystyrene derivative (commonly known as Merrifield[1] resin) may be used for direct loading of carboxylic acids via their cesium salts.[2,3] This resin is also useful as a linker for secondary amines.[4]

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.

PRODUCT INFORMATION

Product: PS-NH_2



Chemical Name: Aminomethyl polystyrene

Capacity: 1.2 - 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)

Resin Swelling: CH_2Cl_2 (9.1 mL/g), THF (7.7 mL/g), DMF (6.5 mL/g)

Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

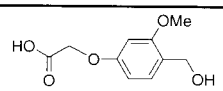
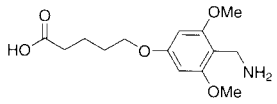
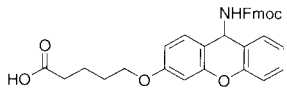
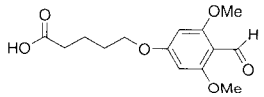
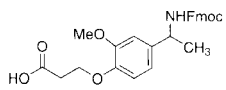
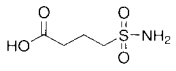
Part #	Qty
800263	10 g
800264	25 g
800265	100 g

This resin is the aminomethyl derivative of polystyrene.[1] PS-NH_2 is useful as a base resin for derivatization by acylation with carboxylic acid-containing linkers.[2]

References

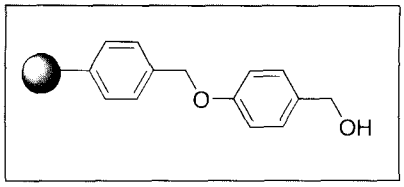
1. Mitchell, A.R., et al. *J. Org. Chem.* **1978**, *30*, 2845.
2. Sheppard, R.C., et al. *Int. J. Pept. Protein Res.* **1982**. *20*, 451.
3. Alberecio, F., et al. *J. Org. Chem.* **1990**, 55, 3730.
5. Sieber, P. *P. Tetrahedron Lett.* **1987**, 2107.
6. Jensen, K.J. *Peptides - Chemistry and Biology: Proceedings of the Fourth American Peptide Symposium,* Mayflower Worldwide Limited, England, **1996**, 30.
7. Holmes, C.P., et al. *J. Org. Chem.* **1995**, *60*, 2318.
8. Backes, B.J., et al. *J. Am. Chem. Soc.* **1996**, *118*, 3055.

TABLE 1. PS-NH_2 Linker Examples

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

PRODUCT INFORMATION

Product: PS-Wang



Chemical Name: [4-(Hydroxymethyl)phenoxy]methyl polystyrene

Capacity: 1.0 - 1.4 mmol/g (determined by UV quantification of Fmoc chromophore after loading Fmoc-glycine)

Bead Size: 100 - 200 mesh (75 - 150 microns)

Resin Swelling: CH_2Cl_2 (6.3 mL/g), THF (8.0 mL/g), DMF (7.0 mL/g)

Linker Functionality: Acids, amines, phenols

Reaction Conditions Tolerated: Mildly acidic, neutral, mildly basic

Typical Cleavage Conditions: Ester and carbamate linked products and generally cleaved with trifluoroacetic acid/dichloromethane mixtures. Carbamate cleavage via amine-mediated cyclization to hydantoins[1] and quinazoline-2,4-diones[2] has also been effected.

Products: Acids, amines, phenols

Part #	Qty
800351	10 g
800295	25 g
800296	100 g
800319	50 #3 ArgoCaps
800320	100 #3 ArgoCaps
800321	500 #3 ArgoCaps
800322	1000 #3 ArgoCaps
800335	50 #5 ArgoCaps
800336	100 #5 ArgoCaps
800337	500 #5 ArgoCaps
800338	1000 #5 ArgoCaps

Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

This resin is modified with p-hydroxybenzyl alcohol (commonly known as Wang linker). Carboxylic acid derivatives are readily coupled onto PS-Wang using DMAP-catalyzed esterification conditions (e.g., diisopropyl carbodiimide (DIC)/methylene chloride/cat. DMAP). Amines can also be attached to PS-Wang using the 4-nitrophenyl carbonate derivative.[1,2] [A] PS-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]

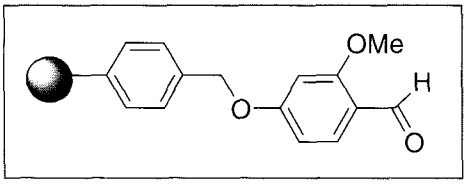
References

1. Dressman, B.A.; Spangle, L.A.; Kaldor, S.W. *Tetrahedron Lett.* **1996**, *37*, 937.
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.

[A] The preparation of the nitrophenyl carbonate derivative of the resin and the subsequent loading with amines is performed by analogy to ArgoGel-Wang. (ArgoGel-Wang Data Sheet DS-006, Argonaut Technologies)

Product Information

Product: PS-MB-CHO



Chemical Name: (4-Formyl-3-methoxyphenoxy)methyl 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)

Resin Swelling: CH_2Cl_2 (8.4 mL/g), THF (7.5 mL/g), DMF (6.2 mL/g)

Linker Functionality: Amines

Reaction Conditions Tolerated: Mildly acidic, basic

Typical Cleavage Conditions: Activation with an isocyanate, sulfonyl chloride or acyl derivative followed by tratment with 95:5 trifluoroacetic acid:water or 95:5 trifluoroacetic acid:triethylsilane. Efficiences for cleavage depend on the nature of the amine and electrophile subsituent.

Products: Amines, amides, sulfonamides, ureas, heterocycles

Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

Part #	Qty
800352	10 g
800298	25 g
800299	100 g
800327	50 #3 ArgoCaps
800328	100 #3 ArgoCaps
800329	500 #3 ArgoCaps
800330	1000 #3 ArgoCaps
800343	50 #5 ArgoCaps
800344	100 #5 ArgoCaps
800345	500 #5 ArgoCaps
800346	1000 #5 ArgoCaps

This resin is useful for attachment of amines by reductive amination.[1] The conditions for reductive amination are similar to those reported for ArgoGel-MB-CHO [A], with the exception that sodium borohydride in THF/ethanol (3:1) is used as the reducing agent.[1(b)] Activation with an isocyanate, sulfonyl chloride or acyl derivative can be used as a diversity step allowing the preparation of amides, sulfonamides and ureas.

References

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

[A] ArgoGel-MB-CHO Data Sheet, Argonaut Technologies, DS-012.

General References for MB-CHO Linker

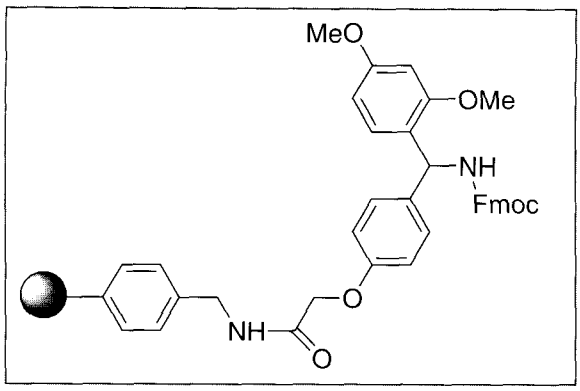
Bilodeau, M.T.; Cunningham, A.M., *J. Org. Chem.*, **1998**, *63*, 2800.

Kearney, P.C.; Fernandez, M.; Flygare, J.A., *J. Org. Chem.*, **1998**, *63*, 196.

Swayze, E., *Tetrahedron Lett.*, **1997**, *38*, 8465.

PRODUCT INFORMATION

Product: PS-Rink-NH-Fmoc



Chemical Name: 4-(2,4-Dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetamido aminomethyl polystyrene

Capacity: 0.7 - 1.2 mmol/g (determined by UV quantification of Fmoc chromophore)

Bead Size: 100 - 200 mesh (75 - 150 microns)

Resin Swelling: CH_2Cl_2 (7.0 mL/g), THF (6.0 mL/g), DMF (5.8 mL/g)

Linker Functionality: 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

Part #	Qty
800353	10 g
800301	25 g
800302	100 g
800323	50 #3 ArgoCaps
800324	100 #3 ArgoCaps
800325	500 #3 ArgoCaps
800326	1000 #3 ArgoCaps
800339	50 #5 ArgoCaps
800340	100 #5 ArgoCaps
800341	500 #5 ArgoCaps
800342	1000 #5 ArgoCaps

Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

This polystyrene resin is functionalized with a modified Rink linker.[1] The linker is attached to an aminomethyl functional polystyrene and 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 a benzylic-phenoxy linked system.

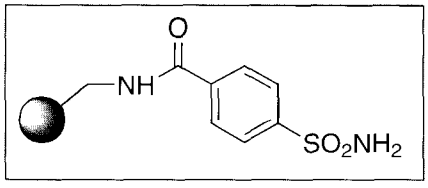
The linker is supplied in Fmoc-protected form and requires treatment with 20% piperidine/DMF prior to use. The derived resin-bound benzhydrylamine is commonly used in the solid phase synthesis of carboxamides and sulfonamides[2] and in condensation reactions.[3]

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 cited therein.

PRODUCT INFORMATION

Product: PS-AS-SO_2NH_2



Chemical Name: Arylsulfonamide polystyrene

Capacity: 0.9 - 1.3 mmol/g (determined by sulfur analysis)

Bead Size: 100 - 200 mesh (75 - 150 microns)

Resin Swelling: CH_2Cl_2 (3.7 mL/g), THF (7.1 mL/g), DMF (7.1 mL/g)

Linker Functionality: 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 (amine, hydroxide, etc.) to release a carboxylic acid derivative (e.g., amide).[1] [A]

Products: Acids, amides, esters

Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

Part #	Qty
800354	10 g
800304	25 g
800305	100 g
800331	50 #3 ArgoCaps
800332	100 #3 ArgoCaps
800333	500 #3 ArgoCaps
800334	1000 #3 ArgoCaps
800347	50 #5 ArgoCaps
800348	100 #5 ArgoCaps
800349	500 #5 ArgoCaps
800350	1000 #5 ArgoCaps

This is an excellent resin for the production of carboxylic acid derivatives since 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]

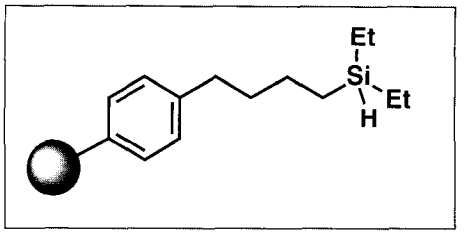
References

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

[A] Loaded by analogy to ArgoGel-AS-SO_2NH_2. (ArgoGel-AS- SO_2NH_2 Data Sheet DS-005, Argonaut Technologies.)

Product Information

Product: PS-DES



Chemical Name: Butyl diethylsilane polystyrene

Capacity: 0.6 - 1.0 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)

Linker Functionality: Alcohols, carbonyl groups, acetylenes, aromatic compounds

Reaction Conditions Tolerated: Acidic, basic

Typical Cleavage Conditions: AcOH/THF/water (6:6:1, 50 - 80 deg. 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]

Products: Alcohols, aromatics, acetylenes, heterocycles

Recommended Agitation: Gentle magnetic stirring, rocking, or overhead stirring for large resin quantities (> 5g)

Part #	Qty
800142	10 g
800143	25 g
800144	100 g
800145	50 #3 ArgoCaps
800146	100 #3 ArgoCaps
800147	500 #3 ArgoCaps
800148	1000 #3 ArgoCaps
800184	50 #5 ArgoCaps
800185	100 #5 ArgoCaps
800186	500 #5 ArgoCaps
800187	1000 #5 ArgoCaps

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:

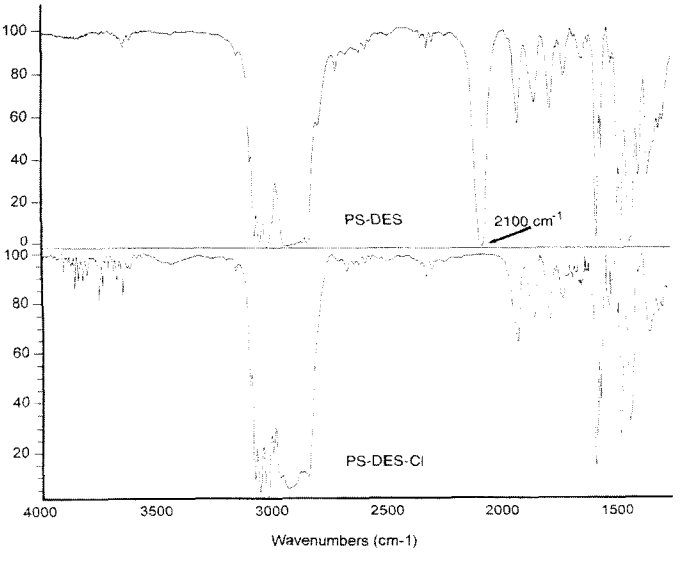
- Polymeric silyl chlorides are reactive and unstable to hydrolysis leading to poor shelf life.
- Displacement of silyl chlorides is difficult to monitor using standard spectroscopic techniques.
- For many traceless applications, aromatic scaffolds are attached to a silicon-containing handle which is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

Argonaut's PS-DES 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,[11,12] carbonyl,[13] aromatic, or unsaturated derivatives) without prior transformation to activated silylating agents (e.g. silyl chloride).
- Efficient transformation into a reactive silyl chloride 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}).

PS-DES resin may be chlorinated to form the silyl chloride derivative by treatment with trichloroiso-

Figure 1



cyanuric acid in DCM, or with1,3-dichloro-5,5-dimethylhydantoin (Aldrich) in DCM (**Scheme 1**).[14] The latter procedure allows complete removal of reagent-derived impurities prior to treatment with nucleophiles and is recommended for all applications where the silyl chloride is utilized (alcohol loading, alkyl lithium, and Grignard addition).

The silyl chloride intermediate is very moisture sensitive and should be handled under an inert environment, washed with anhydrous solvents, and used *in situ* immediately after generation. In this case, examination of the Si-H stretch (IR:2100 cm^{-1}) may be used to effectively monitor the progress of the chlorination (**Figure 1**).

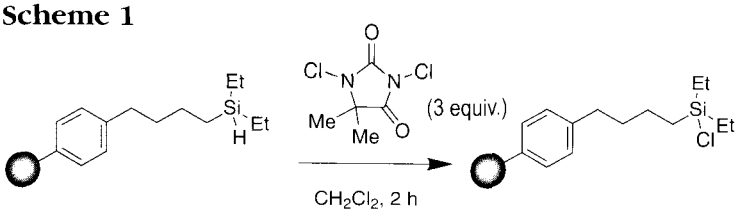
Primary and secondary alcohols (ROH) may be attached to PS-DES-Cl resin by treatment with a DCM solution of alcohol (3 equiv.) and imidazole (3.5 equiv.) for 4 hrs at 25 °C. Representative examples carried out in our laboratories are provided in **Scheme 2**.

A common procedure for both direct attachment of alcohols and hydrosilylation of carbonyl compounds to PS-DES resin in 1-methyl-2-pyrrolidinone (NMP) uses Wilkinson's catalyst to provide resin-bound silyl ether products.[15] (**Scheme 3**)

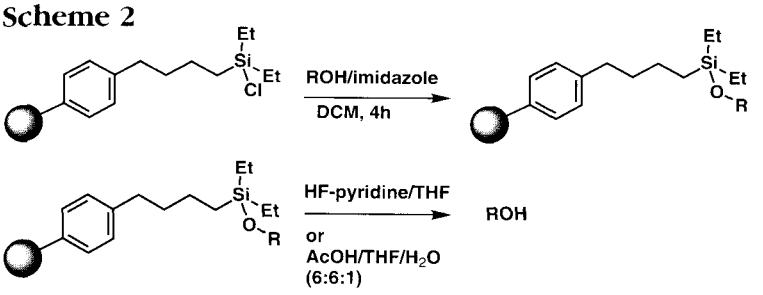
Cleavage of silyl ethers attached to PS-DES may be performed using a 0.3 M HF/pyridine solution in THF for 2 hrs.[16] Alternatively, excess HF may be scavenged using methoxytrimethylsilane ($MeOSiMe_3$) which forms the neutral byproducts $FSiMe_3$ and MeOH and allows direct concentration of cleavage mixtures without further purification.[15] Alternatively, cleavage of silyl ethers derived from primary alcohols was effected by treatment with 6:6:1 AcOH/THF/H_2O (50 °C, 4-8 h). Silyl ethers of secondary alcohols may require longer treatment (e.g. 60-80 °C, 8-12 h).

Aromatic compounds may be loaded to PS-DES resin by chlorination of the resin using 1,3-dichloro-5,5-dimethylhydantoin, washing to remove reagent-based impurities, and addition of aryl lithium reagents in THF (-78 °C) (**Scheme 4**; **Table 1**).[17,18] Electron-rich, neutral, and electron-poor aromatics were loaded using this method and cleaved using TFA/DCM (1:1) for electron-rich aromatic derivatives[19] and TBAF for electron-poor aromatics.[20] Aromatic derivatives attached to the linker thus behave similarly to the traceless linker system reported by Ellman in terms of conditions required for cleavage.[1]

Scheme 1

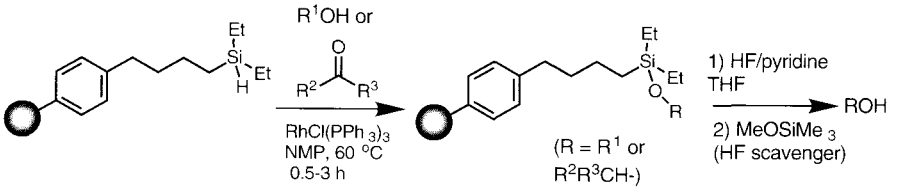


Scheme 2



(1° or 2° ROH)	Yield after cleavage (3 steps)
(s)-(-)-1-(2-methoxybenzoyl)-2-pyrrolidinemethanol	79%
1-naphthaleneethanol	91%
N-Fmoc-ethanolamine	72%
1-(4-methoxyphenoxy)-2-propanol	75%
trans-2-phenylcyclohexanol	60%
epiandrosterone	77%

Scheme 3



Scheme 4

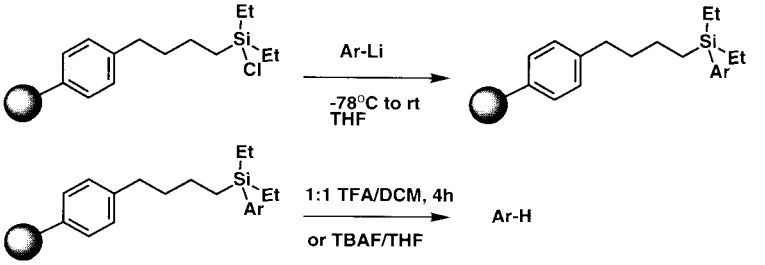
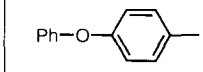
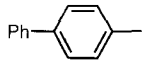
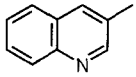


Table 1

Ar	Method	Yield
	TFA/DCM	80%
	TFA/DCM	70%
	TBAF	58%

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 Groups in 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. *J. Org. Chem.* **1976**, 41, 3877.
5. Chan, T.; Huang, W. *J. Chem. Soc., Chem. Commun.* **1995**, 909.
6. Randolph, J. T.; McLure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, 117, 5712.
7. Stover, R. D. H.; Lu, P.; Frechet, J. M. J. *J. Polymer Bulletin* **1991**, 25, 575.
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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. For alcoholysis of hydrosilanes with TBAF in solution, see: Tanabe, Y.; Okumura, H.; Maeda, A.; Murakami, M. *Tetrahedron Lett.* **1994**, 35, 8413.
12. 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.
13. For hydrosilylation of carbonyl compounds in 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.* **1988**, 53, 5405.
14. *Representative procedure for chlorination of PS-DES resin:* To a 5 ml round bottom flask was added under argon 100 mg of PS-DES resin (0.75 mmol/g, 0.075 mmol), and a small magnetic stirring bar. 44 mg (0.225 mmol) 1,3-dichloro-5,5-dimethylhydantoin in 0.8 mL DCM was then added. The mixture was stirred at room temperature. After 2 h, the mixture was washed with anhydrous DCM (3 x 3 mL) and anhydrous THF (3 x 3 mL) under argon. The resin was *immediately* used for further transformations.
15. Hu, Y.; Porco, J. A., Jr.., *Tetrahedron Lett.* **1998**, 39, 2711.
16. After cleavage, the resin was washed with THF (3 x). The filtrate was treated with a saturated solution of $NaHCO_3$, and an EtOAc solution of anthracene (internal standard) was added. After extraction with EtOAc, the organic layer was used for GC quantification.
17. *Loading of 4-phenoxyphenyl bromide:* To 500 mg of PS-DES resin (0.75 mmol/g, 0.375 mmol) was added 220 mg of 1,3-dichloro-5,5-dimethylhydantoin (1.125 mmol) in 4 mL DCM under argon. The mixture was stirred for 2 h at rt. The resin was washed with anhydrous DCM (3 x 7 mL) and anhydrous THF (3 x 7 mL) under argon. To the resin was added at -78 °C 5 equiv. of 4-phenoxyphenyllithium (generated by treating 4-phenoxyphenyl bromide with 1 equiv. of nBuLi at -78 °C for 1 h) in 5 mL THF. The reaction mixture was allowed to warm up to room temperature (4 h). The resulting mixture was washed with THF (3 x 7 mL), THF/H_2O (1:1) (3 x 7 mL), THF (3 x 7 mL), DCM (3 x 7 mL) and dried under vacuum for 12 h to give the 4-phenoxyphenyl silyl resin. IR (cm^{-1}): 1239.8 (Ar-O).
18. *Loading of 3-bromoquinoline:* To a t-BuLi solution in pentane (2 equiv.) was added dropwise a THF solution of 3-bromoquinoline (1 equiv.) under argon at -78 °C. The mixture was stirred at this temperature for 5 mins before transferring via cannula to freshly prepared PS-DES-SiCl resin (~100 mg) at -78 °C. The reaction mixture was allowed to warm up to room temperature in 4 hrs. The resin was washed with THF (3 x 7 mL), THF/H_2O (1:1) (3 x 7 mL), THF (3 x 7 mL), DCM (3 x 7 mL) and dried under vacuum for 12 h.
19. To the 4-phenoxyphenyl silyl resin (100 mg) was added TFA/DCM (1:1, 3 mL). The mixture was stirred at 25 °C for 3 h. The resin was filtered and washed with DCM (3 x 2 mL). The combined filtrate was treated with saturated $NaHCO_3$. The organic layer was used for GC quantification (anthracene as internal standard).
20. Treatment of the silyl quinoline resin with TBAF (1.0 M in THF, 3 mL) for 12 h followed by extraction of the product into DCM led to the recovery of quinoline in 58% yield (GC quantification using anthracene as internal standard).

General Reference for PS-DES

Hu, Y.; Porco, J. A. Jr.; Labadie, J.; Gooding O.; Trost, B. M., *J. Org. Chem.*, **1998**, *63*, 4518.

Solid Phase Toolbox For Organic Synthesis

To facilitate a wide range of solid phase reactions, Argonaut offers a complete Solid Phase Toolbox:

Solid Phase Toolbox

- 10 gram quantities of each: PS-Wang, PS-MB-CHO, PS-Rink, PS-AS-SO_2NH_2, PS-NH_2, PS-Cl, PS-DES
- Product information cards
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Part # 800357

MB-CHO Linker Kit

- 10 gram quantities of each: PS-MB-CHO, ArgoGel-MB-CHO, ArgoPore-MB-CHO

Part # 800358

AS-SO_2NH_2 Linker Kit

- 10 gram quantities of each: PS-AS-SO_2NH_2, ArgoGel-AS-SO_2NH_2, ArgoPore-AS-SO_2NH_2

Part # 800359

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This family of resins is based on a highly crosslinked macroporous polystyrene framework which provides low and predictable swelling in all solvents. The unique design means:

- rapid diffusional access of reagents to reaction sites at the pore surface
- removal of byproducts using virtually any solvent
- suitable for reactions with low-solubility 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 chemistry to solid phase. Yet ArgoPore is well 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 polyethylene glycol-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 faster reaction rates. These properties make ArgoGel resins ideal for reaction development when compared to other polystyrene solid supports.

ArgoGel's high quality beads have very low leachable PEG impurities, higher loading and greater stability due to the unique bifurcated linkage versus more labile benzylic ether linkages and are compatible with a wide range of solvents, including water.

References for ArgoGel and ArgoPore Resins

"Consumables for Organic Synthesis," 1998 Catalog

ArgoPore Data Sheet, Argonaut Technologies, DS-013

ArgoGel Data Sheets, Argonaut Technologies, DS-005 thru DS-012

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Our products include organic synthesizers, software and chemical resins and reagents that facilitate solution and solid phase chemistry. Our worldwide staff of experienced organic chemists are dedicated to providing technical support on all aspects of parallel organic synthesis.

Argonaut has assembled a world-class team of chemists, systems engineers and software programmers who work together to design systems optimized for parallel synthesis based on a wide range of chemistries.

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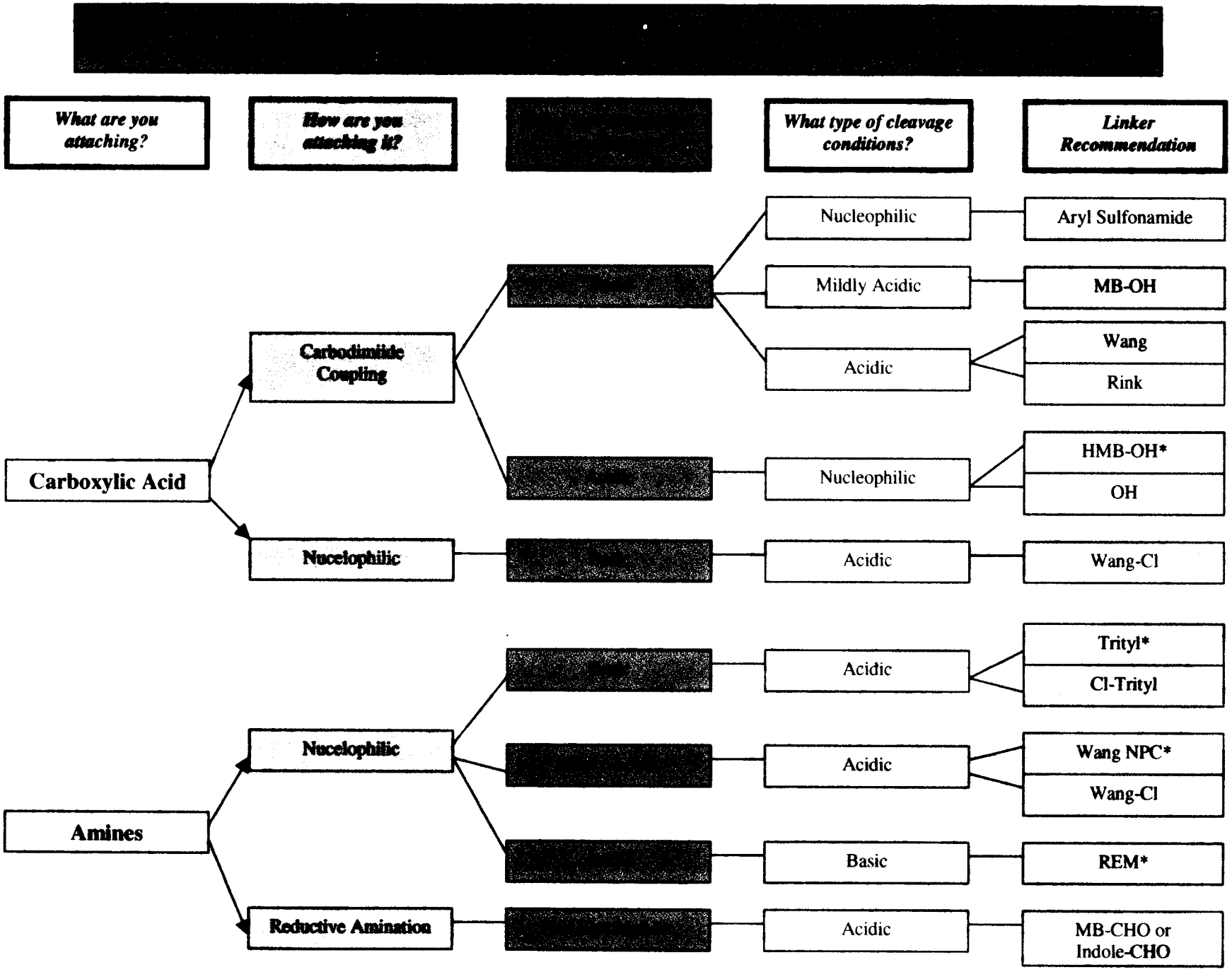

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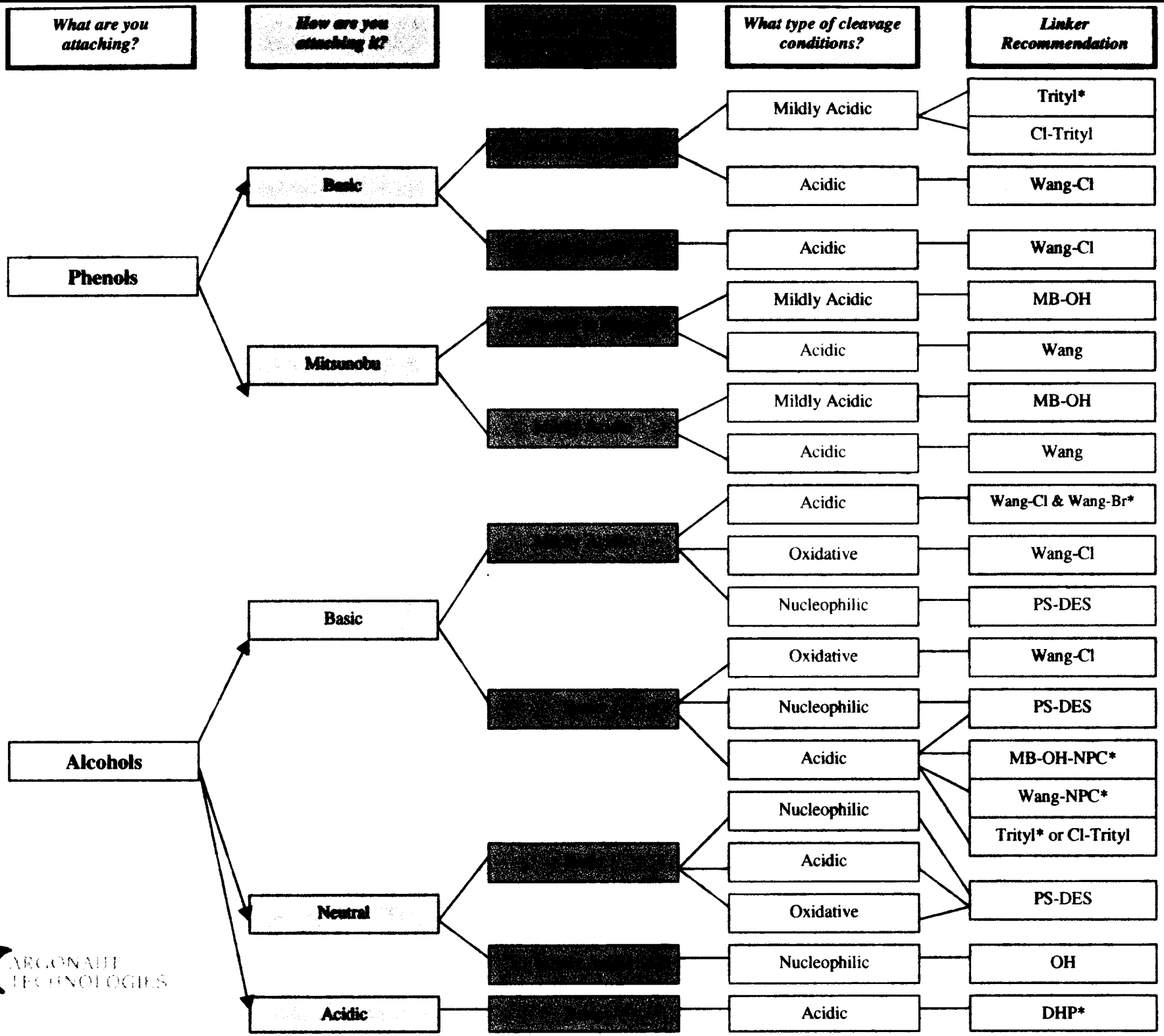
* Denotes that linker is available as a custom synthesis.


What are you attaching?
How are you attaching it?
What type of cleavage conditions?
Linker Recommendation
Phenols
Basic
Mitsunobu
Alcohols
Basic
Neutral
Acidic
Mildly Acidic
Acidic
Trityl*
Cl-Trityl
Wang-Cl
MB-OH
Wang
Oxidative
Nucleophilic
PS-DES
MB-OH-NPC*
Wang-NPC*
Trityl* or Cl-Trityl
OH
DHP*
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Scavengers for Nucleophiles

Which compounds to scavenge?		Recommended Scavengers*
Alcohols		**PS-TsCl-HL**
Amines	Primary, Secondary	**PS-Isocyanate** MP-TsOH PS-TsCl-HL
	Selective for Primary	**PS-Benzaldehyde**
	Anilines (aromatic)	**PS-TsCl-HL** MP-TsOH PS-Isocyanate
Hydrazines		**PS-Benzaldehyde** PS-TsCl-HL
Active methylenes (e.g., keto esters)		**PS-Benzaldehyde**
Thiols/Thiolates		**PS-Isocyanate** PS-Thiophenol
Alkoxides		**PS-TsCl-HL** PS-Isocyanate
Organometallics		**PS-Benzaldehyde** PS-TsCl-HL
Reducing Agents		**PS-Benzaldehyde**
Acids/Acidic Phenols	HOBt Pentafluorophenol 4-Nitrophenol Carboxylic Acid Phenol	**MP-Carbonate** **PS-Trisamine**

*Recommended choice in **red**.

Scavengers for Electrophiles

Which compounds to scavenge?		Recommended Scavengers*
Carbonyls	→	**PS-TsNHNH$_2$** PS-Trisamine
Alkylating Agents	→ Alkyl halides, Mesylates, Tosylates, α-bromoesters, α-bromoketones →	**PS-Thiophenol** PS-Triphenylphosphine
Acid Chlorides	→	**PS-Trisamine** PS-NH$_2$
Sulfonyl Chlorides	→	**PS-Trisamine** PS-DMAP PS-NH$_2$
Isocyanates	→	**PS-Trisamine** PS-NH$_2$
Epoxide	→	**PS-Thiophenol**

*Recommended choice in **red**.

Polymer Reagents

What type of reagent? What application?	Recommended Polymer Reagent

Bases

Basic quenching, neutralize ammonium salts	**MP-Carbonate**
Strong tertiary amine base (e.g. mesylate formation)	**PS-DIEA**
Tertiary amine base (e.g. formation of amides, sulfonamides, carbamates)	**PS-NMM**

Acids

Acid quenching	**MP-TsOH** **PS-DIEA HCl**

Catalysts

Acids	**MP-TsOH**
Acyl Transfer	**PS-DMAP**

Coupling Agents

Amide or Ester Formation	**PS-Carbodiimide,** **PS-HOBt**
Activated Ester Formation	**PS-Carbodiimide**
Protecting Group Transfer	**PS-HOBt**

Polymer Reagents

What type of reagent? What application?	Recommended Polymer Reagent

Electrophilic Activation

Halogenation (chlorination, bromination, iodination)	**PS-Triphenylphosphine**
Phenylether formation (i.e. Mitsunobu reaction)	**PS-Triphenylphosphine**
Thioester active intermediate	**PS-Thiophenol**
Alcohol activation	**PS-TsCl**
Acid and sulfonyl chloride activation	**PS-DMAP**

Nucleophilic Activation

Carbon-carbon bond formation (e.g. Wittig reaction)	**PS-Triphenylphosphine**
Sulfonyl hydrazone formation (e.g. Hurd-Mori thiadiazole synthesis)	**PS-TsNHNH$_2$**