

# Polymer-Supported Toluenesulfonic Acid: A Versatile Tool for Expedient Purification or Scavenging of Amines and Nitrogen Heterocycles

Sukanta Bhattacharyya, Lanchi Vo, Owen W. Gooding,  
Tejal Parekh, and Jeff Labadie  
Argonaut Technologies, 1101 Chess Dr.  
Foster City, CA 94404

# Purification Techniques – SPE, Scavengers and Bound Reagents

- Solid phase extraction (SPE) & scavengers extract compounds onto functional or adsorptive media
  - SPE – reversible
    - Subsequent release into solution
  - Scavengers – mainly irreversible
  - Purification is by filtration or simple passage through a column

# Significance of Amines in Medicinal Chemistry

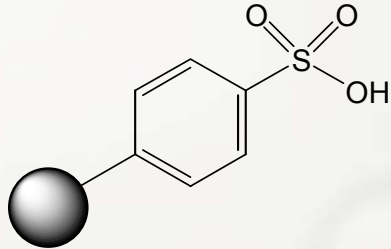
- Amines and their carboxamide derivatives are the most prevalent structural moieties found in the comprehensive medicinal chemistry database<sup>1</sup>
- Aliphatic tertiary amines comprise 25% of drugs currently on the market<sup>2</sup>
- Secondary amines are particularly useful because additional diversity is easily added<sup>3</sup>
- Secondary amines are used as pharmacophores,<sup>4</sup> and as versatile building blocks for ligands<sup>5</sup> and library synthesis

1. Ghose, Viswanadhan, Wendoloski, J. J. *J. Comb. Chem.* **1999**, 1, 55.
2. Morphy et al., *J. Am. Chem. Soc.* **1997**, 119, 3288.
3. See, for example: Bhattacharyya, Fan, Vo, Labadie, *J. Comb. Chem. & Highthroughput Screening*, **2000**, 3, 117.
4. Insaf, Witiak, *Synthesis*, **1999**, 435 and references therein.
5. Swamura, Ito, *Chem. Rev.* **1992**, 92, 857; Togni, Venanzi, *Angew Chem. Int. Ed. Engl.* **1994**, 33, 497;

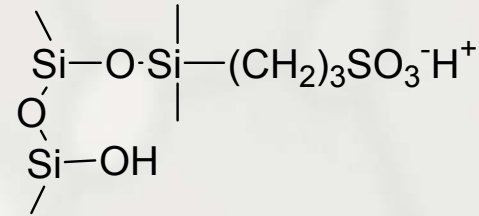
# Amine Purification Using Flow Through Methods

- ISOLUTE<sup>®</sup> SCX-2 Cartridges
  - Silica based
  - Matrix does not swell in solvent
  - 0.4 mmol/g capacity
- MP-TsOH Cartridges
  - Highly crosslinked macroporous polystyrene
  - Very stable under broad range of pH conditions
  - 2.5 mmol/g capacity

## Bound Sulfonic Acid: MP-TsOH and ISOLUTE SCX-2



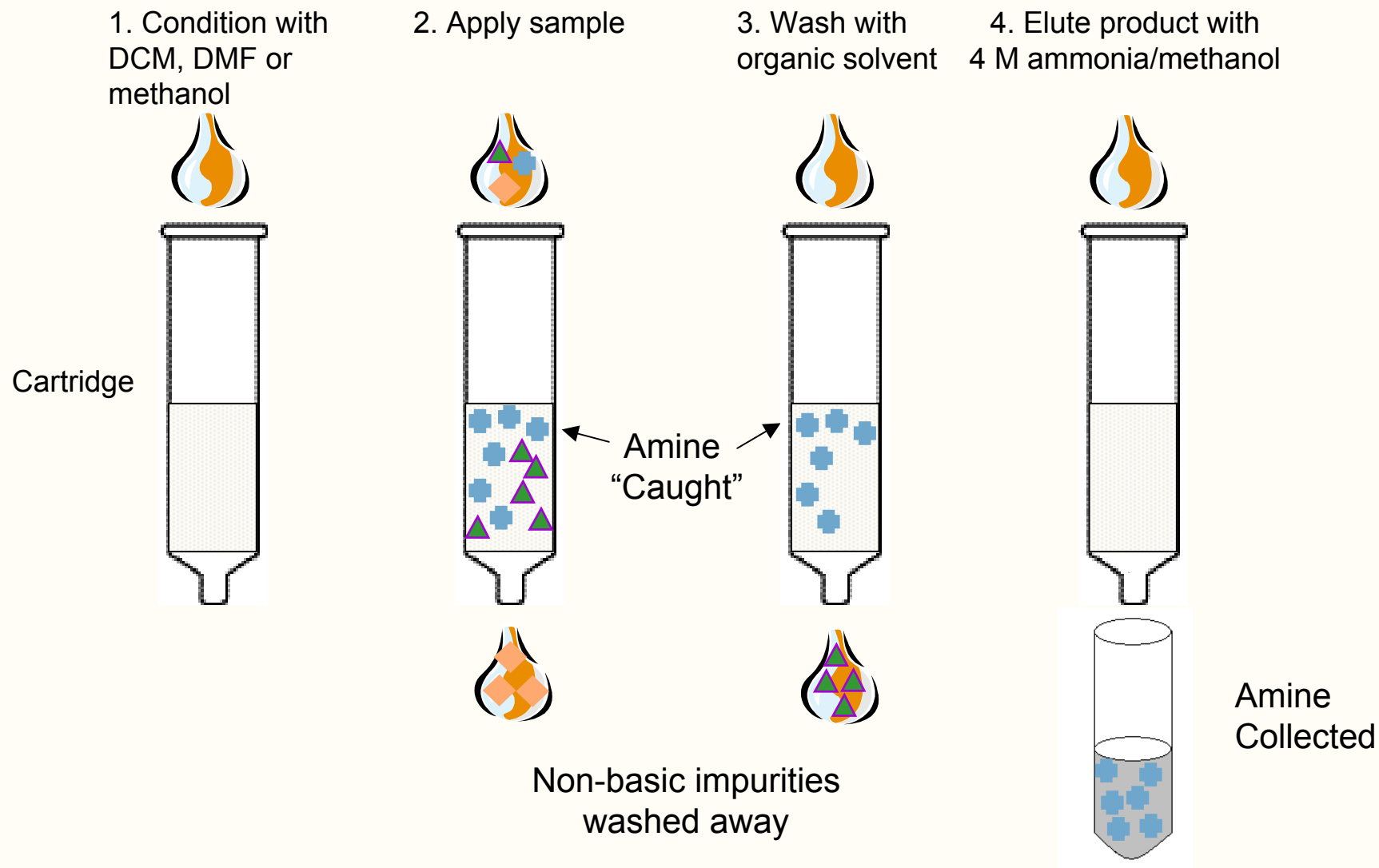
MP-TsOH



ISOLUTE SCX-2

- Bound sulfonic acid equivalents
  - Silica or highly crosslinked polystyrene based
- Scavenge amines, basic compounds
- Catch and Release purifications
  - Catch amines, basic heterocycles
  - Wash impurities
  - Release amine with ammonia/methanol

# MP-TsOH Cartridges for Amine Purification



# Comparison: Procedures for use

|                                  | <b>MP-TsOH</b> | <b>SCX-2</b> |
|----------------------------------|----------------|--------------|
| Media capacity (mmol/g)          | 2.5            | 0.4          |
| Column size (g)                  | 0.1            | 0.5          |
| Column capacity (mmol/g)         | 0.25           | 0.2          |
|                                  |                |              |
| <b>Conditioning vol (mL)</b>     | 0.4            | 2            |
|                                  |                |              |
| Sample application               |                |              |
| Column capacity : Amine          | 1.5            | 1.5          |
| Suggested conc (M)               | 0.2            | 0.2          |
| Max mmol amine                   | 0.16           | 0.13         |
| Max vol (mL)                     | 0.80           | 0.65         |
|                                  |                |              |
| <b>Interference elution (mL)</b> | 0.9            | 5            |
|                                  |                |              |
| Product elution                  |                |              |
| Release vol (mL)                 | 0.19           | 0.15         |
| Wash vol (mL)                    | 1.01           | 3.85         |
| <b>Total vol (mL)</b>            | 1.2            | 4            |
|                                  |                |              |
| <b>Total solvent used (mL)</b>   | 2.5            | 11.00        |

# Comparison Utilizing DoE: Design 1

- Design 1 variables
  - media type: Silica (0.5 g) vs MP resin (0.1 g)
  - Flow rate: 0.5 to 15 mL per minute
  - Solvent DMF or DCM
  - Stoichiometry ratio (acid:amine) 1.5 to 4.5
- Conclusions
  - All combinations worked well except nitroaniline in DMF
  - No difference between media types, flow rates, or stoichiometry ratio

*Both TsOH and SCX procedures perform equally well*

## Comparison Utilizing DoE: Design 2

- Design 2 variables
  - Media type: silica or MP-resin
  - Column size: large or small
    - Large: 2g SCX vs 0.5g MP
    - Small: 0.5g SCX vs 0.1g MP
  - Amine type: benzyl or nitroaniline
  - Solvent: DMF or DCM
  - Release solution concentration: 1 M or 4 M
  - Release stoichiometry: 9 or 3 equivalents

## Comparison Utilizing DoE: Design 2 results

- There is no significant difference between SCX and MP under the conditions studied
- Therefore,
  - MP-TsOH, 100 mg/3 mL cartridge performs equivalently to SCX-2, 500 mg 6 mL cartridge, and
  - MP-TsOH, 500 mg/6 mL cartridge performs equivalently to SCX-2, 2000 mg 15 mL cartridge
- Can use a release stoichiometry of 3 and a release concentration of 4 M

*Solvent usage and final sample volume are substantially higher for SCX*

## Leachable Impurities

- Leachable impurities were tested as follows:
  - 16 cartridges used to get measurable residue quantities
  - SCX, 2000 mg/15 mL and MP, 500 mg/6 mL
  - Catch/release benzylamine (volatile)
  - Used release stoichiometry of 3 and a release concentration of 4 M

| Property                            | MP    | SCX   |
|-------------------------------------|-------|-------|
| mg leached/cartridge                | 1.27  | 0.47  |
| mg leached per mmol amine processed | 0.34  | 0.19  |
| Wt % residue for amine MW=300       | 0.011 | 0.006 |

# Amine Purification on MP-TsOH Cartridges

| Amine                               | Resin (equiv) | Unretained Amine (%) |     | Released Amine (% Recovery)* |
|-------------------------------------|---------------|----------------------|-----|------------------------------|
|                                     |               | DCM                  | DMF |                              |
| 3-Phenylpropylamine                 | 1.5           | 0                    | 0   | 98                           |
| N-Methylbenzylamine                 | 1.5           | 0                    | 0   | 97                           |
| N,N-Dimethylbenzylamine             | 1.5           | 0                    | 0   | 92                           |
| N-Methyl,N,N-di(2-phenethyl)amine   | 1.5           | 0                    | 0   | 95                           |
| 4-(2'-Dimethylaminoethyl)morpholine | 3.1           | 0                    | 0   | 96                           |
| 2-Aminothiazole                     | 1.5           | 0                    | 0   | 96                           |
| Aniline                             | 1.5           | 0                    | 0   | 94                           |
| 4-Nitroaniline                      | 3.1           | 0                    | 30  | 97                           |

\*From experiments using DCM as solvent

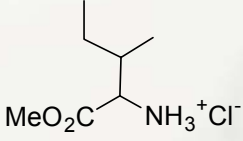
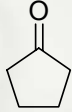
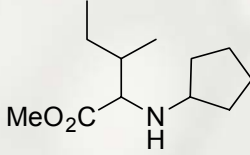
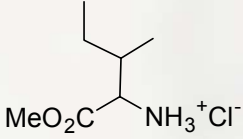
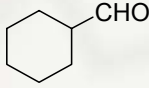
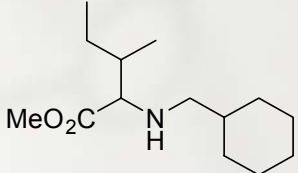
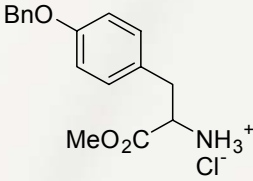
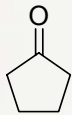
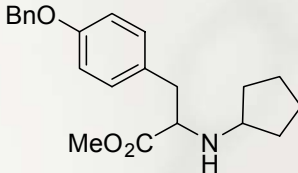
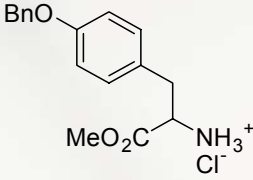
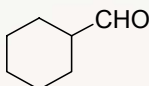
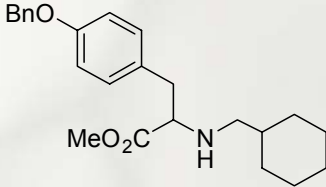
## Solvent Exchange: Amine Isolation from Reductive Amination Reactions in DMF



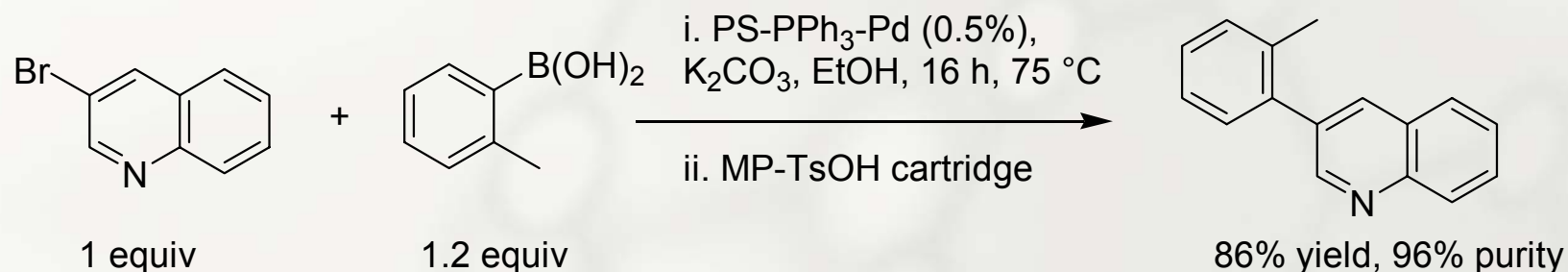
Reductive amination of amino acid ester salt in 100% DMF

- Solvent exchange using MP-TsOH cartridges
- Excellent way to extract amines from DMF or DMSO
  - 100% retention
  - Subsequently concentrate amine from volatile ammonia/methanol solution
- Use as sample prep prior to direct application to flash column

# Solvent Exchange: Amine Isolation from Reductive Amination Reactions in DMF

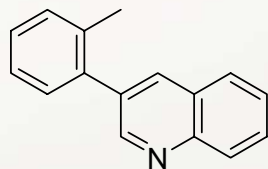
| Starting Amine  | Carbonyl Compound   | Product Amine  | % Yield (isolated) | % Purity |
|---|---|--|--------------------|----------|
|    |    |    | 59                 | 98       |
|    |    |    | 93                 | 99       |
|   |   |   | 60                 | 93       |
|  |  |  | 74                 | 98       |

# Purification of Basic Heterocycles Using MP-TsOH Cartridges



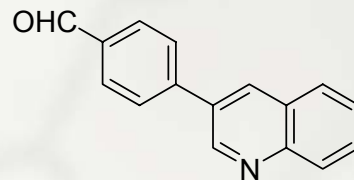
- MP-TsOH catch & release purifies end product after Suzuki coupling
  - Useful with both bound (PS-PPh<sub>3</sub>-Pd) and conventional catalysts such as Pd(Ph<sub>3</sub>P)<sub>4</sub>

# Purification of Basic Heterocycles Using MP-TsOH Cartridges



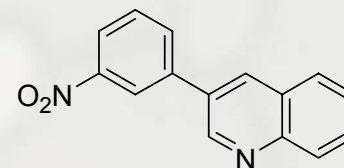
98 ( 98 )

76 (79)



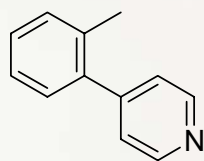
89 ( 85 )

93 (73)



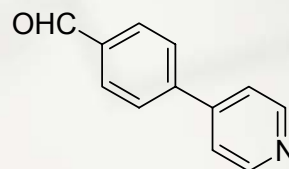
93 ( 69 )

99 (76)



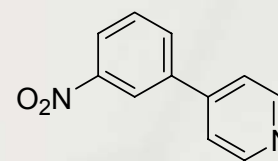
99 ( 97 )

99 (89)



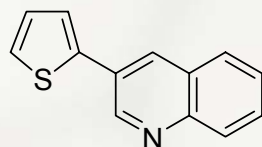
99 ( 94 )

99 (96)



99 ( 90 )

99 (92)



32 ( 45 )

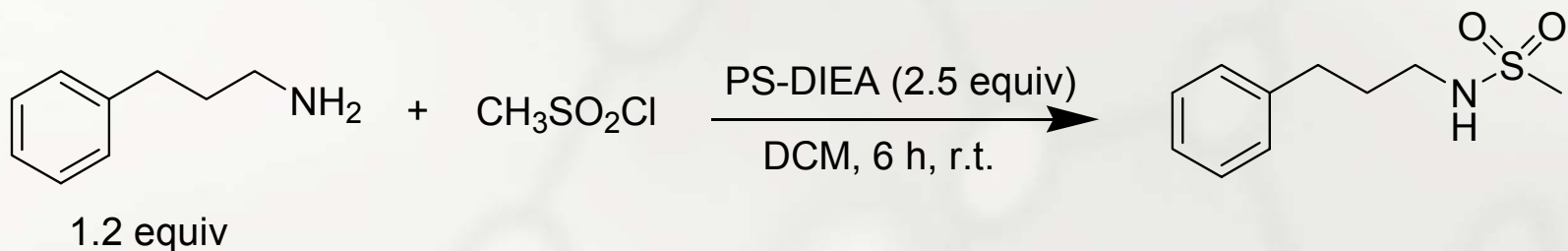
98 (98)

PS-TTP-Pd: Conversion% (Yield %)

Pd(PPh<sub>3</sub>)<sub>4</sub>: Conversion% (Yield %)

Reactions with Pd(PPh<sub>3</sub>)<sub>4</sub> were carried out under inert conditions

# Scavenging of Excess Amine Substrates

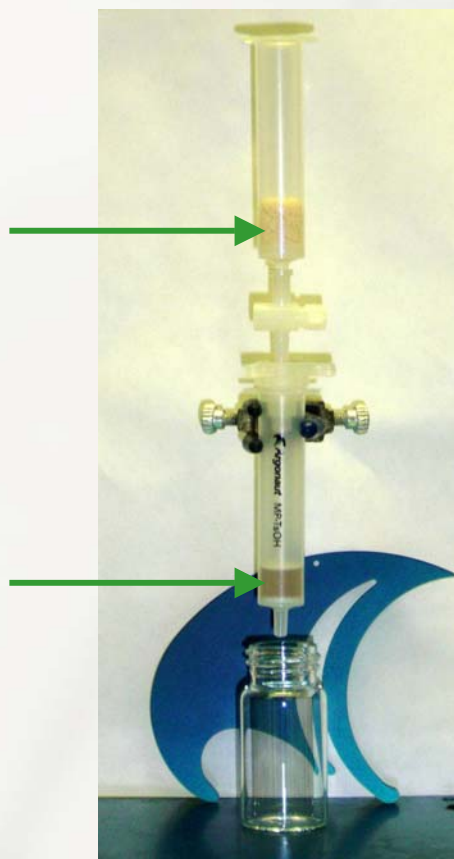


Sulfonamide formation using excess Amine

- Excess amine scavenged using MP-TsOH cartridge
  - Flow thru Purification
  - 100% retention of basic impurities
  - Pure Sulfonamide obtained by filtration followed by concentration

# Sample Prep Prior to Direct Application to Flash Column

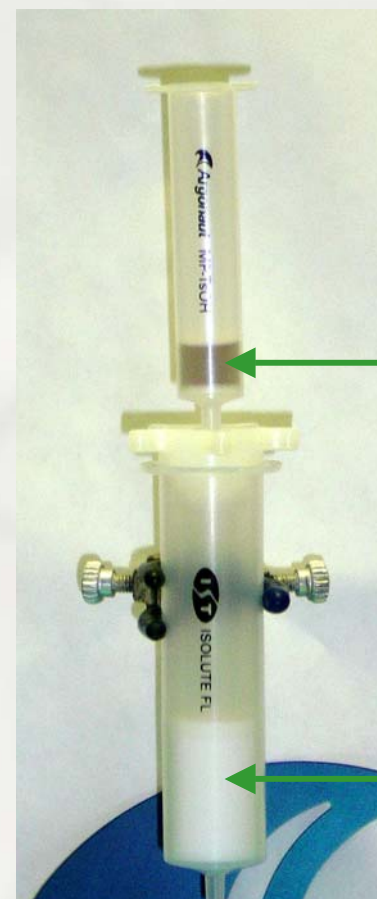
Reaction containing amine mixture



MP-TsOH Cartridge

Catching Amine Mixture on MP-TsOH Cartridge

MP-TsOH Cartridge

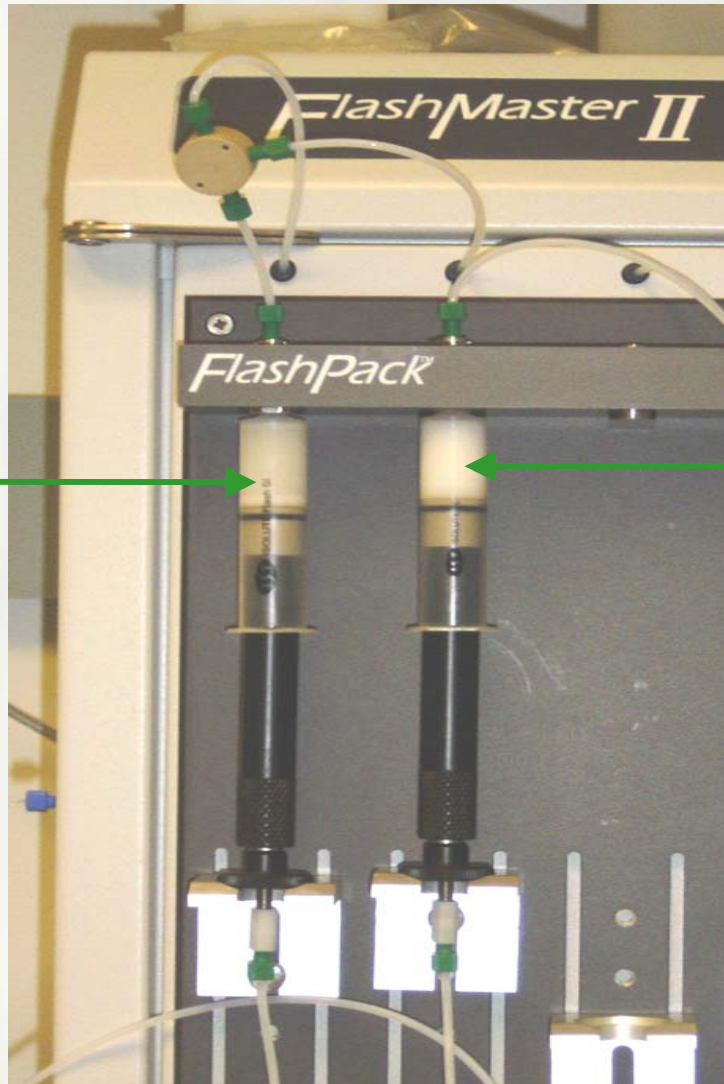


ISOLUTE FL Florisil Cartridge

Release of Amine Mixture onto Florisil Cartridge

# Flash Chromatography on FlashMaster II

Flash chromatography column



Amine mixture packed on ISOLUTE FL florisil cartridge

# Summary

- Bound sulfonic acid cartridges are highly effective in “catch & release” purification of amines with a broad scope including weakly basic aromatic amines and nitrogen heterocycles
- Excellent way to extract amines from high-boiling solvents such as DMF or DMSO
- Scavenge excess amine substrates from neutral products such as amides and sulfonamides
- Both SCX-2 and MP-TsOH perform well for amine purification
- Because the loading of MP-TsOH is 6-9 times higher than SCX-2 it offers several practical advantages
  - Lower total solvent usage
  - Lower final sample volume