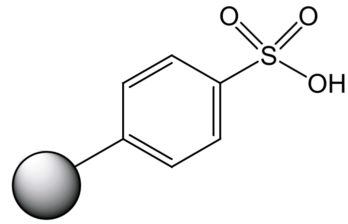
Technical Note 506

MP-TsOH Cartridge

Amine Isolation and Purification Cartridges



Chemical Name: Macroporous polystyrene sulfonic acid

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

Capacity: 2.5 mmol/g nominal

Bead Size: 50–100 microns

Applications: Amine purification by "catch and release"; scavenging basic impurities; purification of compounds containing basic sites

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, DMF

Storage Conditions: Room temperature

INTRODUCTION

MP-TsOH cartridges have been designed specifically for isolation and purification of amines. They can also be used to scavenge basic reagents, substrates, and reaction by-products. The cartridges are 6 mL in size, packed with 0.5 g of Argonaut MP-TsOH resin.

MP-TsOH is a sulfonated macroporous polystyrene resin that is a polymer-bound equivalent of *p*-toluenesulfonic acid (TsOH). The resin shows strong affinity for a wide variety of aliphatic, aromatic and heterocyclic amines that can be protonated to form bound sulfonate salts. MP-TsOH resin has been optimized for use in synthetic organic chemistry. Prepackaging the resin in a cartridge format makes it particularly convenient for use as a scavenger and for amine purification.

The procedure for isolating amines using MP-TsOH is known as "catch and release" and is illustrated in **Table 1**. When a solution containing an amine is passed through a cartridge of MP-TsOH, the amine is retained or "caught" on the resin. Non-basic impurities are removed by washing the cartridge with an organic solvent, such as DCM, THF or MeOH. The product is subsequently "released" from the cartridge by elution with a solution of ammonia in MeOH. Amine salts of weak conjugate acids (*e.g.*, acetate, trifluoroacetate) are exchanged onto the resin and are released as the free amine during the ammonia/methanol wash.

MP-TsOH Cartridge

Description	Pack size	Part Number
0.5 g MP-TsOH resin in 6 mL cartridge	30	800477-C30

Argonaut

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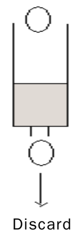
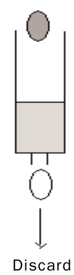
Table 1. Sample Processing for "Catch and Release" Purification of Amines

1. Pre-conditioning



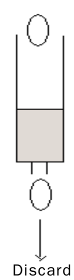
The cartridges are preconditioned by washing with DCM or MeOH or THF (4 mL/g resin).

2. Loading samples on cartridges



After preconditioning, load the amine sample or reaction mixture onto the cartridge. Let the solution flow through the cartridge.

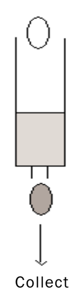
3. Wash to remove non-basic impurities



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

Note: If desired, larger amounts of DCM may be used.

4. Elution of amine



Add 2 M solution of ammonia in MeOH (4 mL/g resin) to elute the amine from the cartridge. Wash with MeOH (2 x 4 mL/g resin) for complete recovery.

AMINE PURIFICATION

MP-TsOH was found to be highly effective at retaining compounds with a range of basicity, including aliphatic, aromatic and heterocyclic amines. Retention and release behaviors of a range of amines were evaluated using 0.2 M solutions of amines in DCM and DMF. The cartridges were preconditioned with DCM. Solvents such as THF and MeOH may also be used for preconditioning. The amine solutions were then applied and the cartridges rinsed with DCM (3 x). The combined DCM washings were analyzed by GC and any unretained amine was quantified using biphenyl as an internal standard (**Table 2**).

Table 2. Catch and Release Purification of Amines using 0.2 M Solutions and 1 g MP-TsOH Cartridges

Amine	Vol (mL)	Amine (mmol)	Resin (mmol)	Unretained Amine (%)		*Released 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

*Values are based on experiments using DCM as the solvent.

Full retention of a range of primary, secondary and tertiary amines was observed. Even weakly basic amines such as aminothiazole and 4-nitroaniline were fully retained from DCM solutions. In general, 1.5–2.0 equivalents of resin relative to the amine were used to assure 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. After concentration, the amines are obtained with excellent recovery and 100% purity (**Table 2**). The isolated amines did not contain any impurity due to media decomposition.

The solvent in which the amine is applied influences the retention of less basic amines (**Table 3**). With 4-nitroaniline, the percent retained followed the order DCM>THF>DMF. Full retention of 4-nitroaniline was achieved when DCM was used, however, retention was less efficient in THF or DMF. With these solvents greater than 3.0 equivalents of resin are recommended for weakly basic amines.

Table 3. Solvent Effect on Retention of Weakly Basic 4-Nitroaniline

Conc. (M)	Resin (mmol)	Amine (mmol)	Unretained Amine (%)		
			DCM	THF	DMF
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 frequently a problem in organic synthesis during product isolation. MP-TsOH cartridges can be used successfully to extract amines from solutions of DMF (**Table 4**). After complete elution of DMF using DCM, the retained amine is released with an ammonia/methanol solution. The amine is then isolated by removal of the volatile ammonia/methanol with a rotovap or solvent concentrator. The slow flow rate of amine solutions in viscous solvents such as DMF and DMSO can be accelerated either by applying pressure or vacuum. MP-TsOH cartridges demonstrate complete retention of amines even at flow rates as high as 13 mL/min. The FlashVac® or VacMaster® systems[1] are convenient tools that allow parallel processing of 20 cartridges under vacuum.

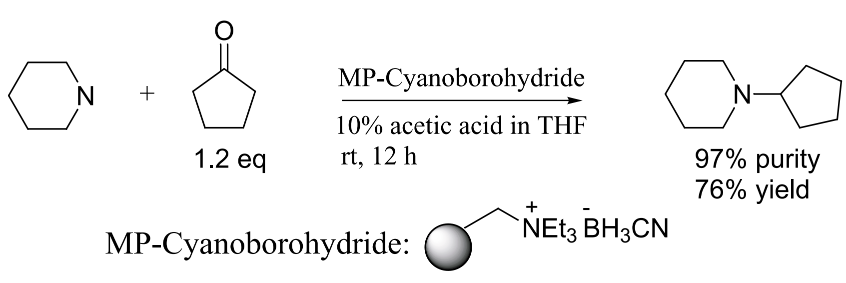
Table 4. Extraction of Amines from DMF or DMSO Solution

Amine	DMF Solution		DMSO Solution	
	Flow Rate (mL/min)	Unretained amine %	Flow Rate (mL/min)	Unretained amine %
Aminothiazole	10.9	0	9.6	0
3-Phenylpropylamine	13.2	0	10.8	0

APPLICATION IN REDUCTIVE AMINATION REACTIONS

The reductive amination of carbonyl compounds is widely used in amine synthesis. Use of MP-TsOH cartridges simplifies purification of the products. 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.[2]

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% acetic acid/THF. Upon completion, the reaction mixture was filtered and the filtrate was passed through an MP-TsOH cartridge to retain the amine product, while the excess carbonyl compound and its reduced product were washed off the cartridge with DCM. 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 ammonia/methanol, which is more readily evaporated in the final step of product isolation.



Scheme 1

SCAVENGING OF BASIC IMPURITIES

MP-TsOH cartridges can also be used to scavenge basic impurities and thereby purify reaction mixtures. As shown in **Table 1**, a variety of amines are retained by MP-TsOH, including weakly basic heterocyclic amines and anilines. Passing a reaction mixture through an MP-TsOH cartridge will result in removal of all basic components in the mixture. If selectivity is required then the use of a more selective scavenger resin is recommended, for example, PS-Isocyanate[3] (for removal of primary and secondary amines), or PS-Benzaldehyde[4] (for selective removal of primary amines).

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 can be used to purify these products when they contain a basic site. The reaction mixture is applied to the cartridge and the product is retained by MP-TsOH. The byproducts can be easily washed away with MeOH or DCM. The product can then be released by eluting the cartridge with 2 M ammonia in methanol.

Representative Experimental Procedures
The following procedures were developed using 1 g MP-TsOH cartridges. While using 0.5 g MP-TsOH cartridges, the same experimental procedures should be followed, while reducing the amounts of the reactants and solvents by 50%.

Purification of Amine from Reductive Amination Reaction with MP-Cyanoborohydride: 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 h 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 an MP-TsOH cartridge (1 g, 2.5 mmol), pre-conditioned with DCM (4 mL). The filtrate was allowed to flow through the cartridge, followed by washing with DCM (3 x 3 mL) to remove any non-basic impurities. The amine was released from the cartridge 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-DIEA[5] (3.2 mmol/g, 0.78 g, 2.5 mmol) in DCM (3 mL) was agitated for 6 h at room temperature. The solution was filtered and the resin was washed with DCM (2 x 3 mL).

A MP-TsOH cartridge was used to scavenge the excess amine from the combined filtrate. The cartridge (1 g, 2.5 mmol) was pre-conditioned with 4 mL DCM and the combined filtrate and washings from the reaction were applied to the cartridge. The cartridge was then washed with DCM (3 x 3 mL). The combined washings from the cartridge were concentrated to afford the product N-(3-phenylpropyl)methane sulfonamide 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 2 mL DME under nitrogen was added a solution of 4-methylbenzeneboronic acid (0.162 g, 1.2 mmol) in EtOH (1 mL), a solution of K_2CO_3 (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 h at 75 °C, cooled to room temperature and diluted with DCM (6 mL).

The reaction mixture was then added onto a MP-TsOH cartridge (1 g, 2.5 mmol), pre-conditioned with DCM (4 mL). The solution was allowed to flow through the cartridge, followed by washing with methanol (3 x 4 mL) to remove non-basic impurities. The product was released from the cartridge 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%)

REFERENCES

1. FlashVac® Part Number 122-2025 VacMaster® Part Number 121-1027 Sample Processing Stations.
2. MP-Cyanoborohydride: Argonaut Technologies, Part Numbers 800405 (10 g), 800406 (25 g), 800407 (100 g).
3. PS-Isocyanate: Argonaut Technologies, Part Numbers 800260 (10 g), 800261 (25 g), 800262 (100 g).
4. PS-Benzaldehyde: Argonaut Technologies, Part Numbers 800360 (10 g), 800361 (25 g), 800362 (100 g).
5. PS-DIEA: Argonaut Technologies, Part Numbers 800279 (10 g), 800280 (25 g), 800281 (100 g).

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