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Too many compounds to synthesize.

Too little time.

- Synthesize more analogs faster for structure activity studies
- Rapidly resynthesize active compounds
- Develop new chemistry more efficiently
Welcome to the Quest Training Workshop specially designed for your needs. The Quest Training Workshop provides you with a 2-day program directed at introducing you to the tools of parallel synthesis utilizing the Quest technology. At the end of the Workshop you should be well on your way to integrating parallel synthesis into your daily medicinal chemistry projects. The program should empower you with the following:

- Quest Operations and Hands-on Multi-Step Synthesis
- Reaction Work-up, Purification and Collection
- Synthetic Reaction Development
- Scaffold Preparation
- SAR Analogueing
- Active Re-synthesis
- Parallel Purification

In addition to the above, the contents of this binder are provided for you as a reference guide as well as giving you a detailed review of the above.

**Thing to remember**

1. **If in doubt, vent**
2. **Never stick anything up the lower manifold**
3. **Unusually solid or solvent probably need to replace restrictor tubes**
4. **Always close upper manifold when heating**
# Quest Training Workshop

## Table of Contents

### Agenda
- Day 1
- Day 2

### Quest Overview
- Parallel Synthesis & Purification for Medicinal Chemists
- About You
- Program Objectives
- Product Overview
- Target Applications

### Synthesis Preparation
- Reaction Development
- SAR/Analoging

### Quest Homepage

### Quest Operations
- Rxn Set-up
- Inert Environment
- Reagent Addition
- Temperature Control
- Refluxing
- Agitation
- Work-up
- Concentration
- Precipitation
- Multi-Step Synthesis
- Resin Washing
- Maintenance
- Synthesis Example

### Purification
- Polymer Assisted Solution Phase Synthesis (PASP)
- Solid Phase Extraction (SPE)
- Solid Supported Liquid Extraction (SLE)
- Parallel Flash Chromatography

### Resins
- Polymer Reagents & Scavengers
  - ArgoGel®
  - ArgoPore®
- Polystyrene
- Resin Price List

### Appendix
- Quest Accessories/Consumables
- Selected Literature
Quest Training Workshop Agenda

Day 1

9:00 – 9:30   Welcome & Introductions
9:30 – 10:15  Quest Overview & Operation Training

10:15 – 10:30 Break

10:30 – 12:00 Hands-on Synthesis: Ketone Preparation
Add PS-TsNHNH2 resin, prepare bromobenzamide solutions in THF, add via syringe, attach chiller to Quest, addition of Grignard via syringe and agitate at 0C for 3 hrs.

12:00 – 1:00  Lunch

1:00 – 2:30   Quest Homepage Surfing

2:30 – 2:45   Break

2:45 – 4:45   Hands-on Synthesis: Ketone Capture
Add MP-TsOH then agitate for 20 min, add AcOH, set-up and execute bank-to-bank transfer, set-up reaction at 50C for 4 hrs and allow to agitate overnight at room temperature.

4:45 – 5:00   Wrap-up of Day 1
## Quest Training Workshop

### Agenda

**Day 2**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 - 9:15</td>
<td>Overview of the Day's activities</td>
</tr>
</tbody>
</table>
| 9:15 - 10:15| Hands-on Synthesis: Cyclization & Cleavage  
Automated washing with THF, hexane and DCM,  
preparation of SOCl2 in DCM, addition of SOCl2 via syringe and agitate for 4 hrs at 50 C |
| 10:15 - 10:30| Break                                                                    |
| 10:30 - 12:00| Presentation/Lecture  
Parallel Methods incorporating resins into synthesis and purification |
| 12:00 - 1:00| Lunch (on-site)                                                          |
| 1:00 - 2:15| Roundtable Discussion  
The Quest, Resins, and life in the lab.                                |
| 2:15 - 2:30| Break                                                                    |
| 2:30 - 4:30| Hands-on synthesis: Purification & Isolation  
Prepare SPE rack, filter through SPE rack and collection into vials, concentration off-line, and NMR/GC analysis for a representative compound. |
| 4:30 - 5:00| Questions/Wrap-up                                                       |
Parallel Synthesis & Purification For Medicinal Chemistry

Agenda

- Introductions
- Mutual updates
- Applications of parallel synthesis in medicinal chemistry
- Quest 210 overview
- Example Quest 210 applications
Overview of Argonaut

- Founded in 1994
- Employees: 90, 33% chemistry and engineering
- Over 400 Quest synthesis systems since 1997
- Customers
  - Merck, HMR, Abbott, RPR, Novartis, Glaxo-Wellcome, Monsanto/Searle, Hoffman-La Roche, Dupont Pharmaceuticals, Dupont Ag, Dupont Central R and D, Amgen, Abbott Laboratories

Provide technology and expertise to accelerate the synthesis of compounds for lead discovery and optimization
Innovative Products to Enhance Discovery Chemistry

- Trident 4192
- Process Consortium
- Process Development
- Analog Synthesis & SAR
- Quest Family
- Nautilus 2400

About You

- Introductions and your department?
- How much do you use parallel synthesis currently? What techniques or systems do you use?
- What medicinal chemistry programs are using parallel synthesis? Has it been useful?
- How much do you know about the Quest? Have you used it?
- What do you want to walk away with from this course?
What will you learn from the program?

- How to increase your productivity using parallel synthesis
- How to integrate parallel synthesis into your syntheses
  - Quest Operations & Hands-on Synthesis
  - Reaction Work-up, Purification & Collection
  - Synthetic Reaction Development
  - Scaffold Preparation
  - SAR Analoging
  - Active Re-synthesis
  - Parallel Purification

When you return to your lab you should be...

- ready to use your Quest for your daily medicinal chemistry projects
- able to develop new chemistry more efficiently
- able to synthesize more analogs faster for SAR
- ready to rapidly re-synthesize active compounds
- ready to adopt parallel synthesis and parallel purification techniques
Traditional Medicinal Chemistry

Compound Design

Analyze

Screen

Synthesis
- Synthetic pathway development
- Target compound synthesis
- Analogy
- Work-up
- Purification

Analytical

Traditional Tools in Medicinal Chemistry
Traditional Tools in Medicinal Chemistry

Shortening SAR Cycle Time

Biological Activity

Time

20 - 40 Compounds/Week
10's - 100's of cycles

1-2 Compounds/Week
100's - 1000's of cycles
**Decreased Time, More Projects**

- **Parallel Synthesis**: 10-20 compounds/week
  - Faster cycle time: 1-2 weeks
  - <1 yr to nmolar leads
- Investigate more options in parallel
- Reaction pathway development
- Analoging/SAR
- Broader support for patent claims

**Applying Parallel Synthesis From Lead Discovery and Optimization through Process Development**

Late Stage Projects
- Focused serial synthesis of compounds
- Parallel Synthesis
  - Broaden patent coverage
Uncover Important Surprises Through Analoging

- Identify compounds with greater activity
- Can't predict surprises
- Never at this juncture in the synthesis again
- Best opportunity to flush out surprises

Argonaut: "If you synthesize 20 analogs instead of one a few times how many surprises do you encounter?"
Medchemist: "Quit a few! We just can't predict where the activity will be"

Our Vision...

To empower you to shorten the time from mmolar to nmolar by 50%
Quest Family of Organic Synthesizers

Quest 210 SLN
Multi-Step Solution Phase Synthesizer

Quest 210 ASW
Easy to Use Solid Phase Synthesizer

Quest 205
Flexible Large Scale Synthesizer

Quest Synthesizer Product History

<table>
<thead>
<tr>
<th>Functionality</th>
<th>Quest 210</th>
<th>1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quest 210</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Quest 205</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>Quest 210 SLN</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Multi-step solution phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine frits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gas manifold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interface to parallel flash chromatography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usability: Upper manifold hinge mod</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larger RV volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLM - bank to bank transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funnel manifold, Automatic Solvent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPE rack, septum fusers, blank RV, bubbler kit, Parallel Synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bench top footprint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of use, chiller interface</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Solution and Solid Phase Synthesis on the Q210 SLN and Q210 ASW**

- **Solution Phase Synthesis**
  - Dispense Resin into RVs
  - Bank-to-Bank Cannulation
  - MAP Reagents into Reaction Vessels
  - Incubate/Agitate
  - Wash Resin
  - Dry Resin
  - Cleave
  - Collect

- **Solid Phase Synthesis**
  - Prepare Reagents
  - x n steps

**Parallel Solvent and Gas Delivery**

- Easy-to-use controls for solvent and gas delivery
- Gas and solvent delivery for Bank A and B independently controlled
- Purge RVs with inert gas for air and moisture sensitive reactions
- Precise control of pressure for RV draining
Easy Programming Minimizes Your Learning Curve

- Menu driven software for ease of use
- Control of agitation frequency and profile
- Independent control of reaction bank temperature and heating duration
- Temperature program starts once programmed temperature is achieved

Clear Teflon® Reaction Vessels

- Clear Teflon RVs
  - Combines capability of a round bottom flask, separatory funnel, erlenmeyer flask and filter funnel
  - Monitor your reactions progress and make adjustments
  - Perform on-line liquid-liquid extractions
- Closed and inert reaction environment
  - Use air and moisture sensitive reagents
  - Operate at the reflux temperature
**Quest 210 SLN Synthesis Platform**

- Port for solid or liquid reagent addition
- Parallel solvent and gas addition
- Proprietary vertical agitation
- Integrated heater controls temperature from ambient to 130°C
- Teflon membrane valve
- Disposable RVs
- Easy-to-use drain valves
- Chiller ports
- Product collection

Perform 20 Reactions in 18 in. of Hood Space

---

**On-Line Purification for Efficiency...**

- Attach workup cartridges directly to the Quest
- Perform multistep solution-phase syntheses
- Collect products into different size vials
Menu of Luer Purification Cartridges for the Quest 210/SLN

<table>
<thead>
<tr>
<th>Media</th>
<th>Surface chemistry</th>
<th>Mass</th>
<th>Synthesis Application</th>
<th>Product Name</th>
<th>Vendor</th>
<th>Part No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica</td>
<td>SiO₂</td>
<td>900 mg</td>
<td>Baseline impurity removal</td>
<td>Maxi-Clean</td>
<td>Alltech</td>
<td>20992</td>
</tr>
<tr>
<td>Silica</td>
<td>SiO₂</td>
<td>1 g</td>
<td></td>
<td>Bond Elut Jr.</td>
<td>Vanhan</td>
<td>12166008</td>
</tr>
<tr>
<td>Florisil</td>
<td>Mg₂SiO₃</td>
<td>900 mg</td>
<td>In-line purification of amines</td>
<td>Maxi-Clean</td>
<td>Alltech</td>
<td>210059</td>
</tr>
<tr>
<td>Alumina-Neutral</td>
<td>Al₂O₃</td>
<td>1800 mg</td>
<td>Baseline impurity removal</td>
<td>Maxi-Clean</td>
<td>Alltech</td>
<td>210098</td>
</tr>
<tr>
<td>Alumina-Basic</td>
<td>Al₂O₃</td>
<td>1 g</td>
<td>Separation/neutralization of acidic cpds.</td>
<td>Bond Elut Jr.</td>
<td>Vanhan</td>
<td>12166044</td>
</tr>
<tr>
<td>SCX</td>
<td>-ArSO₃H</td>
<td>1 g (0.1 mmol)</td>
<td>Synthesis of Amino-Basics</td>
<td>Bond Elut Jr.</td>
<td>Vanhan</td>
<td>12166011</td>
</tr>
<tr>
<td>SCX</td>
<td>-ArSO₃H</td>
<td>500 mg</td>
<td>“Catch and Release” of Amines</td>
<td>Whatman SCA</td>
<td>Whatman</td>
<td>6804-2665</td>
</tr>
<tr>
<td>C₁₈</td>
<td>Octadecyl</td>
<td>900 mg</td>
<td></td>
<td>Maxi-Clean</td>
<td>Alltech</td>
<td>22044</td>
</tr>
<tr>
<td>Aminopropyl</td>
<td>-NH₂</td>
<td>1 g</td>
<td>Removal of electrophiles</td>
<td>Bond Elut Jr.</td>
<td>Vanhan</td>
<td>12166012</td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td>-COOH</td>
<td>x</td>
<td>Removal of amines</td>
<td>Minispeed Plus</td>
<td>Applied</td>
<td>24020</td>
</tr>
<tr>
<td>Diethylamino</td>
<td>Diethylamine</td>
<td>x</td>
<td>Removal of acidic cpds</td>
<td>Minispeed Plus</td>
<td>Applied</td>
<td>24024</td>
</tr>
</tbody>
</table>

... And Off-Line Purification for Flexibility

- Purify more compounds faster with parallel purification
- Purification solutions
  - Silica
  - Florisil
  - Alumina (neutral, basic and acidic)
  - SCX
  - C₁₈
  - Aminopropyl
  - Carboxylic acid
  - Diethylamino
### Menu of SPE Columns for the Quest 210/SLN

<table>
<thead>
<tr>
<th>Media</th>
<th>Surface chemistry</th>
<th>Mass</th>
<th>Synthetic Application</th>
<th>Product Name</th>
<th>Vendor</th>
<th>Part No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica</td>
<td>SiO₂</td>
<td>2 g</td>
<td>Baseline impurity removal</td>
<td>Isolute SI</td>
<td>Jones Chromat</td>
<td>460-0200-C</td>
</tr>
<tr>
<td>Silica</td>
<td>SiO₂</td>
<td>2 g</td>
<td>ADD isolation (on-line purification)</td>
<td>Extract Clean</td>
<td>Arttech</td>
<td>209202</td>
</tr>
<tr>
<td>Florid</td>
<td>Mg₂SiO₃</td>
<td>2 g</td>
<td>Baseline impurity removal, polar solvent retention</td>
<td>Spe-ed Cart.</td>
<td>Applied</td>
<td>2118</td>
</tr>
<tr>
<td>Alumina-A</td>
<td>Al₂O₃</td>
<td>2 g</td>
<td>Baseline impurity removal</td>
<td>Isolute AL-N</td>
<td>Jones Chromat</td>
<td>714-0200-C</td>
</tr>
<tr>
<td>Alumina-B</td>
<td>Al₂O₃</td>
<td>2 g</td>
<td>Further basic purification of acidic sites</td>
<td>Spe-ed Cart.</td>
<td>Applied</td>
<td>2145</td>
</tr>
<tr>
<td>Alumina-B</td>
<td>Al₂O₃</td>
<td>1 g</td>
<td>Adsorption non-polar compounds</td>
<td>MegaBond Eui</td>
<td>Varian</td>
<td>12250044</td>
</tr>
<tr>
<td>C18</td>
<td>Octadecyl</td>
<td>2 g</td>
<td>Multi-organ solvent cleanup</td>
<td>Spe-ed Cart.</td>
<td>Applied</td>
<td>2058</td>
</tr>
<tr>
<td>C18</td>
<td>Octadecyl</td>
<td>2 g</td>
<td>Multi-organ solvent cleanup</td>
<td>Isolute C18</td>
<td>Jones Chromat</td>
<td>220-0200-C</td>
</tr>
<tr>
<td>SCX</td>
<td>ArSO₂Cl</td>
<td>1 g</td>
<td>&quot;Catch and Release&quot; of amines</td>
<td>MegaBond Eui</td>
<td>Varian</td>
<td>12250011</td>
</tr>
<tr>
<td>SCX</td>
<td>ArSO₂Cl</td>
<td>2 g</td>
<td>Multi-organ solvent cleanup</td>
<td>Spe-ed Cart.</td>
<td>Applied</td>
<td>2324</td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td>COOH</td>
<td>2 g</td>
<td>Removal of amino acids</td>
<td>Spe-ed Cart.</td>
<td>Applied</td>
<td>2316</td>
</tr>
<tr>
<td>Amine</td>
<td>NH₃</td>
<td>2 g</td>
<td>Removal of inorganic acids</td>
<td>Spe-ed Cart.</td>
<td>Applied</td>
<td>2216</td>
</tr>
<tr>
<td>Destrification</td>
<td>-OH</td>
<td>2 g</td>
<td>Removal of acidic sites</td>
<td>Spe-ed Cart.</td>
<td>Applied</td>
<td>2335</td>
</tr>
</tbody>
</table>

### Attachment of SPE columns

![Attachment of SPE columns image](image-url)
Tools to Simplify Your Syntheses

- Blank RVs for partially filled reaction banks
- Funnel manifold to simplify solid addition
- Septum luers plugs for maintaining an inert environment

...and a growing list of new accessories

Accessories to Increase Your Productivity

- Quest 205 accessories
  - Weighing funnel
  - Solid addition funnel
  - Round bottom flask rack
  - Reaction vessel caps
  - Reaction vessel rack
  - Transfer cannulas
  - Multi-flask adaptor kit
  - Solid phase extraction adaptor kit
Application of Quest Synthesizers in Lead Optimization

Multidimensional Organic Synthesizer
Perform 90% of All Synthetic Operations

Traditional Tools
- Heat
  - Reflux
- Cool
- Agitate
- Reagent addition
  - Solid, liquid
  - Drop wise
- Work Up
  - LLE
  - Precipitation
- Concentration
- Flash chromatography

Quest
- Heat - 130°C
  - Heat at reflux temp
- Cool - common chillers
- Agitate - novel, robust
- Reagent addition
  - solid, liquid
  - Fast drop wise
- Work Up
  - LLE
  - Precipitation
- Concentration
- Interface to Flash Chrom

Medicinal Chem Operations
### 90% of all Medicinal Chemistries & Work up

#### C-C Bond Formation
- Alkyllithium, Grignard Addn./Displ. Reactions
- Enolate Alkylation
- Micheal Addition
- Wittig
- Horner-Emmons
- Claisen Rearrangement

#### Reduction
- Hydrogenation (low P)
- Lithium aluminum hydride
- Hydrosilation
- Borane
- Sodium Borohydride

#### Oxidation
- Dess Martin periodinane
- MCPBA
- Jones Oxidation
- Baeyer Villiger
- Sharpless dihydroxylation

#### C-Hetero Bond Formation
- Williamson Ether
- Mitsunobu
- Nucl. Aromatic Subst. (N,S)
- Gabriel Synthesis
- Reductive Amination
- Hydroboration
- Amides, esters, sulonamides

#### Elimination
- Shapiro
- Hoffman
- Dehydrohalogenation

#### Organometallic
- Heck Reaction
- Stille/Suzuki Coupling
- Sonogashira
- Pd Cat. Enyne Cyclization
- Addition to π-allyl Pd
- Transfer Hydrogenation
- Rh Cat. Carbene Insertion

#### Heterocycle Formation
- Thiazoles
- Oxadiazoles
- Benzimidazoles
- Fisher Indole Synthesis
- Quinolines
- Hydantoins
- Ugi
- Pictet-Spengler
Set Up and Install

Set up and Install
Target Quest Applications

- Synthetic Pathway Development
  - Run multiple conditions/reagents simultaneously
- Scaffold preparation
  - Non-commercially available building blocks
- SAR/Analoging
  - Same reaction with multiple reagents
- Active re-synthesis

Parallel synthesis of β-Ketoester analogs n-Butyllithium followed by on-line post synthesis work-up

1. $n$-BuLi (2 equiv) THF, -40°C to -5°C, 2 h
2. NaHCO$_3$, H$_2$O on-line

- Refrigerated recirculating chiller interfaced to Quest 210 SLN
- Reaction quenched with HCl and extracted with ether on-line
- Products washed 2 x NaHCO$_3$ and 2 x H$_2$O on-line

Characterization of β-Ketoester Products

<table>
<thead>
<tr>
<th>Reaction No.</th>
<th>Acyl Chloride</th>
<th>β-Ketoester Product</th>
<th>Recovery (%)</th>
<th>GC % Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV 01</td>
<td></td>
<td></td>
<td>65%</td>
<td>85%</td>
</tr>
<tr>
<td>RV 02</td>
<td></td>
<td></td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>RV 03</td>
<td></td>
<td></td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>RV 04</td>
<td></td>
<td></td>
<td>75%</td>
<td>70%</td>
</tr>
<tr>
<td>RV 05</td>
<td></td>
<td></td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>RV 06</td>
<td></td>
<td></td>
<td>95%</td>
<td>90%</td>
</tr>
<tr>
<td>RV 07</td>
<td></td>
<td></td>
<td>70%</td>
<td>80%</td>
</tr>
<tr>
<td>RV 08</td>
<td></td>
<td></td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>RV 09</td>
<td></td>
<td></td>
<td>85%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Analog Synthesis on the Quest 210 SLN

- Synthesis yielded 10 β-Ketoester products in good yield and purity
  - Recovery 76-94% (excluding sterically hindered RV4)
  - Purity 82-100% (excluding sterically hindered RV 4)

- Closed and inert reaction environment allowed use of reactive n-butyllithium

- Work-up of 10 products on-line saved time and effort

- External chiller able to cool reactions to -40°C
Preparation of Starting Materials on the Quest 205

Reactions were performed on the Quest 205 using fine frit reaction vessels to prepare gram quantities of 2-aminothiazole hydrobromide monohydrates as bulk starting materials.


Results of Aminothiazole synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thion:</th>
<th>α-Bromoketone</th>
<th>Product</th>
<th>Amount Prepared</th>
<th>Yield</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>O</td>
<td>N</td>
<td>0.91 g</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>O</td>
<td>N</td>
<td>1.34 g</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>O</td>
<td>N</td>
<td>1.24 g</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>O</td>
<td>N</td>
<td>1.96 g</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>O</td>
<td>N</td>
<td>1.50 g</td>
<td>32%</td>
<td></td>
</tr>
</tbody>
</table>

*Based on NMR, purity of the products is over 95%.
Multistep Synthesis of Free-based Aminothiazoles

R\textsuperscript{1} S \textsuperscript{N} \textsuperscript{NH_{2}} + \textsuperscript{Br} \textsuperscript{O} \textsuperscript{R_{1}} \xrightarrow{1. \text{acetone, } 57^\circ \text{C, } 12 \text{ h}} \xrightarrow{2. \text{MeOH, } 25^\circ \text{C, } 3 \text{ h}} R_{1}' R_{1}' S \textsuperscript{N} \textsuperscript{R_{1}} \textsuperscript{R_{1}} \textsuperscript{\text{amine}^{+}} \textsuperscript{CO_{3}^{2-}}

- Reactions were performed on the Quest 210 using µfrit reaction vessels
- Using the solid phase reagent, MP-Carbonate, the hydrobromide salts could be effectively free-based after redissolution in methanol in the same reaction vessel to generate the free base of 2-aminothiazoles.

Results of Multistep Aminothiazole Synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Threonine</th>
<th>α-Bromoacetone</th>
<th>Product</th>
<th>Yield</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n\textsuperscript{H} \textsuperscript{H}</td>
<td>\textsuperscript{Br}</td>
<td>n\textsuperscript{H} \textsuperscript{N}</td>
<td>87%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>- \textsuperscript{H}</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>- \textsuperscript{H}</td>
<td>-</td>
<td>-</td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>- \textsuperscript{H}</td>
<td>-</td>
<td>-</td>
<td>65%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>n\textsuperscript{H} \textsuperscript{H}</td>
<td>-</td>
<td>n\textsuperscript{H} \textsuperscript{N}</td>
<td>87%</td>
<td>95%</td>
</tr>
<tr>
<td>6</td>
<td>- \textsuperscript{H}</td>
<td>-</td>
<td>-</td>
<td>31%</td>
<td>94%</td>
</tr>
</tbody>
</table>
New Products

- New µFrit reaction vessels
  - Isolate compounds by precipitation
  - Purify by recrystallization
- Gaseous reaction and concentration manifold
  (product release 9/99)
  - Add gaseous reagent to Quest 210 RV
  - Concentrate reaction solutions on-line

Parallel Product Precipitation on the
Quest 210/205

- To facilitate the collection of precipitates on the Quest 210 and 205, new reaction vessels with 7µm Teflon frits were developed.
  - The frit is rugged allowing the chemist to collect solid products by scraping.
  - In addition, dissolution and further reaction of products in a second synthesis step, or dissolution and transfer to another RV is possible for multistep solution-phase synthesis.
Parallel Precipitation of 3-Substituted Indolin-2-ones on the Quest 210:

\[
\text{Ar} > \text{HO} + \text{Ar-CHO} \quad \text{piperidine (0.1 equiv)} \quad \text{EtOH, 90 °C}
\]

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yield (Solid) (%)</th>
<th>Yield (Dissolution) (%)</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzaldehyde</td>
<td>31</td>
<td>32</td>
<td>100</td>
</tr>
<tr>
<td>2,5-dimethoxybenzaldehyde</td>
<td>67</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>Piperonal</td>
<td>70</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>o-anisaldehyde</td>
<td>85</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>4-bromobenzaldehyde</td>
<td>42</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

Utilizes new "μfrit" reaction vessel

Gas Manifold Accessory

- Addition of gaseous reagents through lower manifold thru luer ports
Preliminary Results on Use of Gas Manifold Accessory for Hydrogenation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hydrogenation time (15 psi)</th>
<th>% Hydrogenated after 6 h (5 psi)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-phenyl-1-butene</td>
<td>2.5 h</td>
<td>100</td>
<td>MeOH</td>
</tr>
<tr>
<td>CBz-Trp-OH</td>
<td>&lt;1 h</td>
<td>100</td>
<td>MeOH</td>
</tr>
<tr>
<td>CBz-Phe-Osu</td>
<td>&lt;1 h</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>m-Nitro xylene</td>
<td>6.5 h (&gt;90%, 4.5 h)</td>
<td>99.5</td>
<td>EtOAc</td>
</tr>
<tr>
<td>Trans-5-decene</td>
<td>4.5 h</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>Benzal benzoate</td>
<td>6.5 h (&gt;90%, 4.5 h)</td>
<td>&gt;97</td>
<td>MeOH</td>
</tr>
<tr>
<td>4-nitrobenzyl alcohol</td>
<td>-</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>4-nitrobenzaldehyde</td>
<td>-</td>
<td>84</td>
<td>EtOAc</td>
</tr>
<tr>
<td>4-nitrobenzoic acid</td>
<td>-</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>5-Benzoyloxycetanol</td>
<td>6.5 h (&gt;80%, 4.5 h)</td>
<td>99</td>
<td>MeOH</td>
</tr>
</tbody>
</table>

- Preliminary results indicate that pressures of 5-15 psi are likely obtainable
- Apparatus also being evaluated for on-line concentration (in progress).

Demonstrated Performance

- Abbott Laboratories
  - “One chemist made 250 compounds in a couple of months versus a chemist who doesn’t use a Quest made only 20 compounds in the same amount of time”.

- Lilly
  - “Synthesized 70 compounds in 3 weeks. It would have taken 3x longer using our traditional methods”
Quest Applications Within Medicinal Chemistry

Solid Phase Solution Phase
Compatability with Semi-automated Purification (CombiFlash)
Parallel Purification SPE/SLE/LLE
Parallel Preparation of In-house Scaffolds in Solution or Polymer-supported

Quest

Chemistry Development
Lead Generation
Lead Identification
Lead Optimisation

Combinatorial Chemistry Traditionnal Chemistry

Generation of Small Size Libraries
Parallel Multi-step Synthesis of Substituted Benzimidazoles via Hydrogenation of Aromatic Nitro Compounds on the Quest 210 Organic Synthesizer

Young K. Yun, John A. Porco, Jr., Jeff Labadie

Argonaut Technologies
San Carlos, California
www.argotech.com

Pharmacologically Active Benzimidazoles

Neuroprotective YY1 Receptor Antagonists

Antiarrhythmic agents

ATP-site Inhibitor of platelet-derived growth factor
Objectives

1-Phenylbenzimidazoles
ATP-site inhibitor of PDGF

- Apply the Quest 210 in a Linear synthesis of a target molecule including Reaction Development
- Rapid synthesis of target molecule analogs
- Demonstration of Parallel Hydrogenation

Based on this criteria 1-Phenylbenzimidazole was chosen as target molecule

Strategies for Parallel Multi-step Synthesis

- Synthetic Target
  - Literature Studies
  - Synthetic Methodologies
  - Retrosynthesis of a target molecule

- Parallel Multi-step Synthesis
  - Rxn. Optimization
  - Synthetic Pathway Development
  - Streamlined Organic Synthesis
  - Execution of Parallel Multi-step Synthesis
Retrosynthetic Study

Synthetic Pathway Development:
1-Phenylbenzimidazoles

Reaction Development:
- $S_{N}Ar$ Reaction: Determine Base, Solvent, and Rxn. Temp.
- Nitro Reduction: Validate use of 2-methoxyethanol
Questions ?

- S_NAr Reaction
  - How many o-halonitrobenzenes are commercially available ?
    - Screening Substrates

  - What kind of bases will I use ?
    - K_2CO_3, DIEA or NMM : Rxn. Optimization

  - How about stoichiometry ?
    - Stochiometric ratio between aniline and base : Rxn. Optimization

  - Work up ?

Questions ?

- Nitro Reduction
  - Parallel Nitro Reduction ?
  - Possibility of Bank to Bank Transfer
  - Common Solvent for both Nitro reduction and Cyclization

- Formation of Benzimidazoles
  - Utilization of imidate or amidine
  - Any other routes for cyclization
Stoichiometry Screening with $K_2CO_3$

$$\text{R}^+X^- \rightarrow \text{R}_2\text{NH}_2$$

DMF/130 °C/19h
1.0 N HCl workup

<table>
<thead>
<tr>
<th>RV #</th>
<th>Base/ Eq.</th>
<th>Aniline/ Eq.</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$ / 2.0 eq.</td>
<td>2.0 eq.</td>
<td>DMF</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$ / 3.0 eq.</td>
<td>2.0 eq.</td>
<td>DMF</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$ / 4.0 eq.</td>
<td>2.0 eq.</td>
<td>DMF</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$CO$_3$ / 5.0 eq.</td>
<td>2.0 eq.</td>
<td>DMF</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$CO$_3$ / 6.0 eq.</td>
<td>2.0 eq.</td>
<td>DMF</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$CO$_3$ / 7.0 eq.</td>
<td>3.0 eq.</td>
<td>DMF</td>
</tr>
</tbody>
</table>

$S_NAr$ Reaction Optimization

- $S_NAr$ products, diphenylamines remained in organic layer in the aqueous acid workup.
- Aqueous acid workup removed excess anilines.
Base Screening with NMM

<table>
<thead>
<tr>
<th>RV #</th>
<th>Base/ Eqiv.</th>
<th>Aniline/ Eqiv.</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMM/2.0 eqv.</td>
<td>1.7 equiv.</td>
<td>DMF</td>
</tr>
<tr>
<td>2</td>
<td>NMM/1.1 eqv.</td>
<td>2.0 equiv.</td>
<td>DMF</td>
</tr>
<tr>
<td>3</td>
<td>NMM/1.1 eqv.</td>
<td>1.2 equiv.</td>
<td>DMF</td>
</tr>
<tr>
<td>4</td>
<td>NMM/2.0 eqv.</td>
<td>2.0 equiv.</td>
<td>DMF</td>
</tr>
<tr>
<td>5</td>
<td>NMM/5.0 eqv.</td>
<td>5.0 equiv.</td>
<td>DMF</td>
</tr>
<tr>
<td>6</td>
<td>NMM/2.0 eqv.</td>
<td>5.0 equiv.</td>
<td>DMF</td>
</tr>
<tr>
<td>7</td>
<td>NMM/5.0 eqv.</td>
<td>3.0 equiv.</td>
<td>DMF</td>
</tr>
</tbody>
</table>

S_NAr Reaction Optimization

- Using 2.0 equiv. of NMM S_NAr Rx. Optimization was accomplished with 98 % conversion rate of halo-nitrobenzenes
Screening Substrates

Only chloro-nitropyridine yielded S<sub>Ar</sub>

Preliminary Results on Parallel Hydrogenation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hydrogenation time (15 psi)</th>
<th>% Hydrogenated after 6 h (5 psi)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-phenyl-1-butene</td>
<td>2.5 h</td>
<td>100</td>
<td>MeOH</td>
</tr>
<tr>
<td>CBz-Trp-OH</td>
<td>&lt;1 h</td>
<td>100</td>
<td>MeOH</td>
</tr>
<tr>
<td>CBz-Phe-Osu</td>
<td>&lt;1 h</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>m-Nitro xylene</td>
<td>6.5 h (&gt;90%, 4.5 h)</td>
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<td>EtOAc</td>
</tr>
<tr>
<td>Trans-5-decene</td>
<td>4.5 h</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>Benzyl benzoate</td>
<td>6.5 h (&gt;90%, 4.5 h)</td>
<td>&gt;97</td>
<td>MeOH</td>
</tr>
<tr>
<td>4-nitrobenzyl alcohol</td>
<td>-</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>4-nitrobenzaldehyde</td>
<td>-</td>
<td>84</td>
<td>EtOAc</td>
</tr>
<tr>
<td>4-nitrobenzoic acid</td>
<td>-</td>
<td>100</td>
<td>EtOAc</td>
</tr>
<tr>
<td>5-Benzoxyl-1-pentanol</td>
<td>6.5 h (&gt;80%, 4.5 h)</td>
<td>99</td>
<td>MeOH</td>
</tr>
</tbody>
</table>

- Preliminary results indicate that pressures of 5-15 psi are obtainable.
- 5 psi utilized in 1-Phenylbenzimidazole synthesis.
Parallel Hydrogenation

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Reaction Time</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&lt;sub&gt;N&lt;/sub&gt;, NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Pd/C 5%</td>
<td>MeOH/ EtOAc</td>
<td>3h</td>
<td>100% Conversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lit. Condition</td>
</tr>
<tr>
<td>R&lt;sub&gt;N&lt;/sub&gt;, NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Pd/C 10%</td>
<td>Methoxyethanol</td>
<td>6h</td>
<td>100% Conversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rsn. Condition adapted from Lit. to offer Bank to Bank Transfer</td>
</tr>
</tbody>
</table>

Multistep synthesis of benzimidazoles on the Quest 210

1) ether addition
2) LLE with 1.0 N HCl
3) dil. with hexane
4) in-line SPE column

Y = N, CH

H<sub>2</sub> - Pd/C
2-methoxyethanol
3 h, 5-8 psi

2) LLE with water
3) on-line evaporation
4) in-line SPE column with 2:1 hexane/ethyl acetate

Results of $S_N$Ar reactions

\[
\begin{align*}
\text{Entry} & & \text{2-Nitrophenylhalide} & & \% \text{ Yield} & & \text{GC Purity}^1 \\
1 & & & & 65\% & & 99\% \\
2 & & & & 65\% & & 97\% \\
3 & & & & 98\% & & 99\% \\
4 & & & & 65\% & & 100\% \\
5 & & & & 65\% & & 80\%
\end{align*}
\]

- Liquid Liquid Extraction with Ether/1.0 N HCl, followed by SPE column

O-Nitrodiarylamines
### Parallel hydrogenation of nitro anilines

\[ \text{H}_2, 10\% \text{ Pd/C} \]
\[ 25\, ^\circ \text{C}, 6\, \text{h} \]
\[ 2\text{-methoxyethanol} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-aminoaniline structure</th>
<th>% Yield (assayed)</th>
<th>% GC purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Structure1]</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>![Structure2]</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td>![Structure3]</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>![Structure4]</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>![Structure5]</td>
<td>92%</td>
<td>90%</td>
</tr>
</tbody>
</table>

### Parallel Synthesis of 1-Phenyl benzimidazoles

\[ \text{MnO} + \text{OH}_2 \rightarrow \text{NH}_2 + \text{HOAc} \]
\[ 125\, ^\circ \text{C}, 3\, \text{h} \]
LLE On-line column

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzimidazole structure</th>
<th>% Yield (assayed)</th>
<th>% GC purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Structure6]</td>
<td>77%</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>![Structure7]</td>
<td>60%</td>
<td>94%</td>
</tr>
<tr>
<td>3</td>
<td>![Structure8]</td>
<td>52%</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td>![Structure9]</td>
<td>60%</td>
<td>94%</td>
</tr>
<tr>
<td>5</td>
<td>![Structure10]</td>
<td>82%</td>
<td>94%</td>
</tr>
</tbody>
</table>

LLE with EtOAc/water, followed by on-line evaporation
Benzimidazole derivatives were synthesized in three steps on the Quest 210 using 1) S<sub>N</sub>Ar Reaction of substituted anilines to o-halo-nitrobenzenes 2) parallel hydrogenation to form aminodiphenyl amines and 3) cyclization of diamines with formimididine acetate.

Utilization of the Gas Rxn. And Concentration Manifold Accessory permitted the parallel hydrogenation of nitro diphenylamines.

The Quest 210 synthesizer allows parallel solution phase organic reaction, LLE, on-line concentration, gas reagent addition, and SPE purification to be performed on a common platform.
Argonaut's innovative technology enables synthetic organic chemists to benefit from the speed and efficiency of parallel synthesis.
When you need a simple, straightforward way to accelerate organic synthesis, Quest synthesizers give you the **hands-on control** of traditional synthesis combined with the **speed** of parallel synthesis and purification.

From analog synthesis for SAR/SPR work to chemistry development to scale-up, the Quest family can help you meet your goals.

**Hands-on Chemistry**
Quest synthesizers work the way you do at the bench, only faster. Quest is compact, convenient and easy-to-use.

**The Versatility Your Chemistry Demands**
In spite of their simplicity, Quest synthesizers do not limit your choice of chemistry. In either solution or solid phase, Quest has the features you need.

**Synthesis and Purification**
Combine parallel synthesis with on-line workup and sample collection and you can manage the synthesis process - from start to finish - on a single instrument.

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For more information about Quest and Argonaut's other technology for accelerating organic synthesis, contact Argonaut at info@argotech.com or visit www.argotech.com

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**Headquarters:** 887 Industrial Boulevard, Suite G, San Carlos, CA 94070  
Tel: 650-598-1350 FAX: 650-598-1359

**Switzerland:** St. Jacobs-Strasse 148, Postfach 43, 4132 Muttenz 2, Switzerland  
Tel: 41-61-465-9898 FAX: 41-61-465-9899

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http://www.argotech.com/quest/index.htm
Scientific Resources

The following documents and references provide a wealth of information about chemistry applications using Argonaut synthesizers and chemistry products.

Application Notes

discuss the use of Argonaut instruments and chemical products for a particular application and provide supporting scientific data.

Synthesis & Purification Letters

provide detailed experimental procedures and instrument operations for the parallel preparation and purification of compounds on the Quest 210 and Quest 205 synthesizers, including the use of Argonaut resins and reagents.

Chemistry Product Data Sheets

provide technical specifications and usage recommendations for Argonaut chemistry resins and reagents.

Literature References

are for papers authored by Argonaut chemists, customers and affiliates.

Quest Tips

provide standard usage and maintenance procedures for Quest synthesizers.

Nautilus Procedures

are pre-programmed procedures for Nautilus users (password required).

Want to stay informed?

Subscribe and learn about special offers, events and products by e-mail.
These Quest Operational Tips are designed to assist users with common instrument operations and synthesis procedures.

If you would like to contribute a Quest Operational Tip, please contact Dave Yamane.

For additional information regarding instructions and procedures for your Quest synthesizer, please consult the Quest manual.

- Recommended Quest Agitation Settings for Various Solid Supports
- Bank-to-Bank Transfer Cannula Protocol
- Use of In-line Purification Cartridges with the Lower Manifold Luer Upgrade Kit
- Cleaning Procedures
- Delivery, Agitation and Draining Procedures
- RV Removal and Installation Procedures
- Filling Solvent to the Top of the Frit Procedures
- Individual Draining Procedures
- Refluxing Procedures
Quest Operations

Entering A New Paradigm
Operational Integration

This single setup and operations replaced *twentyfold* on the Quest.

![Image of setup and equipment](image-url)
Quest Plumbing Schematic
Reactor Unit Cross Sectional View

Upper Manifold

Reaction Vessel Magnet Agitator

Teflon Frit

100 µL Dead Volume

Reagent Addition Port, Angled for Solid and Pipette Deliveries

Delivery Manifold Parallel Delivery of Solvents and Gas

Teflon Valve Manifold

Manual Toggle Valve

Caution: drain path is not straight - DO NOT address clogs with a needle!!
Precision Machined Upper Manifold

Reagent Addition Port

Pneumatically Activated Teflon Upper Manifold Seal Prevents Reaction Vessel Cross Contamination

Parallel Delivery of Solvent and Gas to Reaction Vessels

Parallel Venting of Reaction Vessels

Tip: Avoid splashing RV contents onto upper manifold. This eliminates potential plugging of restricter tubes and any cross-contamination.
Control Valve Functions

Control Valves: Analogous to a 4-position stopcock

**Drain Gas:**
Delivers 30 PSI gas to RV; resin wash, resin/solid drying

**Vent:**
releases P to atm, **Always vent before opening RVs**

**Metered Gas:**
Delivers 10 PSI gas to RV w/adjustable flow, similar to standard gas manifold; product collection, headspace sweep

**Solvent:**
addition of solvent

**Closed:**
Off position; closed stopcock

**Utility1/Utility2:**
allow for hook-up of additional equipment (bubbler, scrubber, automated vent, etc.)
Overview

A comparison of traditional synthetic operations (Left side of slide)

And the comparable operations on the (Right side of slide)
Reaction Set Up

- Round bottom
- Clamp

- Remove reaction vessels (RVs)

REMOVAL:
1. Raise upper manifold and lock in highest position
2. Place an upside down upper manifold port plug into RV opening.
3. Grasp RV top with red RV extraction tool and pull up with a twisting motion (Heater block or safety shield can act as leverage point for 5 mL RV).
4. Remove RV after separation from lower manifold.

- Insert new RV
Inerting Reaction Environment

- Gas purge; septa or stopcock

- Solid SM or empty RV
  - Straight drain
    - Upper Manifold Membrane Valve: OPEN
      - Drain Gas
      - Solvent Closed
      - Vent Closed
      - Utility1
      - Utility2
      - CONTROL VALVE 1
      - CONTROL VALVE 2
    - Open lower manifold drain valves to empty RVs

- Liquid SM
  - Headspace sweep purges top of RV with 30 PSI gas
    - Upper Manifold Membrane Valve: OPEN
      - Drain Gas
      - Solvent Closed
      - Vent Closed
      - Utility1
      - Utility2
      - CONTROL VALVE 1
      - CONTROL VALVE 2
Reagent Addition

- Funnel, needle, pipette, spatula
- Funnel, needle, pipette, micro-spatula
Addition Under Inert Conditions

- Septa
- Septa, head-space sweep, cannulation

Purging RVs with Inert Gas
Upper Manifold Membrane Valve: OPEN

1. Attach Bubbler to Utility 1 Port
2. Adjust inert gas flow rate with Metered Gas Needle Valve.

Remove RV upper manifold port fitting
Reagent Addition Tips

- Addition of a common reagent, not requiring a needle, to multiple RVs can be done by attaching a cannula tube to a syringe barrel. The septa luer cap can then be placed at the RV positions for reagent delivery.

- The funnel manifold can be used for solids addition to a single RV by using one end of the funnel manifold.

- Inert deliveries without septa caps necessitate establishing a head-space sweep using metered gas.

- When adding solids to RVs off the instrument: wrap the RV with a Kimwipe, add the solid and then drag the Kimwipe down the length of the RV. This helps combat static.

- Inert deliveries with Metered Gas and a funnel; ensure that the funnel dip tube goes below the restrictor tubes.

- Repeater pipette simplifies common reagent additions.
Temperature Regulation: Heat/cool

- Bath, heating mantle or tape, recirculator
- Heating block $\Rightarrow 130 \, ^\circ C$
  - Temperature controlled by controller
  - Volume entry in program
- Chiller $\Rightarrow -40 \, ^\circ C$
  - Temperature controlled by chiller
  - Remove condensation with towel or acetone
- Two temperatures; max $\Delta = 40 \, ^\circ C$

Connections for chiller; 1/4" MPT
Heating Temperature Programming

- Set temperature for bank A or bank B
- Input time (hh:mm) to heat
- Enter approximate volume to nearest mL
- Push start/stop button
- Timer counts down when set point is reached
- Heaters turn off when time expires
- Power failure default; Quest off when power resumes
Heating Under Reflux Conditions

- Condenser at 1 ATM
- Condensate regulates rxn temperature

- **Seal upper manifold**

- Heat to bp of solvent; 
  **Do not exceed!**

- Rxn temperature regulated by controller

- Sealed tube conditions

- 10 ml RV mimics condenser with 3-4 ml volumes

- Double check to heat the desired bank!
Agitation

- Shaker
- Magnetic stirrer
- Overhead stirrer

- Place magnet in RV, dimple down
- Mixing via vertical oscillation
Set Agitation

- Stir plate, variac

- Program on controller

  - Mix every = seconds/cycle
  - Up stroke = time in up position
  - % Upward = % time in up position

- Adjust physical stops for height
- Fine control with needle valve
Recommended Agitation Parameters

- **Programming flexibility to meet your needs**

The recommended agitation parameters for gel-type resins are: ArgoGel (polyethylene glycol-polystyrene graft copolymer) or lightly-crosslinked poly (styrene-codivinyl benzene)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MixEvery:</td>
<td>3.0-4.0 sec</td>
</tr>
<tr>
<td>UpStroke:</td>
<td>1.8-2.6 sec</td>
</tr>
<tr>
<td>%Upwards:</td>
<td>60%</td>
</tr>
</tbody>
</table>

Adjust the agitation parameters accordingly to achieve the desired mixing.

Use the following procedure to achieve effective mixing of ArgoPore and macroporous resins.

1. Press the Mode key on the controller unit until the LCD displays the agitation menu. Using the left and right and PARAMETER SETTING (+ and -) keys, adjust the agitation parameters to:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MixEvery:</td>
<td>5.0 sec</td>
</tr>
<tr>
<td>UpStroke:</td>
<td>4.8 sec</td>
</tr>
<tr>
<td>%Upwards:</td>
<td>96%</td>
</tr>
</tbody>
</table>

2. Turn on the agitator and mix the solution for 5 agitation strokes. Decrease the % Upwards by 1% per 5 agitation strokes until the % Upwards equals 90%.
3. Decrease the % Upwards to 60% and agitate the resin for the desired time period.

- **Keep magnets ~5 mm below solvent surface**
- **Minimize splashing onto upper manifold**
- **Use a large mix every value for viscous solutions (e.g. 4-5 s)**
- **Use external magnet to dislodge stuck magnets**
Reaction Work Up: LLE

- Pour rxn sol’n into separatory funnel with aqueous sol’n
- All operations combined into Quest RV
- Split phases
Reaction Work Up: LLE

- Dry in Erlenmeyer
- Add drying agent to RV
Reaction Work Up: LLE

- Filter and concentrate

- Filter and concentrate
  - Place collection vessels under lower manifold

Upper Manifold Membrane Valve: OPEN

1. Close the Metered Gas Needle Valve.
2. Select Metered Gas delivery.
3. Open lower manifold drain valve
4. Slowly open Metered Gas Needle Valve (counterclockwise) for appropriate draining.
5. Close lower manifold valve.
Reaction Work-up: Alternatives

- Use of resin-bound scavengers and reagents $\Rightarrow$ RV filter provides purification
- Drain through cartridges and SPE
  Columns: on-line purification
- Drain into SPE or SLE cartridges:
  Off-line purification
Reaction Concentration

- Rotary evaporator
- Speed-vac/Genevac
- Blow-down

- Volume reduction in RV
- Blow down

Upper Manifold Membrane Valve: OPEN

Attach condenser to Utility Port 1
Adjust gas flow with Metered Gas Needle Valve

- Gas reagent concentration manifold - released later this year
In-situ Product Isolation

- Precipitation or crystallization in RV
- Re-crystallize in RV
- 5-7 μm fine frit rvs
Multi-step Synthesis

- Pour from flask
- Cannula

- Bank-to-bank cannula
  - Install cannula
  - Pressurize RV with solution using metered gas
  - Vent receiving bank
  - Open drain valve to start transfer
Routine Maintenance

- Uneven Filling: replace restrictor tubes of slow filling RV
- Slow draining or plugged Lower Manifold: open drain valve and add solvent through Lower Luer fitting with a syringe barrel
- Store unused Quest with RVs in place or cover reactor unit to keep away dust
  - Tip: take frits out of old RVs and use them for storage periods

- Cleaning
  - Swab and wipe down with solvent
  - Post Use Check List
Post Use Check List

Solvent Wash 3 x (THF or DCM) – check for solvent flow during washing

Replace any plugged or contaminated restrictor tubes

Blow dry lines with Drain Gas

Clean Luer Ports and Plugs with acetone

Rinse collection lines (Teflon® tubes or luers) of Lower Manifold

Remove and dispose of reaction vessels

Empty waste tank into the appropriate solvent waste

Check 4 L solvent bottle levels and replace if needed

Clean magnets with acetone

Ensure that the following items are in an accessory drawer or near the instrument: magnet, RV removal tool, scintillation vial rack

Insert storage RVs or cover reactor unit

If you encounter any difficulties with your Quest contact your local Argonaut Applications Chemist for assistance. Additionally Bob Horn, Quest Depot Engineer, can assist with diagnosis; ext. 245.
Multistep synthesis and purification of 1,2,3-thiadiazoles using ‘bank-to-bank’ transfer

- Quest SPE rack
- Quest lower luer manifold (LLM) and bank-to-bank cannulas
- Quest funnel manifold
- PS-TsNHNH$_2$ and MP-TsOH resins
Ketone Synthesis

1) $RCH_2MgX$ in THF, 0 $^\circ$C, 3 h

- Instrument pre-run maintenance
- Starting material loading into RVs and inerting of RV environment
- Chilling RVs to 0 $^\circ$C
- Addition of Grignard reagent through septa cap ports
- Reaction work-up with addition of MP-TsOH
- Addition of HOAc for next step
- Transfer of contents to other side of Quest using transfer cannulas
Ketone Capture

- Ketone solutions transferred to RVs containing PS-TsNHNH$_2$
- Ketone capture incubation
- Resin washing protocol using automated solvent wash
Thiadiazole Formation

Release and cyclization affected by addition of SOCl₂
Product work-up using SLE. SLE cartridges held in SPE cartridge rack
Post-reaction maintenance
Parallel Solid Liquid Extraction (SLE) using ChemElut Plus Cartridges

Step 1: Prep Cartridge
Add aqueous solution (e.g., 2N HCl)
Aqueous buffer coats hydrophilic support and is immobilized on stationary phase

Step 2: Wait 5 to 10 min.

Step 3: Add reaction mixture in water immiscible solvent

Products eluted with water immiscible solvent e.g. ether, methylene chloride, toluene, ethyl acetate

Alternative to aqueous work-up and dying
Multistep Synthesis and Purification of 1,2,3-Thiadiazoles Using “Bank-to-Bank” Transfer

Fred Hu, Sylvie Baudart, Terry Long, John A. Porco, Jr.
Argonaut Technologies, San Carlos, CA 94070

INTRODUCTION

Many novel methodologies have been developed in the course of applying combinatorial solid phase\(^1\) and solution phase\(^2\) synthesis toward making compound libraries with potential biological and therapeutic significance. These include “catch and release”\(^3\) and “resin capture”\(^4\) strategies for the expedited workup and purification of compounds synthesized in solution. Here we demonstrate a catch and release strategy to synthesize 1,2,3-thiadiazoles. Ketones are prepared in solution on bank A of the Quest 210 organic synthesizer, transferred to a sulfonylhydrazine resin in bank B, and converted using further transformations to 1,2,3-thiadiazoles (Scheme 1).

1,2,3-Thiadiazoles are an important class of biologically active\(^5\) compounds as well as useful intermediates in organic synthesis\(^6\). For example, 4,5-bis-(4’-methoxy-phenyl)-1,2,3-thiadiazole was found to be an active inhibitor of collagen-induced platelet aggregation in vitro.\(^7\) Many methods have been developed for the synthesis of 1,2,3-thiadiazoles,\(^8\) including the Hurd-Mori cyclization of \(\alpha\)-methylene ketones employing \(p\)-toluene-sulfonyl hydrazone intermediates.\(^8\)

Argonaut Technologies supplies a gel-type polystyrene-sulfonylhydrazide resin (PS-Ts-NHNH\(_2\)) originally designed for carbonyl scavenging applications.\(^9\) We felt

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that the sulfonylhydrazide resin could also serve as a linker for carbonyl compounds and be used for 1,2,3-thiadiazole synthesis. In addition, we used several accessories that expand the capabilities of the Quest 210 organic synthesizer in order to facilitate the synthesis and purification of 1,2,3-thiadiazoles. These accessories include:

1) Bank-to-bank transfer cannulas
2) Funnel manifold
3) Solid phase extraction (SPE) rack
4) Septum luer plugs

MATERIALS
Reagents required for the synthesis of 1,2,3-thiadiazoles on the Quest 210 are outlined in Table 1.

EXPERIMENTAL PROCEDURE
All parallel synthesis transformations were performed on the Quest 210 organic synthesizer. A series of five Grignard reagents were used with a representative Weinreb amide in reaction vessels in bank A. The tetrahedral intermediates thus generated were quenched with MP-TsOH resin to afford aryl ketones. Parallel addition of MP-TsOH resin to reaction vessels was facilitated using the Quest funnel manifold. Ketones were then transferred via a bank-to-bank transfer cannula to reaction vessels containing PS-TsNHNH₂ resin in bank B to form polymer sulfonylhydrazones. Using a bank-to-bank transfer cannula to transfer reagents synthesized on bank A to bank B facilitates multistep solution-phase sequences. After sulfonylhydrazone formation and Hurd-Mori cyclizative cleavage, excess thionyl chloride was neutralized in parallel utilizing Extube™ extraction columns, preloaded with saturated Na₂CO₃ and mounted on the Quest SPE rack. Final workup involved filtration and concentration of the products.

The Quest 210 was cleaned and prepared for synthesis as described in the Quest 210 User Manual. Septum luer plugs were used for reaction vessels on bank B. PS-TsNH₂ resin (200 mg, 2.4 mmol/g, 0.48 mmol) was loaded into five 5 mL Teflon® reaction vessels on bank A of the Quest 210. The reaction vessels containing the resin were then purged with nitrogen for 2 minutes. On bank B of the Quest 210, N-methoxy-N-methyl-p-bromobenzamide (215 mL, 1.25 mmol) was added into five 5 mL Teflon reaction vessels with 3 mL dry THF. The agitation parameters were programmed as follows: 2.5 sec, UpStroke: 1.5 sec, % Upward: 60%. The reaction vessels on bank B were cooled to 0 °C using a Julabo® recirculating chiller. Using Metered Gas to maintain an inert environment, the appropriate Grignard reagents (1.38 mmol, 1.1 equiv.): CH₃MgCl (3.0 M, 465 mL), n-BuMgCl (2.0 M, 695 mL), EtMgBr (3.14 M, 442 mL), iso-BuMgCl (2.0 M, 695 mL), PhCH₂MgCl (2.0 M, 695 mL)) were then added to the reaction vessels through the septum luer plugs via syringe. Reaction mixtures were agitated at 0 °C for 3 hours.

While maintaining a gas flow using Metered Gas and Utility (bubbler attachment), the upper manifold luer plugs were removed and the funnel manifold mounted. To each

<table>
<thead>
<tr>
<th>MATERIAL</th>
<th>SOURCE</th>
<th>PROPERTY</th>
<th>AMOUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS-TsNH₂ resin</td>
<td>Argonaut</td>
<td>2.4 mmol/g</td>
<td>1.0 g</td>
</tr>
<tr>
<td>MP-TsOH resin</td>
<td>Argonaut</td>
<td>1.45 mmol/g</td>
<td>10 g</td>
</tr>
<tr>
<td>N-Methoxy-N-methyl-p-bromobenzamide</td>
<td>Prepared</td>
<td>FW 244.09 d 1.434</td>
<td>1.08 mL</td>
</tr>
<tr>
<td>CH₃MgCl</td>
<td>Aldrich</td>
<td>3.0 M</td>
<td>465 μL</td>
</tr>
<tr>
<td>n-BuMgCl</td>
<td>Aldrich</td>
<td>2.0 M</td>
<td>695 μL</td>
</tr>
<tr>
<td>EtMgBr</td>
<td>Alfa Aesar</td>
<td>3.14 M</td>
<td>442 μL</td>
</tr>
<tr>
<td>iso-BuMgCl</td>
<td>Aldrich</td>
<td>2.0 M</td>
<td>695 μL</td>
</tr>
<tr>
<td>PhCH₂MgCl</td>
<td>Aldrich</td>
<td>2.0 M</td>
<td>695 μL</td>
</tr>
<tr>
<td>CH₃COOH</td>
<td>Fisher Scientific</td>
<td>FW 60.05 d 1.049</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>SOCl₂</td>
<td>Aldrich</td>
<td>FW 118.97 d 1.631</td>
<td>3.5 mL</td>
</tr>
</tbody>
</table>
reaction vessel was then added 1 gram (1.45 mmol/g, 1.45 mmol) of MP-TsOH through the Funnel Manifold. After reinsertion of the septum luer plugs, the reaction mixtures were agitated for 10 min at 0 °C, followed by addition of 0.3 mL of AcOH. The Manifold Control Valves on bank A were set to “Closed” and “Metered Gas” and the upper manifold luer removed. The shorter end of the bank-to-bank transfer cannula was attached to the luer ports and Metered Gas allowed to flow through for complete purging of the lines. The Manifold Control Valves were then set to “Closed” and “Vent.” The female luer fittings were then attached to the male luer fitting under lower valve manifold to the adjacent RV position on bank B. The bank B manifold control valves were set to “Closed” and “Metered Gas.” By toggling the RV lower manifold valve lever of bank B to the open position, Metered Gas pressure was used to transfer the solution to RVs of bank A. When the transfer was complete and the RV lower manifold valve lever closed, the bank A manifold control valves were set to “Closed” and “Metered Gas.” The reaction vessels in bank A were then agitated at 50 °C for 4 hours. The vessels were cooled to room temperature, drained, and washed with THF (3 X), hexane (2 X), and dichloroethane (3 X). To perform product cleavage, 2.3 mL of dichloroethane and 700 mL of SOCl₂ (9.6 mmol, 20 equiv.) were added to each reaction vessel and the reaction mixtures agitated for 5 hours at 60 °C.

Five liquid-liquid extraction cartridges (Extube™ Extraction Columns) were mounted on the SPE rack. To each cartridge was added 2.5 mL saturated Na₂CO₃, and the cartridges were allowed to soak for 10 min. The

Table 2. Thiadiazoles prepared via “resin capture” of ketones on the Quest 210

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Thiadiazole</th>
<th>Yield (%)</th>
<th>GC Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br (\text{OCH}_3) (\text{Br}) (\text{N}=\text{S}) (\text{N}=\text{S}) (\text{OCH}_3) (\text{Br})</td>
<td>98</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Br (\text{OCH}_2\text{Pr}) (\text{Br}) (\text{Br}) (\text{N}=\text{S}) (\text{N}=\text{S}) (\text{CH}_3) (\text{CH}_3) (\text{OCH}_3) (\text{Br})</td>
<td>82</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Br (\text{OCH}_2\text{CH}_3) (\text{Br}) (\text{Br}) (\text{Br}) (\text{OCH}_3) (\text{Br}) (\text{Br}) (\text{N}=\text{S}) (\text{N}=\text{S})</td>
<td>77</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Br (\text{OCH}_3) (\text{Br}) (\text{Br}) (\text{CH}_3) (\text{N}=\text{S}) (\text{N}=\text{S}) (\text{CH}_3) (\text{CH}_3) (\text{OCH}_3) (\text{Br})</td>
<td>59</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Br (\text{OCH}_2\text{CH}_3) (\text{Br}) (\text{Br}) (\text{N}=\text{S}) (\text{N}=\text{S}) (\text{OCH}_3) (\text{Br})</td>
<td>67</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>
reaction mixtures (and three dichloroethane washes) were filtered through the liquid-liquid extraction cartridges into scintillation vials. The solutions were concentrated to afford the 1,2,3-thiadiazole products.

RESULTS AND DISCUSSION

The formation of support-bound sulfonylhydrazones from non-commercially available ketones was facilitated using "resin capture" wherein ketones synthesized in solution are captured as resin-bound sulfonylhydrazones (Scheme 1, Table 2). Five p-bromophenyl ketones were prepared in parallel on the Quest 210 organic synthesizer by reacting N-methoxy-N-methyl-p-bromobenzamide with a variety of Grignard reagents (THF, 0 °C). The reaction mixtures were then quenched with a macroporous polystyrene-sulfonic acid resin (MP-TsOH) to decompose the tetrahedral intermediate. Acetic acid (10% v/v) was added and the ketone solutions were directly transferred via cannula to reaction vessels containing PS-TsNHNH$_2$ resin. The sulfonylhydrazone formation was complete in 4 h at 50 °C in the presence of acetic acid. After thionyl chloride cleavage (Hurd-Mori cleavage, dichloroethane, 60 °C, 5 h) and product purification (liquid-liquid extraction cartridges), thiadiazoles were obtained in high chemical yield and purity. A series of 1,2,3-thiadiazoles were prepared with various substituents at 5 position. All products were characterized by GC (GC method: 175 °C (3 min), ramp up to 300 °C (20 °C/min), 300 °C for 5 min.) and were found to have high purity (>90% GC area). The 1,2,3-thiadiazoles were isolated with chemical yields ranging from 59-98%. All compounds were characterized by $^1$H and $^{13}$C NMR (see spectroscopic data section). Bisaryl compounds similar to those shown in entry 5 are of great interest since antithrombotic compounds have been found to bear aromatic substituents at both 4 and 5 positions of the 1,2,3-thiadiazole ring.

SPECTROSCOPIC DATA

Gas chromatography, $^1$H NMR, $^{13}$C NMR and MS (APCI) for 1,2,3-thiadiazole compounds are provided below:

Entry 1, 4-(4'-bromophenyl)-1,2,3-thiadiazole: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.65 (s, 1 H, =CH), 7.93 (d, 2 H, J = 8.7 Hz, Ar-H), 7.65 (d, 2 H, J = 8.7 Hz, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.68, 132.24, 129.97, 129.63, 128.72, 123.50 ppm.

Entry 2, 4-(4'-bromophenyl)-5-n-propyl-1,2,3-thiadiazole: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.62 (m, 4 H, Ar-H), 3.02 (t, 2 H, J = 7.7 Hz, -CH$_2$-), 1.78 (m, 2 H, -CH$_2$-) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 158.03, 153.12, 131.89, 130.34, 120.27, 123.00, 27.50, 24.95, 13.48 ppm; MS (APCI) showed [M +1]+: 283.0 (calcd for C$_{14}$H$_8$N$_2$Br: 282.1).

Entry 3, 4-(4'-bromophenyl)-5-methyl-1,2,3-thiadiazole: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.65 (m, 4 H, Ar-H), 2.71 (s, 3 H, -CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 158.46, 146.55, 132.76, 131.91, 130.07, 123.02, 10.10 ppm.

Entry 4, 4-(4'-bromophenyl)-5-isopropyl-1,2,3-thiadiazole: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.65 (d, 2 H, J = 8.4 Hz, Ar-H), 7.56 (d, 2 H, J = 8.4 Hz, Ar-H), 3.51 (septet, 1 H, J = 6.6 Hz, -CH$_3$), 1.39 (d, 6 H, J = 6.6 Hz, -CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.39, 157.71, 131.92, 130.50, 130.34, 123.05, 26.85, 25.56 ppm.

Entry 5, 4-(4'-bromophenyl)-5-phenyl-1,2,3-thiadiazole: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.51 (m, 5 H, Ph-H), 7.33 (m, 4 H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 156.31, 151.07, 131.82, 131.60, 130.48, 129.83, 129.18, 129.13, 127.51, 123.18 ppm; MS (APCI) showed [M +1]+: 317.2 (calcd for C$_{18}$H$_{12}$N$_2$SBr: 316.2).

CONCLUSIONS

- A multistep, solution/solid-phase sequence for the synthesis of 1,2,3-thiadiazoles employing "resin capture" of ketones has been performed on the Quest 210 using the lower luer manifold upgrade.
- The transfer of ketones prepared in situ was facilitated using the Quest bank-to-bank transfer cannula accessory.
- Ketones were captured to the solid support as sulfonylhydrazones using PS-TsNHNH$_2$ resin.
- Cleavage of resin-bound sulfonylhydrazones was accomplished using thionyl chloride to afford 1,2,3-thiadiazoles without silica gel chromatography.
- Parallel product purification was performed using liquid-liquid extraction cartridges and the Quest SPE rack.
REFERENCES


9. PS-TnNH₂ resin (1.8-2.5 mmol/g, 1% crosslinked polystyrene-co-divinylbenzene) is commercially available from Argonaut Technologies.


13. Extube™ liquid-liquid extraction cartridges (part number 1219-8003, 3 mL aqueous capacity) were purchased from Varian Sample Preparation Products, Harbor City, CA. The cartridges were preloaded with 2.5mL saturated Na₂CO₃ for 10 min. before use.

14. MP-TsOH resin (1.1-1.6 mmol/g, macroporous polystyrene-co-divinylbenzene) is commercially available from Argonaut Technologies.
**1,2,3-Thiadiazole Synthesis**

### Table of Reagents

**Ketone Synthesis**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Molecular Weight (FW)</th>
<th>Density (d)</th>
<th>Molarity (M)</th>
<th>Solvent</th>
<th>Equiv. (EQ)</th>
<th>Mmols per RV (mmol)</th>
<th>Am't per RV (mL)</th>
<th>Total # of RVs</th>
<th>Total Req Am't (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>3</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30.00</td>
</tr>
<tr>
<td>Weinreb amide</td>
<td>165.19</td>
<td>1.085</td>
<td>N/A</td>
<td>THF</td>
<td>1</td>
<td>1.25</td>
<td>0.224</td>
<td>10</td>
<td>2.24</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>3.0</td>
<td>THF</td>
<td>1.1</td>
<td>1.38</td>
<td>0.458</td>
<td>10</td>
<td>4.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EtMgBr</td>
<td>2.0</td>
<td>THF</td>
<td>1.1</td>
<td>1.38</td>
<td>0.688</td>
<td>10</td>
<td>6.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BnMgCl</td>
<td>2.0</td>
<td>THF</td>
<td>1.1</td>
<td>1.38</td>
<td>0.688</td>
<td>10</td>
<td>6.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BuMgBr</td>
<td>2.0</td>
<td>THF</td>
<td>1.1</td>
<td>1.38</td>
<td>0.688</td>
<td>10</td>
<td>6.88</td>
<td></td>
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</tr>
<tr>
<td>i-BuMgBr</td>
<td>2.0</td>
<td>THF</td>
<td>1.1</td>
<td>1.38</td>
<td>0.688</td>
<td>10</td>
<td>6.88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Workup**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Loading (mmole/g)</th>
<th>Equiv. (EQ)</th>
<th>Mmols per RV (mmol)</th>
<th>Weight/Vol g or mL</th>
<th>Total # of RVs</th>
<th>Total Req Am't (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP-TsOH</td>
<td>1.45</td>
<td>1.16</td>
<td>1.45</td>
<td>1.0</td>
<td>10</td>
<td>10.00</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.00</td>
</tr>
<tr>
<td>THF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90.00</td>
</tr>
<tr>
<td>hexane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90.00</td>
</tr>
<tr>
<td>dichloromethane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90.00</td>
</tr>
</tbody>
</table>

**Resin Catch**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Loading (mmole/g)</th>
<th>Equiv. (EQ)</th>
<th>Mmols per RV (mmol)</th>
<th>Weight</th>
<th>Total # of RVs</th>
<th>Total Req Am't (mL or g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS-TsNHNH₂</td>
<td>2.4</td>
<td>0.384</td>
<td>0.48</td>
<td>0.2</td>
<td>10</td>
<td>2.00</td>
</tr>
<tr>
<td>THF</td>
<td></td>
<td></td>
<td></td>
<td>9.0</td>
<td>10</td>
<td>90.00</td>
</tr>
<tr>
<td>hexane</td>
<td></td>
<td></td>
<td></td>
<td>9.0</td>
<td>10</td>
<td>90.00</td>
</tr>
<tr>
<td>dichloromethane</td>
<td></td>
<td></td>
<td></td>
<td>9.0</td>
<td>10</td>
<td>90.00</td>
</tr>
</tbody>
</table>

**Cleavage**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Molarity (M)</th>
<th>Equiv. (EQ)</th>
<th>Mmols per RV (mmol)</th>
<th>Weight/Vol g or mL</th>
<th>Total # of RVs</th>
<th>Total Req Am't (mL or g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thionyl Chloride</td>
<td>2.00</td>
<td>20</td>
<td>9.60</td>
<td>4.8</td>
<td>10</td>
<td>48.00</td>
</tr>
</tbody>
</table>

ThiodiazCalc 1

7/27/99
Reagent Planning/Handling for Parallel Synthesis

Traditional Reagent Delivery

*Case where reagents are added accurately according to a specific stoichiometry.*

- Two Methods
  - Neat Reagents
  - Molar Solutions

- Neat Reagents:
  - *Add reagents as neat liquids and solids*
  - *Advantage:*
    - Avoids "reagent preparation"
    - solubility not an issue
  - *Disadvantage:*
    - Multiple measurement required, amount depends on reagent MW
    - Solids may require rinsing (funnel, reaction vessel walls)
    - Easier to make a mistake in reagent addition
      - Miss a reaction vessel, Add twice, Wrong amount
Reagent Planning/Handling for Parallel Synthesis

- **Molar Solutions:**
  - Add reagents as solutions of known molarity
  - Includes cocktails of multiple reagents prepared for delivery
- **Advantage**
  - *Multiple additions of same volumes, or stoichiometric multiple, for all reagents*
  - *Quicker*
  - *Easier to keep additions straight*
- **Disadvantage**
  - *Time/Effort for preparation of solutions*
  - *Reagents must be soluble in solvent compatible with reaction*
  - *Poorly soluble reagents may precipitate*
Reagent Planning/Handling for Parallel Synthesis

“Approximate” Reagent Delivery

Case where reagents are added “approximate” to the desired stoichiometry.

- Requires the use of excess reagent so that variances do not effect the reaction
- Reaction must tolerate the use of excess reagent
- Determine an average delivery amount for a particular reagent:
  - Add same volume with Pippette
  - Add same mass with scoop
- Remove excess reagent at the end by:
  - liquid-liquid extraction
  - Scavengers

Apply the methods to a particular synthesis as appropriate

Strive for best balance of chemistry performance and speed
Improved Purification Methods
For Parallel Solution Phase Synthesis

Parallel Solution Phase Synthesis:
Improved Purification Techniques

- Although Quest provides a good platform for parallel liquid-liquid extraction and integration to parallel Flash Chromatography,....
  - Liquid-liquid extraction and chromatography are tedious to implement in parallel
  - Advantageous to utilize techniques that allow separation by filtration or simple cartridge-based processes
- Techniques:
  - Polymer Assisted Solution Phase (PASP) Synthesis
    - Polymeric Scavengers
    - Polymer-Bound Reagents
  - Solid Phase Extraction (SPE)
  - Solid-Supported Liquid Extraction (SLE)
Polymer Assisted Solution Phase Synthesis: Scavengers

Polymeric Scavengers are functional polymers designed to react with and bind excess reagents and/or byproducts.

Solution Phase Reaction | Scavenger Resin | Product
--- | --- | ---
1.5 $R_1 + C \rightarrow P + 0.5 R_1 + O-S \rightarrow P$

- $C$ = Core Substrate
- $S$ = Scavenger Resin
- $R_1$ = Reagent

Technique relies on a chemically-driven separation.
- Polymers added after reaction is complete in solution.
- Multiple Scavengers can be used in a single step.
- Mixtures of "incompatible" functionality possible.
- Purified reaction solution is isolated by filtration.

Polymer Scavengers: Functional Polymers

Functional Polymers for Scavenging applications are generally based on lightly crosslinked polystyrene (1-2% crosslinking):
- loading = 1 - 3 mmole/g
- lower cost relative to specialty polymer support backbones

Functional polymers have functional groups covalently bonded to the Polymer Backbone:

$X = -\text{CHO}, -\text{CH}_2\text{NCO}, -\text{SO}_2\text{NHNH}_2$
**Polymer Scavengers: Based on Anion Exchange Resins**

- Anion exchange resins are based on quaternary benzyl trialkyl ammonium salts of polystyrene
- Scavengers based on a variety of active counterions possible

\[
\text{NM}_3^+ \text{X}^-
\]

\[X = \text{OH, (CO}_3\text{)}_{1/2} \cdot (\text{S}_2\text{O}_3)_{1/2}\]

- Often based on more highly crosslinked, macroporous resins
  - Beads are larger and somewhat more fragile than those based on lightly crosslinked polystyrene
  - Dry resins often are difficult to handle due to static problem
  (many commercial materials are packed in water)

---

**Polymer Scavengers: Based on Cation Exchange Resins**

- Cation exchange resins are based on sulfonic acid and salts of polystyrene
- Sulfonic acid scavenges bases

\[
\text{SO}_3^- \text{X}^+
\]

\[X = \text{H, Ca}\]

- Macroporous and lightly crosslinked forms available
- Amberlyst A-15 (macroporous) has been most often used
  - Organic leachable polysulfonated impurities present
Functional Polymers:
Resin Swelling

Swelling is the uptake of solvent by dry resin
- Swelling solvents enlarge beads by 4 - 12 X
- Swelling solvents interact well with the polymer
- Swelling solvents for polystyrene are THF, DMF, dichormethane

Swelling is affected by functional groups on the polymer
- Sulfonated polystyrene swells well in water, poorly in THF
- Solute diffusion into the bead generally requires swelling in the solvent

Functional Polymers:
Chemistry Considerations

Chemical reactions on polymer bound reactive sites requires diffusion of reagent into the bead
- The "Microenvironment" associated with the neighboring polymer can effect the course of reactions
- Reagents may partition differently between the solution and polymer "phase"
- Agitation serves to refresh reagent concentration around the boundary layer
Polymer Scavengers: Considerations for Use

- Reactivity
  - Relative reactivity towards "Hot" and "Dead" Reagents (e.g. Primary amines vs anilines)
  - Equivalents
  - Scavenging Time/Temperature
- Selectivity
  - Byproducts/Reagents vs Product
- Solvent
  - Resin Swelling
  - Solvent effects in scavenging

Polymer Scavengers: Critical Requirements

- Reactivity
  - Scavenging time < 16 h
  - Room Temperature preferred
- High loading
  - Measured in mmole/g
  - Greater capacity for scavenging
  - Greater scavenger excess possible
- Low swelling
  - Balance Between:
    • accessibility to bound reactive site
    • volumetric productivity
  • Negligible leachable impurities
Polymer Scavengers: 
Urea Synthesis Example

1) DCM, RT, 1h

\[ \text{GNCO} \rightarrow \text{NH}_2 \]

2) 0.30 mmole H, \( \text{H} \text{NH}_2 \)

0.25 mmole \( \text{H} \text{NH}_2 \)

PS-Trisamine

<table>
<thead>
<tr>
<th>Resin</th>
<th>Mmole/g</th>
<th>Weight (mg)</th>
<th>Mmole</th>
<th>Equiv.</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS-Trisamine</td>
<td>3.2</td>
<td>50</td>
<td>0.16</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>


Argonaut Solution Phase Toolbox: 
Material Screening and Use Testing

- Scavenger Resins
  - Capacity (mmole/g) based on model sequestration
    - Value for calculation of requisite scavenging resin
    - Elemental Analysis can be misleading
  - Performance Testing:
    - Substrate Reactivity
    - Equivalents, Time and Temperature
  - Application to chemical reaction(s)
    - Representative small molecule synthesis
    - Scope/limitations of substrates
  - Resins meet purity and capacity specifications
### Polymer Scavengers

<table>
<thead>
<tr>
<th>Reagent Sequestered</th>
<th>Polymer Functionality</th>
<th>Type</th>
<th>Argonaut Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Chloride, anhydrides</td>
<td>Amine</td>
<td>F</td>
<td>PS-Trisamine</td>
<td></td>
</tr>
<tr>
<td>Sulfonyl Chloride</td>
<td>Amine</td>
<td>F</td>
<td>PS-Trisamine</td>
<td></td>
</tr>
<tr>
<td>Isocyanate, Isothiocyanate</td>
<td>Amine</td>
<td>F</td>
<td>PS-Trisamine</td>
<td></td>
</tr>
<tr>
<td>Alkyl halide</td>
<td>Thiol</td>
<td>F</td>
<td>PS-Thiophenol</td>
<td></td>
</tr>
<tr>
<td>Acidic OH</td>
<td>Phosphine</td>
<td>F</td>
<td>PS-triphosphine</td>
<td></td>
</tr>
<tr>
<td>Carboxylic Acid</td>
<td>Carbonate</td>
<td>IE</td>
<td>MP-Carbonate</td>
<td></td>
</tr>
<tr>
<td>Inorganic Acid</td>
<td>Carbonate</td>
<td>IE</td>
<td>MP-Carbonate</td>
<td></td>
</tr>
<tr>
<td>Aldehyde</td>
<td>Tosyl hydrazide</td>
<td>F</td>
<td>PS-DIEA, PS-NMM</td>
<td></td>
</tr>
<tr>
<td>Ketone</td>
<td>Tosyl hydrazide</td>
<td>F</td>
<td>PS-DIEA, PS-NMM</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Tosyl hydrazide</td>
<td>F</td>
<td>PS-DIEA, PS-NMM</td>
<td></td>
</tr>
<tr>
<td>Aniline</td>
<td>Tosyl hydrazide</td>
<td>F</td>
<td>PS-DIEA, PS-NMM</td>
<td></td>
</tr>
</tbody>
</table>

### Polymer Scavengers

<table>
<thead>
<tr>
<th>Reagent Sequestered</th>
<th>Polymer Functionality</th>
<th>Type</th>
<th>Argonaut Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Amine</td>
<td>Aldehyde</td>
<td>F</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td>Thiol</td>
<td>Thiol</td>
<td>F</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td>Hydrazines</td>
<td>Isocyanate</td>
<td>F</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td>Fluoride</td>
<td>Aldehyde</td>
<td>F</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td>Grignard, alkyl lithium</td>
<td>Calcium Sulfonate</td>
<td>IE</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td>Dess-Martin Periodinane</td>
<td>Aldehyde</td>
<td>F</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td>DDQ</td>
<td>Thiosulfate</td>
<td>F</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td>Fluoride</td>
<td>Citrate, Carbonate</td>
<td>IE</td>
<td>PS-CHO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium Sulfonate</td>
<td>IE</td>
<td>PS-CHO</td>
<td></td>
</tr>
</tbody>
</table>
Scavenger Resins: 
PS-Isocyanate

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Nucl Conc M</th>
<th>Ps-Isocyanate (eq)</th>
<th>Time 100% Scavenged (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diisopropylamine</td>
<td>0.05</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Piperidine</td>
<td>0.015</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>Methylcyclohexylamine</td>
<td>0.015</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Aniline</td>
<td>0.05</td>
<td>2</td>
<td>16h, 20°C - 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16h, 60°C - 99%</td>
</tr>
<tr>
<td>2-Amino Benzenophenone</td>
<td>0.05</td>
<td>2</td>
<td>16h - 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16h - 81%</td>
</tr>
</tbody>
</table>

- Readily scavenges alkylamines
- Anilines more sluggish

Isocyanate Resins: Comparison of IR spectra

- Low levels of urea crosslinking present by IR in Argonaut resin
### Scavenger Resins: PS-Trisamine

- Two equivalents of PS-Trisamine per acid or sulfonyl chloride is required when tertiary amine resin is not present.

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Ps-Trisamine (equiv)</th>
<th>Time 100% Scavenged (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-ClBzCl (0.05 M)</td>
<td>3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2-PhBuCOCl</td>
<td>3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2,6-MeOPhCOCl</td>
<td>3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>PhSO₂Cl</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>4-MeOPhNCO</td>
<td>2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Use of PS-Trisamine: Dihydropyridone Synthesis

- Work performed by Parke Davis (Creswell et. al. Tetrahedron 1998, 54, 3983).
- PS-Trisamine removes both unreacted imine 1 and diene product 2.
Scavenger Resins:
PS-TsNHNH₂

<table>
<thead>
<tr>
<th>Carbonyl Compound (DCM solvent)</th>
<th>AcOH added</th>
<th>Ps-TsNHNH₂ (equiv)</th>
<th>Time 100% Scavenged (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCHO (0.05 M)</td>
<td>no</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hexanal</td>
<td>no</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2,6-MeOPhCHO</td>
<td>no</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>10 %</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Acetophenone</td>
<td>10 %</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>2,6-Me-Cyclohexanone (10 % DCM/DCM 70°C)</td>
<td>3</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

- Polymer equivalent of p-toluenesulfonyl hydrazide
- DCM, THF > DMF (requires acetic acid)
- Scavenging of ketones accelerated by addition of acetic acid
- May also be utilized as a polymeric reagent (Bound tosylhydrazine equivalent)

Scavenger Resins:
PS-Thiophenol

PS-Thiophenol

- General scavenger for alkylating agents
- Capacity = 1.0 - 1.3 mmole/g
- “Wash and Ready” Disulfide Reduction
  - Bu₃P in THF/water, 30 min
  - Storable for several weeks
- Possible linker for SPOS
Scavenger Resins: 
PS-Thiophenol

- 2 equiv. DIEA and MP-Carbonate relative to PS-Thiophenol
- Scavenging more effective in EtOH/THF than DMF

Phenyl Ether Synthesis: 
PS-Thiophenol workup

- Quest 210 provides platform for Ether Synthesis (Bank A)
- Resin Scavenger Preparation (Bank B)
  - Disulfide Reduction
  - Thiophenolate formation with TMSOK
- Cannula transfer to Bank B to scavenge R-Br
General Acid and Base Resins: 
**MP-Carbonate**

- Resin bound tetraalkylammonium carbonate equivalent
- Low odor relative to trimethylammonium analogue
- Scavenger for Carboxylic acids, sulfonic acids, and acidic phenols
- Also useful to neutralize amine salts to provide free amines

Partow, J.J.; Naing, W.; South, M.S.; Flynn Tetrahedron Lett. 1997, 46, 7959

---

**MP-Carbonate: Use in Purification of Solution-Phase Libraries**

- MP-carbonate used for scavenging excess activated ester and N-hydroxysuccinimide byproduct
- Flynn et al. Medicinal Chemistry Research 1998, 8, 219-243
Polymer Scavengers:
Sequestering Enabling Reagents

- Approach involves delivery of soluble sequeatering enabling reagent to reaction mixture
- Reaction with excess results in the release of functionality for scavenging
- Advantageous for separating species of low reactivity


Bound Reagents and Scavengers

- Scavenger Resins designed for sequestering a range of substrates.
- Bound Reagents for common organic synthesis transformations.

<table>
<thead>
<tr>
<th>Scavenger Resin</th>
<th>Reagents Sequestered</th>
<th>Bound Reagent</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS-Trisamine</td>
<td>Electrophiles</td>
<td>Ps-TsCl</td>
<td>Catch &amp; Release</td>
</tr>
<tr>
<td>PS-NCO</td>
<td>Nucleophiles</td>
<td>PS-DIEA</td>
<td>Amine Base</td>
</tr>
<tr>
<td>PS-TsNHNNH₂</td>
<td>Aldehydes, Ketones</td>
<td>PS-NMM</td>
<td>Non-Benzylc Amine Base</td>
</tr>
<tr>
<td>PS-Thiophenol</td>
<td>Alkylating Agents</td>
<td>PS-DMAP</td>
<td>Catalyst, Catch &amp; Release</td>
</tr>
<tr>
<td>PS-benzaldehyde</td>
<td>Nucleophiles</td>
<td>MP-Carbonate</td>
<td>Base, Catch &amp; Release</td>
</tr>
<tr>
<td>PS-TsCl (HL)</td>
<td>Nucleophiles</td>
<td>MP-TsOH</td>
<td>Acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PS-HOBT</td>
<td>Coupling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PS-Carbodiimide</td>
<td>Coupling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PS-Triphenylphosphine</td>
<td>Mitsunobu/Wittig/etc.</td>
</tr>
</tbody>
</table>
**Polymer Assisted Solution Phase Synthesis:**

**Polymeric Reagents**

- Polymeric Reagents are functional polymers designed to perform synthetic transformations by analogy to their solution counterparts.

\[ \text{Solution Phase Reaction} + \text{Bound Reagent} \rightarrow \text{Product} \]

\[ \text{R} + \text{C} \rightarrow \text{P} \]

- \( \text{R} = \text{Bound Reagent} \)
- \( \text{C} = \text{Core Substrate} \)

- Simplifies purification by filtration to remove spent and excess reagent.
- One-Pot Multistep reactions possible.
- Mixtures of "incompatible" functionality possible.
- Reagent performance is affected by polymer.

---

**Functional Polymers:**

**Chemistry Considerations**

- Chemical reactions at polymer bound reactive sites requires diffusion of substrate into the bead.
- The "Microenvironment" associated with the neighboring polymer can affect the course of reactions.
- Conversion of functionality on the polymer can affect the microenvironment and swelling properties.
- Generally polymer reagents are prepared in "modest loading" (~ 1 mmole/g).
- Agitation serves to refresh reagent concentration around the boundary layer.
Polymer Reagents and Scavengers: Critical Requirements

- Bound Reagents:
  - High functional group purity
  - High synthetic fidelity
  - Moderate loading (high loading for acid/base type reagents)
    - High loading for acid/base reagents
  - Reasonable swelling (gel-type resins)
    - 5 mL/g
  - Negligible leachable impurities

Polymer Reagents: Reagent Classes

- Bases
- Acids
- Phosphine
- Coupling
  - Carbodiimides
  - Active esters
- Silane
- "Catch and Release"
Tertiary Amine Bases

- Amine base resins in literature are typically bound through a benzylic linkage.

- Polymeric benzylic linkage are readily prepared from Merrifield resin.
- These linkages are susceptible to cleavage by certain electrophiles.
  - Small molecule impurities possible
- Screen benzylic bases for stability.
### Tertiary Amine Bases

**Stability to Electrophiles**

- Benzyllic amines underwent most significant cleavage with chloroformates.
- Sterically hindered di-isopropylamine substitution is the most stable.
- Amine stability most pertinent with an excess of base and electrophile.

#### Table

<table>
<thead>
<tr>
<th>R</th>
<th>Loading (mmole/g)</th>
<th>% Cleavage</th>
<th>R1 = Ph</th>
<th>R1 = MeO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>4.8</td>
<td>9</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Morpholine</td>
<td>3.6</td>
<td>0</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>i-Pr</td>
<td>3.8</td>
<td>-</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

**PS-DIEA:**

**Mesylate Formation**

- PS-DIEA afforded high purity mesylate under analogous conditions to the solution phase reaction. (Gooding, et al. Synth Commun 1995, 25, 1155)
Tertiary Amine Bases:
Sulfonamide-Linked Bases

PS-NMM

- PS-NMM is a bound non-benzylic analogue of N-methylmorpholine
- Stability studies with methyl chloroformate showed no cleavage under reaction conditions that afford 70% cleavage of a benzylic morpholine resin.

PS-NMM: Stability of Tethered vs. Benzylic Linked Bases

<table>
<thead>
<tr>
<th>Resin</th>
<th>RNH₂</th>
<th>% Yield</th>
<th>% Desired Product</th>
<th>% Cleavage Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS-NMM</td>
<td>BnNH₂</td>
<td>99.3</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>P-Morpholine</td>
<td>BnNH₂</td>
<td>76.5</td>
<td>95.8</td>
<td>4.2</td>
</tr>
<tr>
<td>PS-NMM</td>
<td>Aniline</td>
<td>67</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>P-Morpholine</td>
<td>Aniline</td>
<td>67</td>
<td>83.6</td>
<td>16.4</td>
</tr>
</tbody>
</table>
General Acid and Base Resins: 
MP-Carbonate

- Resin bound tetraalkylammonium carbonate equivalent
- Low odor relative to trimethylammonium analog
- General base for reaction quenching, acid removal and neutralization of amine hydrochlorides
- Useful in the formation of resin bound phenolates for Williamson ether synthesis, sequestering excess phenolate on the resin.

Carbodiimide Resins: Structures and Stability

 предоставляется таблица и диаграмма, содержащая данные о стабильности карбодиимидных резин в условиях комнатной температуры.
Comparison of Amide Coupling Efficiency

<table>
<thead>
<tr>
<th>Entry</th>
<th>Resin</th>
<th>Acid</th>
<th>Amine</th>
<th>HPLC Puritv</th>
<th>GC Amine</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PS-Carbodiimide</td>
<td>3,3-Diphenylpropionic</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>90</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>PS-Carbodiimide</td>
<td>3,3-Diphenylpropionic</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>90</td>
<td>11</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>PS-Carbodiimide</td>
<td>3,3-Diphenylpropionic</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>88</td>
<td>7-20</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>PS-Carbodiimide</td>
<td>3,3-Diphenylpropionic</td>
<td>3,3-diphenylpropylamine</td>
<td>100</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>PS-Carbodiimide</td>
<td>3,3-Diphenylpropionic</td>
<td>3,3-diphenylpropylamine</td>
<td>100</td>
<td>10-25</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>PS-Carbodiimide</td>
<td>3,3-Diphenylpropionic</td>
<td>3,3-diphenylpropylamine</td>
<td>84</td>
<td>30</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>PS-Carbodiimide</td>
<td>3-Iodobenzoic acid</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>95</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>PS-Carbodiimide</td>
<td>3-Iodobenzoic acid</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>96</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>PS-Carbodiimide</td>
<td>3-Iodobenzoic acid</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>97</td>
<td>10</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>PS-Carbodiimide</td>
<td>Ben-Phe</td>
<td>3,5-dimethylamine</td>
<td>100</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>PS-Carbodiimide</td>
<td>Ben-Phe</td>
<td>3,5-dimethylamine</td>
<td>98</td>
<td>0</td>
<td>83</td>
</tr>
<tr>
<td>12</td>
<td>PS-Carbodiimide</td>
<td>Ben-Phe</td>
<td>3,5-dimethylamine</td>
<td>96</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>

In general, couplings with PS-Carbodiimide lead to full amine consumption.

PS-Carbodiimide Couplings using added HOBt

1. $RCO_2H, CH_2Cl_2$
   or DMF, HOBt
2. $R_1R_2NH$
3. $N\text{H}_2$

<table>
<thead>
<tr>
<th>Acid</th>
<th>Amine</th>
<th>% Yield (isolated)</th>
<th>HPLC Puritv</th>
<th>GC Amine</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,3-Diphenylpropionic</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>95</td>
<td>85</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3,3-Diphenylpropionic</td>
<td>Benzylamine</td>
<td>92</td>
<td>85</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3-Iodobenzoic acid</td>
<td>1,2,3,4-tetrahydroxysquamine</td>
<td>96</td>
<td>85</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3-Iodobenzoic acid</td>
<td>Benzylamine</td>
<td>94</td>
<td>98</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

HOBt scavenged with PS-Trisamine resin

"Catch and Release" Synthesis of Amides Using PS-HOBt

1. RCOOH (2 equiv.)
   PyBOP (2 equiv.)
   DIEA (4 equiv.)
   DMF, 25°C, 3 h

2. Wash and repeat step 1

PS-HOBt Protecting Group Transfer

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protecting Group</th>
<th>Amine R''NH</th>
<th>Protected Amine PNR'R'</th>
<th>Yield HPLC Purify</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fmoc-Cl</td>
<td>NH2</td>
<td>Fmoc</td>
<td>77% (1st cycle)</td>
</tr>
<tr>
<td>2</td>
<td>Fmoc-Cl</td>
<td>NH</td>
<td>Fmoc</td>
<td>75% (2nd cycle)</td>
</tr>
<tr>
<td>3</td>
<td>Fmoc-Cl</td>
<td>NH2</td>
<td>Fmoc</td>
<td>76%</td>
</tr>
<tr>
<td>4</td>
<td>Cbz-Cl</td>
<td>NH2</td>
<td>Cbz</td>
<td>87%</td>
</tr>
<tr>
<td>5</td>
<td>Cbz-Cl</td>
<td>NH</td>
<td>Cbz</td>
<td>42%</td>
</tr>
<tr>
<td>6</td>
<td>Cbz-Cl</td>
<td>NH2</td>
<td>Cbz</td>
<td>70%</td>
</tr>
</tbody>
</table>

- Resin is recycleable
**PS-Triphenylphosphine resin**

- **Capacity:** 1.0 – 1.5 mmole/g (benzyl bromide uptake)
- **Resin Type:** 1% crosslinked polystyrene
- **Applications:**
  - Halogenations
  - Wittig
  - Mitsunobu

**Chlorination of Alcohols and Acids using PS-Triphenylphosphine**

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROH or RCOOH</th>
<th>RCI or RCOCI</th>
<th>Yield</th>
<th>GC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>73%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Wittig Reaction using PS-Triphenylphosphine

\[
R-\text{CH}_2-X \xrightarrow{65^\circ C, \text{DMF}} \xrightarrow{25^\circ C, \text{NaHMDS, THF}} \xrightarrow{65^\circ C, \text{DMF}} R_2\text{COR}_3
\]

- Wittig reactions using a commercial higher crosslinked polymer-bound Triphenylphosphine (2 % DVB), led to recovery of starting materials.

Results of Representative Wittig Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Wittig Reaction</th>
<th>Carbonyl compound</th>
<th>Yield</th>
<th>Isolated yield (%)</th>
<th>GL Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>86%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>94%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>94%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>86%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>94%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
</tr>
</tbody>
</table>
Mitsunobu Reaction using PS-Triphenylphosphine

After the reaction, resin was filtered and washed with CH₂Cl₂.

The solvent was concentrated and the product was purified by filtration thru an SPE column (6 mL/2 g silica gel, Alltech) with 10:1 of hexane/ether.


Results of Mitsunobu reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Phenol</th>
<th>Aryl ether</th>
<th>% Yield (%)</th>
<th>GC Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>98%</td>
<td></td>
</tr>
</tbody>
</table>
**Trialkylsilane Resins**

- **Advantages of Polymer-Supported Trialkylsilanes with Pendant Si-H Functionality**
  - Stability to moisture providing shelf-storable silane resins
  - Potential for direct attachment of various functional groups (e.g. alcohol, carbonyl, aromatic, or unsaturated derivatives) without prior transformation to activated silylating agents.
  - Optional transformation into a reactive silyl chloride if necessary.
  - The ability to monitor reaction progress using IR spectroscopy by examination of the distinctive Si-H stretch (2000-2200 cm⁻¹).

**Silyl Triflate Resin: Ireland-Claisen Rearrangement**

1. 1) 2.5% Me₃SiCl/CH₂Cl₂
2. 2) CF₃SO₂H (6 equiv) CH₂Cl₂, 10 m
3. 3) CH₃Cl, 2 h
4. 4) 50 °C, THF 5 h
5. 5) 55 °C, 12 h

- *Claisen rearrangement monitored by IR microscopy (1710-1720 cm⁻¹ for silyl esters)*
Solid-supported Ireland-Claisen Rearrangement:

- Quest 210 provides convenient and necessary inert environment for PS-DES drying (TMS-Cl) and conversion to triflate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Ester (1)</th>
<th>Product (6)</th>
<th>Yield (%)</th>
<th>GC Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>58</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>56</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Multi-Step Reaction Sequences Utilizing Quest and PASP

- Quest and PASP provide a synergistic approach to efficient multi-step solution phase synthetic schemes
- Readily adapted to parallel processing
- Quests Provides:
  - Capability to add solid polymer-bound reagents scavengers
  - Agitation, Heat
  - Filtration, Cannulation from bank-to-bank
  - Concentration
  - flow through cartridge purification
- PASP provides:
  - Reagent and byproduct removal by filtration
Multi-Step Reaction Sequences Utilizing Quest and PASP: Benzoxacinones

1) $\text{RCOCI}$
2) $\text{P-NH}_2$

1) Add SER, Add Scavenger resin
Cannulate to Bank 2
Bank 2: Concentrate

1) $\text{2N HCl}$
2) Evaporate

1) Amide Formation, Acid Chloride Scavenging
Cannulate to Bank 1A
Bank 1A: Concentrate

1) $\text{TBAF (aq)}$
2) $\text{P-SO}_4^-$ $\text{Ca}^{2+}$

1) SEM deprotection, TBAF scavenge
Cannulate to Bank 2A
Bank 2A: Concentrate

Multi-Step Reaction Sequences Utilizing Quest and PASP: Benzoxaxinones

"Catch and Release" Resins

- Multi-step synthetic sequences performed using "Catch and Release"
- Polymer reagent is used to purify reaction products by:
  - Selective reaction of polymer functionality with desired product
  - Removal of byproducts/starting material by filtration/washing
  - Release of desired product
    - Acid-Base
    - Chemical transformation
- Additional reaction(s) may be performed with the product prior to release from resin
- Quest Capability facilitates execution of "Catch and Release"
  - Solids Addition
  - Filtration
  - Bank-to-Bank Transfer
**Catch and Release Resins**

"Catch and Release" resins: a subset of polymer-bound reagents
- "Catch" small molecule as activated polymer intermediate
- Resin can be washed to remove soluble by-products
- Cleave to "release" product or perform additional transformations

**"Catch and Release": Acidic Resins**

- Sulfonic Acid Resins can be used to bind amines and basic heterocycles
- Release performed with 2 M NH₃/MeOH or 2 M triethylamine/MeOH

\[
\begin{align*}
\text{BOCNH} & \quad \text{OH} \\
1 \text{ mmol} & \\
+ & \\
\text{NCO} & \\
1.2 \text{ mmol} & \\
\rightarrow & \\
\text{Et}_{3} \text{N, DCM, 8h} & \\
\rightarrow & \\
\text{MeOH, 5h} & \\
\rightarrow & \\
\text{SO}_{3} \text{H} & \\
1) & \\
2) \text{THF, MeOH} & \\
3) \text{NH}_{3}, \text{MeOH} & \\
\text{83% yield} & \\
\end{align*}
\]

Resin concomitantly removed BOC and purified product amine

### General Acid and Base Resins: MP-TsOH

- Resin-bound toluenesulfonic acid equivalent
  - "Clean" Amberlyst A-15 (high purity, low leachables)
  - Loading: 1.4 mmol/g
- Surface functionalized macroporous resin
  - Fast Kinetics
- Useful for Amine "Catch and Release" Purification (ion exchange)
  - high loading, low particulate contamination relative to SPE media

### "Catch and Release": Functional Resins

#### Synthetic Transformations Utilizing "Catch and Release":

<table>
<thead>
<tr>
<th>Resin Functionality</th>
<th>Substrate</th>
<th>&quot;Release&quot;</th>
<th>Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TsCl</td>
<td>Alcohol</td>
<td>2° amine</td>
<td>3° amine</td>
<td></td>
</tr>
<tr>
<td>TsNHNNH₂</td>
<td>Carbonyl</td>
<td>Cyclization</td>
<td>Thiadiazole</td>
<td></td>
</tr>
<tr>
<td>PPh₃</td>
<td>Alkyl Bromide</td>
<td>Carbonyl (Wittig)</td>
<td>Olefin</td>
<td></td>
</tr>
<tr>
<td>TBD, OH⁻</td>
<td>Phenol</td>
<td>Alkyl Halide</td>
<td>Ethers</td>
<td></td>
</tr>
<tr>
<td>Active Esters</td>
<td>Carboxylic Acids</td>
<td>Amines</td>
<td>Amides</td>
<td></td>
</tr>
<tr>
<td>DMAP</td>
<td>Acid Chloride</td>
<td>Sulfonyl Chloride</td>
<td>Amines</td>
<td>Amides</td>
</tr>
</tbody>
</table>
"Catch and Release":
Tertiary Amine Synthesis via Bound Tosylate

Alcohol is captured on PS-TsCl Resin on Quest
Release involves S_n2 displacement with amine
Product mixture drained into PS-Isocyanate into Cartridges for scavenging excess amine
High Purity (>98%) products obtained

"Catch and Release":
Ether Synthesis

- Phenols and hydroxylheterocycles caught on a Anion exchange resin
- Used in Williamson ether synthesis
**“Catch and Release” Synthesis of 1,2,3-Thiadiazoles**

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Thiadiazole</th>
<th>Yield (%)</th>
<th>GC Purity (Area %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>94</td>
<td>98</td>
</tr>
</tbody>
</table>

- Workup reactions using SLE cartridges impregnated with aqueous sodium carbonate.

**Multistep Synthesis of 1,2,3-Thiadiazoles: “Catch and Release”**

![Multistep reaction diagram]
Results of 1,2,3-Thiadiazole Synthesis Employing "Catch and Release"

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Thiadiazole</th>
<th>Yield (%)</th>
<th>GC Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Ketone 1" /></td>
<td><img src="image2.png" alt="Thiadiazole 1" /></td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Ketone 2" /></td>
<td><img src="image4.png" alt="Thiadiazole 2" /></td>
<td>82</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Ketone 3" /></td>
<td><img src="image6.png" alt="Thiadiazole 3" /></td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Ketone 4" /></td>
<td><img src="image8.png" alt="Thiadiazole 4" /></td>
<td>59</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Ketone 5" /></td>
<td><img src="image10.png" alt="Thiadiazole 5" /></td>
<td>67</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Ketone 6" /></td>
<td><img src="image12.png" alt="Thiadiazole 6" /></td>
<td>48</td>
<td>71</td>
</tr>
</tbody>
</table>

- In situ generation of non-commercially available aryl ketones (Bank A of Quest)
- MP-TsOH resin for the quenching of intermediate
- Resin capture of ketones from Friedel-Crafts reactions, aryl Grignard addition to Weinreb amides also possible

Solid Phase Extraction

- Solid phase extraction is a form of digital liquid chromatography
  - Removes solute from solution on to a solid phase sorbent
  - Variety of sorption mechanisms
    - polar
    - non-polar
    - ionic
  - Impurities removed by elution with poor solvent
  - Purified product released by elution with strong solvent
  - Does not require collection of multiple fractions per eluent type
- Amenable to automation
- Various formats available (e.g., 96-well SPE plates, syringe barrels, cartridges, disks, etc)
Solid Phase Extraction (SPE) Process

1. Condition Sorbent
2. Apply sample and analyte
3. Interference elution
4. Analyte elution

Eluted Interferences

Solid Phase Extraction Media: Examples

Common SPE Media used in Organic Synthesis:

<table>
<thead>
<tr>
<th>Type</th>
<th>Media</th>
<th>Loading (mmole/g)</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Phase</td>
<td>Silica</td>
<td></td>
<td>Absorb polar species</td>
</tr>
<tr>
<td></td>
<td>Alumina</td>
<td></td>
<td>&quot;plug chromatography&quot;</td>
</tr>
<tr>
<td></td>
<td>Fluorisil</td>
<td></td>
<td>Absorb nonpolar species</td>
</tr>
<tr>
<td></td>
<td>C-18</td>
<td></td>
<td>- Absorb basic impurities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- &quot;catch-release&quot;</td>
</tr>
<tr>
<td>Reverse Phase</td>
<td>Silica-Ar-SO₃H (SCX)</td>
<td>0.6-1.0</td>
<td>amines, basic heterocycles</td>
</tr>
<tr>
<td>Cation Exchange</td>
<td></td>
<td></td>
<td>- Absorb acidic species</td>
</tr>
<tr>
<td>Anion Exchange</td>
<td>Silica-(CH₂)₃NR₃⁺X⁻ (SAX)</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>
Synthetic Examples with SPE

- Cationic SPE useful for purifying reductive amination
  - Allows large excess of aldehyde
  - Not affected by acetic acid in reaction mixture
  - Equally effective for preparation of secondary amines


\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
1 \text{ equiv} \\
\text{Ph} & \quad \text{CHO} \\
3 \text{ equiv} \\
\rightarrow & \\
\text{Ph} & \quad \text{N} \quad \text{Ph}
\end{align*}
\]

SPE:
1. Precondition methanol
2. Apply sample: 0.5 mL, 0.124 mmole amine, 500 mg SCX (0.6 mmole/g)
3. Rinse 3 mL MeOH
4. Elute product with 1 mL of 2 M ammonia

Use of SPE to remove Reagents/Byproducts

- Amide Synthesis used anionic (SAX) and cationic (SCX) SPE
  - SAX - removes nitrophenol
  - SCX - removes xylanamine

\[
\begin{align*}
\text{BOC} & \quad \text{N} \quad \text{C} \quad \text{OMe} \\
1 \text{ equiv} \\
\text{Ph} & \quad \text{CHO} \\
1.5 \text{ equiv} \\
\rightarrow & \\
\text{BOC} & \quad \text{N} \quad \text{H} \quad \text{RR} \\
2) & \text{Anionic SPE} \\
3) & \text{Cationic SPE}
\end{align*}
\]

Anionic SPE:
1. Condition KOH(aq)/MeOH, MeOH, DCM
2. Apply sample: 1 mL, 0.2 mmole amine, 1 g SAX (0.7 mmole/g)
3. Rinse 1 mL THF, 2 mL DCM

Cationic SPE:
1. Condition SCX with DCM
2. Pass effluent from SAX-SPE through 1 g SCX (0.6 mmole/g)
3. Rinse with 2 mL DCM, collect
Solid Supported Liquid Extraction

- Solid supported liquid extraction* (SLE)
  - Extension of SPE concept
  - Useful for the removal of inorganic salts, amines and acids
  - Separations are essentially the same as liquid-liquid extractions in a separatory funnel
- Varian Hydromatrix cartridge format allows for parallel purification of products
  - Matrix is hydrophilic diatomaceous earth


Parallel Solid Supported Liquid Extraction (SLE)

Prep Cartridge
Load Rxn Mixture
Product Collection

Add aqueous acid or base (e.g., 2N HCl)
Add Reaction Mixture
Add Water

Aqueous buffer coats hydrophilic support and is immobilized on stationary phase

Add Reaction Mixture to Column and Gravity Elute Product with Water Immiscible Solvent
Compound Purification using Parallel Flash Chromatography

Medicinal Chemistry Bottleneck, Work Up and Purification!

- Accurate QSAR requires >95% pure compounds
- Work up/purification required after each step in the synthesis
- Efficient work up/purification methods required to keep up with synthesis
  - Parallel synthesis requires integration of parallel work up/purification techniques
**Flash Chromatography**

- Load Sample onto Column
- Isocratic or Gradient Elution
- MPLC Pump or 10 PSI Pressure
- Collect fractions using the Quad3 FLASH Collector

**Parallel Flash Chromatography Systems**

- **Biotage Quad3**
  - Purification of up to 12 compounds in parallel
  - Pre-packed columns for ease of use
  - Individual pump heads for solvent delivery
  - Collect fractions using the Quad3 FLASH Collector
Parallel Flash Chromatography Systems

- Isco CombiFlash System Si 1000s
  - Rapid purification of up to 10 compounds in parallel
  - Pre-packed columns for ease of use
  - Programmable solvent gradients for better resolution and faster separations
  - Collect up to 40 fractions/column using fraction collector

Evaluation of Isco Si1000s

- Separation conditions easily determined from TLC data
  - Solvent composition at gradient mid-point corresponds to optimum TLC conditions
- Solvent mixture chosen so compounds would separate with a Rf difference of ~0.15 unit
- Sample size for 10 g silica column ranged from 50-150 mg
- Application methods
  - Direct loading of mixture onto column
  - Quest transfer method
**Quest Transfer Method**

- Sandwich 3 g silica between two polypropylene frits in a 6 mL empty SPE cartridge
- Using SPE cartridge adapter attach SPE cartridge to lower luers of Q210
- Load 1 mL of mixture II in THF into Quest 210 RV
- Open lower manifold valves and transfer sample to cartridge using Metered Gas
- Rinse RV with 0.5 mL THF and transfer to SPE cartridge
- Dry SPE cartridge for 5 min using metered gas and 20 min of drain gas
- Remove cartridge and attach to Solid Loading Module of CombiFlash

---

**Comparison of Direct Liquid Loading and Quest Transfer Method**

<table>
<thead>
<tr>
<th>Run</th>
<th>Sample V (1 mL,THF solution)</th>
<th>Loading Method</th>
<th>Compound</th>
<th>Delta RF</th>
<th>Wt Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>75 mg</td>
<td>Liquid</td>
<td>1</td>
<td>0.21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:3 EtOAc, v/v</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>75 mg</td>
<td>Liquid</td>
<td>2</td>
<td>0.19</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:3 EtOAc, v/v</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>75 mg</td>
<td>Quest Transfer</td>
<td>1</td>
<td>0.21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(1:100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>75 mg</td>
<td>Quest Transfer</td>
<td>2</td>
<td>0.21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(1:100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>75 mg</td>
<td>Quest Transfer</td>
<td>3</td>
<td>0.21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(1:100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>75 mg</td>
<td>Quest Transfer</td>
<td>1</td>
<td>0.21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(1:100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Later elution of compound on the Quest transfer samples was due to added silica in SPE cartridges.*
Evaluation of Quest Transfer Method with Increasing Solution Volume

Mixture I:
1. Ethyl-4-bromobenzose (Rf = 0.86)  
2. Ethyl-4-dimethylaminobenzose (Rf = 0.74)  
3. Methyl-4-hydroxybenzoate (Rf = 0.87)

*All values obtained from SiliHexanes EtOAc 2:1

<table>
<thead>
<tr>
<th>Run</th>
<th>Sample Wt (mL solvent)</th>
<th>Transfer Method</th>
<th>Wt Load Method</th>
<th>Compound 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 mg (1 mL solvent)</td>
<td>Quest Transfer</td>
<td>3 g</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>100 mg (2 mL solvent)</td>
<td>Quest Transfer</td>
<td>3 g</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>150 mg (3 mL solvent)</td>
<td>Quest Transfer</td>
<td>3 g</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: * Some sample blow through was observed when turning on the drain gas for the 3 mL sample.

Maximum transfer volume is between 2-3 mls

Separation of Compounds with High Rf and low ∆Rf

Mixture III:
1. 4-Bromobiphenyl (Rf* = 0.63)  
2. Phenanthrene (Rf* = 0.74)

*Rf values obtained from SiliHexanes

<table>
<thead>
<tr>
<th>Run</th>
<th>Sample Wt</th>
<th>Loading Method</th>
<th>Compound 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>36 mg</td>
<td>Solid</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>110 mg</td>
<td>Liquid</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Condition: Flow rate = 12 mL/min  
Hexanes 100% Hexanes

Notes: * Some sample blow through was observed when turning on the drain gas for the 3 mL sample.
Results

- Sample size for 10 g columns range from 50 mg to 120 mg
- Si1000s can resolve components with an Rf difference of 0.15
- Samples were successfully transferred to the Si1000s using the SPE cartridges filled with silica
  - Yielded similar data as direct liquid loading onto Si1000s
  - Additional silica in SPE cartridge caused compounds to elute slightly later
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