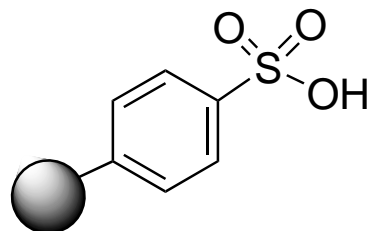


MP-TsOH(65) Columns

Amine Isolation and Purification Columns



Chemical Name: Macroporous polystyrene sulfonic acid

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

Capacity: 2.5 mmol/g nominal

Bead Size: 50–100 μm

Application: Amine purification by “catch-and-release”, scavenging basic impurities, purification of compounds with basic groups

Typical Conditions for use: Flow through under gravity or vacuum, 1.5–3.0 equiv. resin relative to amine or other basic compound

Compatible Solvents: DCM, THF, methanol and DMF

Storage Conditions: Room temperature

INTRODUCTION

MP-TsOH(65) columns have been designed specifically for isolation and purification of amines. The columns may also be used to scavenge basic reagents, substrates and reaction byproducts. A range of configurations is available from 100 mg/3 mL to 2.5 g/25 mL, including tab-less 3 and 6 mL for 48 and 24-well applications respectively. **See page 6** for ordering information.

MP-TsOH(65) is a sulfonated macroporous poly (styrene-*co*-divinylbenzene) and a polymer-bound equivalent of *p*-toluenesulfonic acid (TsOH). The sulfonic acid functional group retains aliphatic, aromatic and heterocyclic amines from common organic solvents. As part of the process, the basic species is protonated to form bound sulfonate salts. Making the resin available in a column format makes it particularly convenient for use as a scavenger and for amine purification.

CATCH-AND-RELEASE PURIFICATION OF AMINES

The procedure for isolating amines using MP-TsOH(65) columns is known as catch-and-release and is detailed below. When a solution containing an amine is passed through a MP-TsOH(65) column the amine is retained or “caught” by the resin. Non-basic impurities are not retained and are further removed by washing the column with an organic solvent, such as DCM, THF or methanol. The product is subsequently “released” from the column by elution with a solution of ammonia in methanol. Amine salts of weak conjugate acids (e.g. acetate and trifluoroacetate) are exchanged onto the resin and are released as the free amine during the ammonia/methanol wash.

CATCH-AND-RELEASE PROCEDURE

1. Column Pre-conditioning

Wash the column with DCM, methanol or THF (4 mL/g resin).

2. Sample Loading

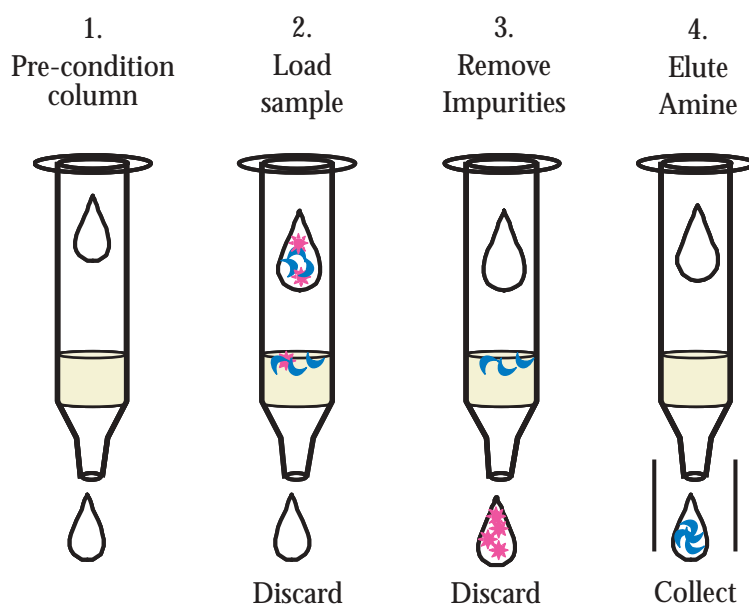
Load the amine sample or reaction mixture onto column under gravity and discard the eluent.

3. Wash Impurity

Remove the non-basic impurities by washing with DCM (3 x 3 mL/g resin). Discard the wash.

4. Amine Elution

Elute basic amines with a solution of ammonia in methanol (2 M, 4 mL/g resin). Evaluate the use of 4 M ammonia/methanol solution (2 mL/g resin) to improve elution efficiency and reduce elution volume. Collect the eluent. Wash with methanol (2 x 4 mL/g resin) for complete recovery of the amine.



Schematic showing catch-and-release of amines using MP-TsOH(65) columns

AMINE PURIFICATION

MP-TsOH(65) columns were found to be highly effective at retaining compounds with a range of basicity, including aliphatic, aromatic and heterocyclic amines. Retention and elution characteristics of a range of amines were evaluated using a 0.2 M solution of amine in two solvents, DCM and DMF. The columns were pre-conditioned with DCM. Solvents such as THF and methanol can also be used for this step. The amine solutions were then applied and the columns rinsed with DCM (3 x 1.5 mL). The DCM fractions were combined and then analyzed by GC. Unretained amine was quantified using biphenyl as an internal standard (**Table 1**).

Table 1. Catch-and-Release Purification of Amines using MP-TsOH(65) 500 mg/6 mL Columns

Amine	Volume (mL)	Amine (mmol)	Resin Capacity (mmol)	Unretained Amine (%)		*Amine Recovery (%)
				DCM	DMF	
3-Phenylpropylamine	8.5	1.7	2.5	0	0	98
N-Methylbenzylamine	8.5	1.7	2.5	0	0	97
N,N-Dimethylbenzylamine	8.5	1.7	2.5	0	0	92
N-Methyl,N,N-di(2-phenethyl)amine	8.5	1.7	2.5	0	0	95
4-(2'-Dimethylaminoethyl)morpholine	4.0	0.8	2.5	0	0	96
2-Aminothiazole	8.5	1.7	2.5	0	0	96
Aniline	8.5	1.7	2.5	0	0	94
4-Nitroaniline	4.0	0.8	2.5	0	30	97

*DCM used as the sample solvent

Full retention of a range of primary, secondary and tertiary amines were observed. In addition, weakly basic amines such as aminothiazole and 4-nitroaniline were fully retained from DCM. In general, 1.5–2.0 equivalents of resin relative to the amine were used to ensure complete retention. For amines with more than one basic functional group, 1.5 equivalents of resin relative to each basic site were used. Three equivalents of resin were used for less basic substrates such as 4-nitroaniline.

The amines were eluted with a 2 M solution of ammonia in methanol. The ammonia exchanges with the amine on the resin, releasing it into the solution. Following elution and concentration, the amines gave excellent recovery and 100% purity (Table 1). In addition, the isolated amines did not contain any impurities due to media decomposition. The solvent in which the amine is applied influences the retention of very weakly basic amines, e.g. 4-nitroaniline (Table 2). Complete retention of 4-nitroaniline was observed when DCM was used, with retention less efficient in THF or DMF. When using these solvents, greater than 3.0 equivalents of resin is recommended for weakly basic amines.

Table 2. Solvent Effect on Retention of Weakly Basic 4-Nitroaniline

Conc. (M)	Resin (mmol)	Amine (mmol)	Unretained Amine (%)		
			DCM	THF	DFM
0.1	2.5	1.7	13	28	40
0.1	2.5	1.3	8	30	33
0.1	2.5	0.85	0	0	26

Removal of high-boiling reaction solvents, such as DMF and DMSO, is a frequent problem in product isolation following organic synthesis. MP-TsOH(65) columns can be used successfully to isolate amines from solutions of DMF (**Table 3**). After complete removal of the DMF using DCM, the retained amine is eluted with an ammonia/methanol solution. The amine is then isolated by removal of the volatile ammonia/methanol solution by evaporation. The slower sample flow rate exhibited by certain viscous solvents including DMF and DMSO, can be improved by increasing the vacuum, applying positive pressure to the column, or diluting with a less viscous solvent. MP-TsOH(65) 500 mg/6 mL columns demonstrate complete retention of amines even at flow rates as high as 13 mL/min.

Table 3. Extraction of Amines from DMF or DMSO Solution with MP-TsOH(65) 1 g/15 mL Columns

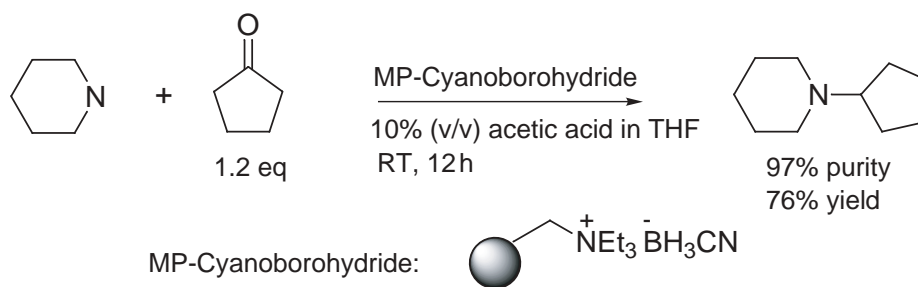
Amine	DMF Solution		DMSO Solution	
	Flow Rate (mL/min)	Unretained Amine (%)	Flow Rate (mL/min)	Unretained Amine (%)
Aminothiazole	11	0	10	0
3-Phenylpropylamine	13	0	11	0

APPLICATION IN REDUCTIVE AMINATION REACTIONS

The reductive amination of carbonyl compounds is widely used in amine synthesis. MP-TsOH(65) columns can be used to simplify the purification process following this type of reaction. When using this approach, the stoichiometry of the reaction is usually adjusted towards excess carbonyl compound (10–20%) to drive the reaction to completion. It is therefore best suited for reactions where product over-alkylation is not an issue. The catch-and-release purification approach is particularly useful when used in conjunction with a bound reducing agent, such as MP-Cyanoborohydride.¹

An example of this approach is provided by the synthesis of N-cyclopentylpiperidine (**Scheme 1**). Reductive amination of 1.2 equivalents of cyclopentanone with 1 equivalent of piperidine was carried out with MP-Cyanoborohydride in 10% (v/v) acetic acid/THF. On completion, the reaction mixture was filtered and the filtrate passed through a conditioned MP-TsOH(65) column to retain the amine product. The excess carbonyl compound and its reduced product passed directly through the column, with an additional DCM wash removing any remaining non-basic impurities. The free amine was "released" with ammonia/methanol to afford the product in 76% yield and 97% purity. In addition to product purification, the process serves to exchange the product solution from acetic acid/THF to a more volatile ammonia/methanol solution.

Scheme 1



SCAVENGING OF BASIC IMPURITIES

MP-TsOH(65) columns can also be used to scavenge basic impurities and thereby purify reaction mixtures. As shown in **Table 1**, a variety of amines are retained, including weakly basic heterocyclic amines and anilines. Passing a reaction mixture through an MP-TsOH(65) column will result in removal of all basic components in the mixture. If additional selectivity is required, the use of a more selective scavenger resin is recommended, for example, PS-Isocyanate² (for removal of primary and secondary amines), or PS-Benzaldehyde³ (for selective removal of primary amines). An alternative approach to selectivity enhancement is the use of derivatization purification techniques in conjunction with silica based strong cation exchange columns ISOLUTE SCX-2.⁴

OTHER APPLICATIONS

In Mitsunobu, Suzuki and Heck reactions, it is often challenging to isolate pure products from the byproducts such as triphenylphosphine oxide and palladium. MP-TsOH(65) columns can be used to purify these products when they contain a basic functional group. The reaction mixture is applied to the column and the product is retained by MP-TsOH(65). The byproducts can be easily removed with a methanol or DCM wash step. The product can then be released by eluting with 2 M ammonia in methanol.

Representative Experimental Procedures

The following procedures were developed using 1 g/15 mL MP-TsOH(65) columns. While using 500 mg/6 mL MP-TsOH(65) columns, the same experimental procedures should be followed, while reducing the volumes of the reactants and solvents by 50%.

Purification of Amine from Reductive Amination Reaction with MP-Cyanoborohydride (see page 4):

A mixture of piperidine (0.043 g, 0.5 mmol), cyclopentanone (0.050 g, 0.6 mmol), acetic acid (0.5 mL) and MP-Cyanoborohydride (2.4 mmol/g, 0.32 g, 0.75 mmol) in dry THF (4 mL) was agitated for 12 hours at room temperature. The solution was filtered and the resin washed with THF (2 x 2 mL). The combined filtrate and washings from the reaction were added onto a MP-TsOH(65) column (1 g, 2.5 mmol), pre-conditioned with DCM (4 mL). The filtrate was allowed to flow through the column, followed by washing with DCM (3 x 3 mL) to remove any non-basic impurities. The amine was released from the column by the addition of ammonia in methanol (2 M, 4 mL), followed by washing with methanol (2 x 4 mL). The resulting solution was concentrated to afford N-cyclopentylpiperidine in 76% yield (GC purity 97%).

Scavenging Excess Amine from Sulfonamide Reactions:

A mixture of 3-phenylpropylamine (0.162 g, 1.2 mmol), methanesulfonyl chloride (0.114 g, 1 mmol) and PS-DIEA⁵ (3.2 mmol/g, 0.78 g, 2.5 mmol) in DCM (3 mL) was agitated for 6 hours at room temperature. The solution was filtered and the resin was washed with DCM (2 x 3 mL).

A MP-TsOH(65) column was used to scavenge the excess amine from the combined filtrate. The column (1 g, 2.5 mmol) was pre-conditioned with DCM (4 mL) and the combined filtrate and washings from the reaction were applied to the column. The column was then washed with DCM (3 x 3 mL). The combined washings from the column were concentrated to afford the product N-(3-phenylpropyl) methane sulphonamide at 93% yield (GC purity 100%).

Purification of an N-Heterocyclic Product from Suzuki Coupling:

To a solution of 3-bromopyridine (0.158 g, 1 mmol) in DMF (2 mL) under nitrogen was added a solution of 4-methylbenzeneboronic acid (0.162 g, 1.2 mmol) in ethanol (1 mL), a solution of K₂CO₃ (0.207 g, 1.5 mmol) in water (1 mL) and tetrakis(triphenylphosphine)palladium (0.010 g, 0.01 mmol). The reaction mixture was agitated for 16 hours at 75 °C, cooled to room temperature and diluted with DCM (6 mL). The reaction mixture was then added onto a MP-TsOH(65) 1 g/15 mL column (2.5 mmol), pre-conditioned with DCM (4 mL). The solution was allowed to flow through the column, followed by washing with methanol (3 x 4 mL) to remove non-basic impurities. The product was "released" from the column by the addition of ammonia in methanol (2 M, 4 mL), followed by washing with methanol (2 x 4 mL). The resulting solution was concentrated to afford 3-(p-tolyl)pyridine in 87% yield (GC purity 96%).

PROCESSING OPTIONS

The MP-TsOH(65) columns have industry standard Luer tips and can be processed manually using a FlashVac™ Sample Processing Manifold or by automation using some commercially available liquid handling systems. Contact Argonaut Technologies for further information on these processing options.

ORDERING INFORMATION

MP-TsOH(65) Columns

Description	Pack size	Part number
MP-TsOH(65) 100 mg/3 mL	50	800477-0010-B
MP-TsOH(65) 250 mg/6 mL	30	800477-0025-C
MP-TsOH(65) 500 mg/6 mL	30	800477-0050-C
MP-TsOH(65) 1 g/15 mL	20	800477-0100-D
MP-TsOH(65) 2.5 g/25 mL	20	800477-0250-E

TAB-LESS MP-TSOH(65) COLUMNS

Argonaut Technologies' tab-less MP-TsOH(65) columns are ideal for high throughput purifications using specific liquid handling systems. Racks available for these systems can accommodate tab-less 3 and 6 mL configurations arranged in a microplate footprint containing 48 or 24 columns respectively.

The tab-less 6 mL MP-TsOH(65) columns are compatible with the ISOLUTE® Array-24 base plates for use on the VacMaster™-96 Sample Processing Manifold. Contact Argonaut Technologies for further information on these high throughput formats.

ORDERING INFORMATION

Tab-less MP-TsOH(65) Columns

Description	Pack size	Part number
MP-TsOH(65) 100 mg/3 mL (tab-less)	50	800477-0010-BG
MP-TsOH(65) 250 mg/6 mL (tab-less)*	30	800477-0025-CG
MP-TsOH(65) 500 mg/6 mL (tab-less)*	30	800477-0050-CG

** Compatible with the ISOLUTE Array-24 system*

REFERENCES

1. MP-Cyanoborohydride: Argonaut Technologies, Part Numbers 800405 (10 g), 800406 (25 g), 800407 (100 g).
2. PS-Isocyanate: Argonaut Technologies, Part Numbers 800260 (10 g), 800261 (25 g), 800262 (100 g).
3. PS-Benzaldehyde: Argonaut Technologies, Part Numbers 800360 (10 g), 800361 (25 g), 800362 (100 g).
4. Request Technical Note **TN128 Increasing the Selectivity of Silica Based Cation Exchange Sorbents for the Purification of Reaction Mixtures Using Derivatization Purification Techniques.**
5. PS-DIEA: Argonaut Technologies, Part Numbers 800279 (10 g), 800280 (25 g), 800281 (100 g).

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