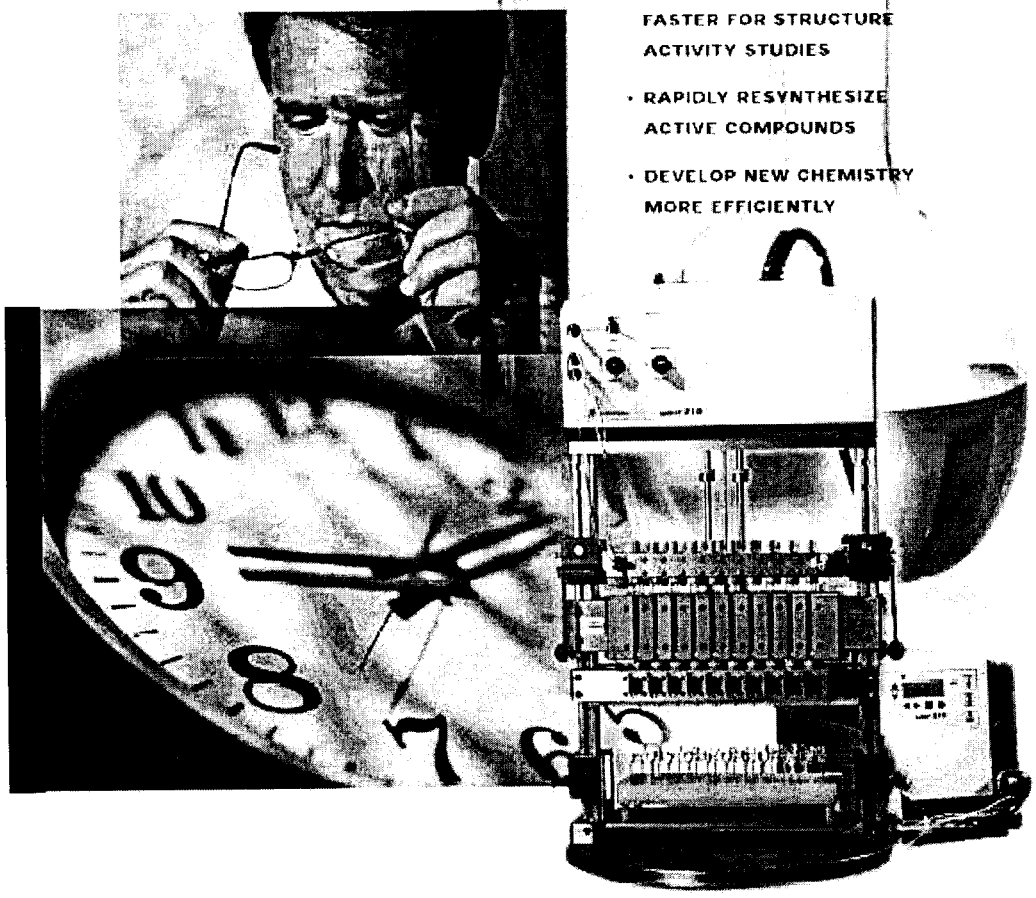
Quest Training Workshop

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



ARGONAUT
TECHNOLOGIES

Welcome

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 Analoging
- 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 bee-manifold
3) Uneven addn of solvent probably need to replace restrictor tubes
4) Always close upper manifold when heating

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Quest Training Workshop

Table of Contents

Quest Training Workshop
Agenda

Day 1

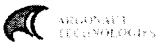
9:00 – 9:30	Welcome & Introductions
9:30 – 10:15	Quest Overview & Operation Training
10:15 – 10:30	Break
10:30 – 12:00	Hands-on Synthesis: Ketone Preparation Add PS-TsNHNH2 resin, prepare bromobenzamide solutions in THF, add via syringe, attach chiller to Quest, addition of Grignard via syringe and agitate 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

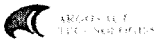
9:00 – 9:15	Overview of the Day's activities
9:15 – 10:15	Hands-on Synthesis: Cyclization & Cleavage Automated washing with THF, hexane and DCM, preparation of SOCl2 in DCM, addition of SOCl2 via syringe and agitate for 4 hrs at 50 C
10:15 – 10:30	Break
10:30 – 12:00	Presentation/Lecture Parallel Methods 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

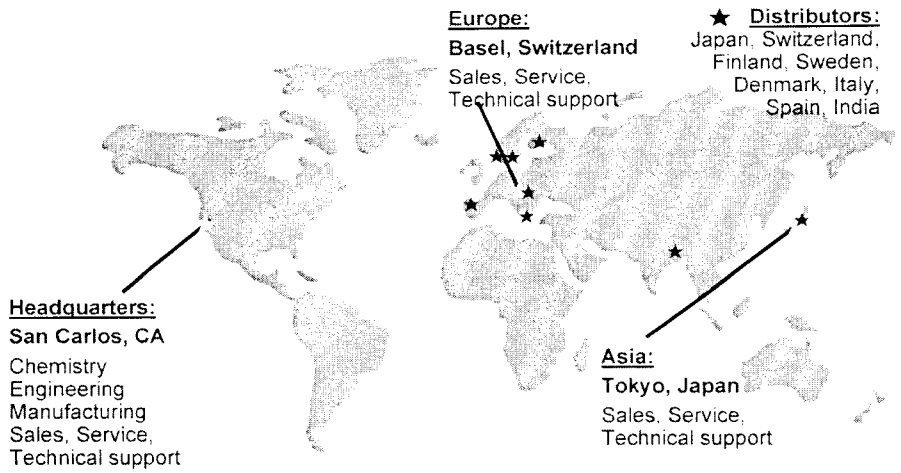


Agenda

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



Argonaut Technologies Worldwide Operations



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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

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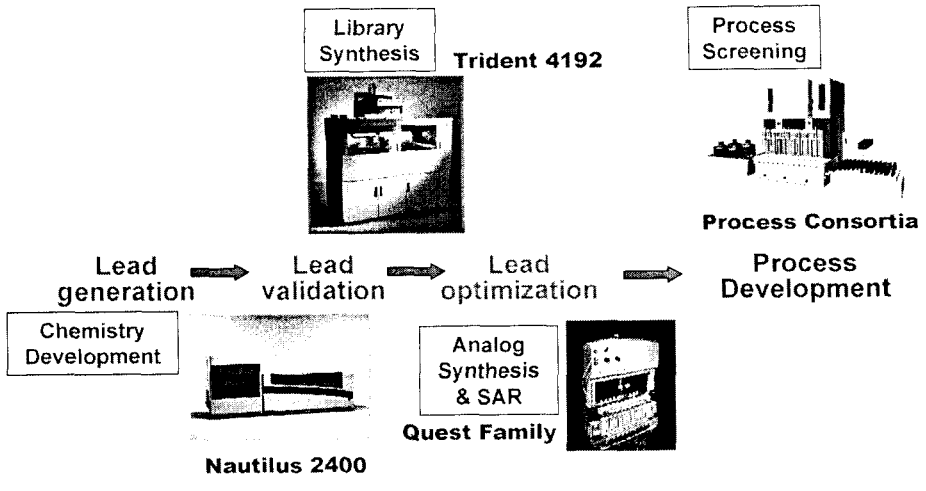
Innovative Products to Enhance Discovery Chemistry

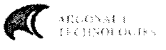


About You

- *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?*

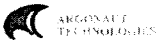
What will you learn from the program?

- *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*

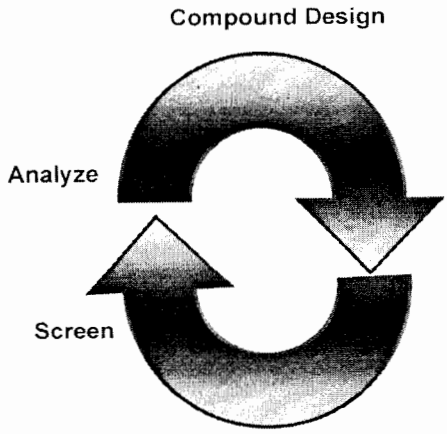


When you return to your lab you should be…

- *….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*

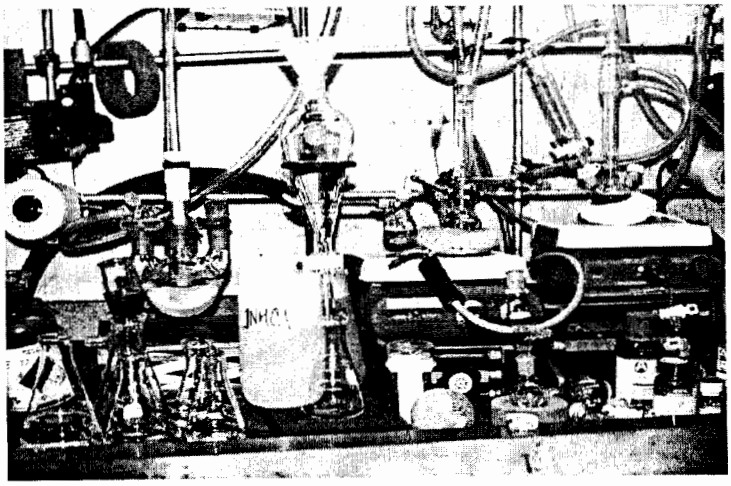


Traditional Medicinal Chemistry

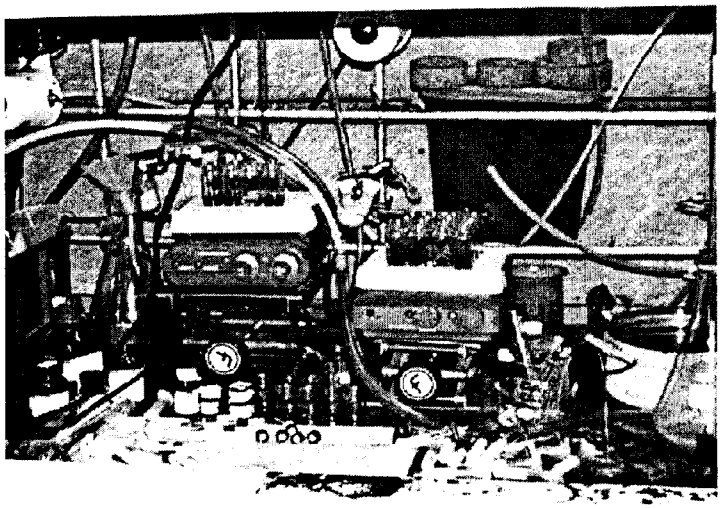


Synthesis
- Synthetic pathway development
- Target compound synthesis
- Analoging
- Work-up
- Purification

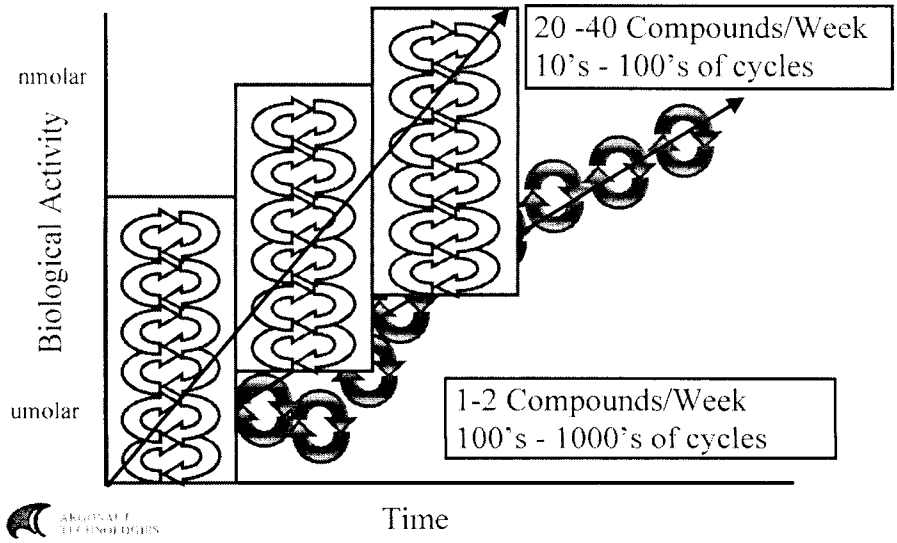
Traditional Tools in Medicinal Chemistry



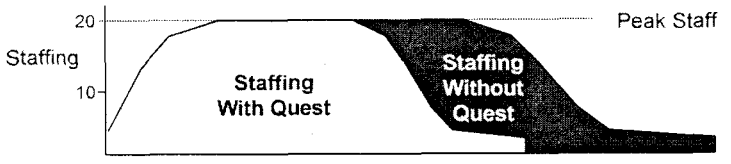
Traditional Tools in Medicinal Chemistry



Shortening SAR Cycle Time

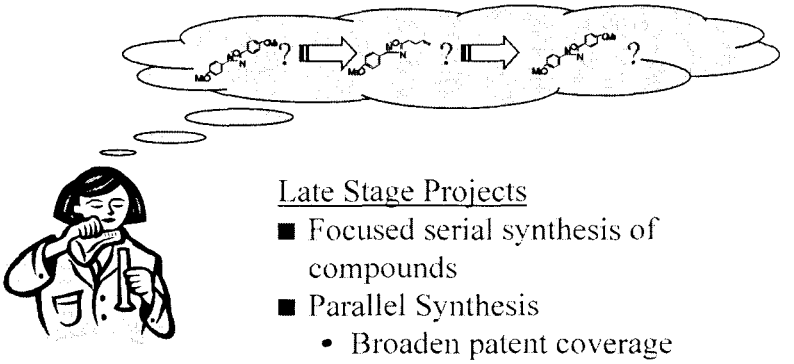


Decreased Time, More Projects



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

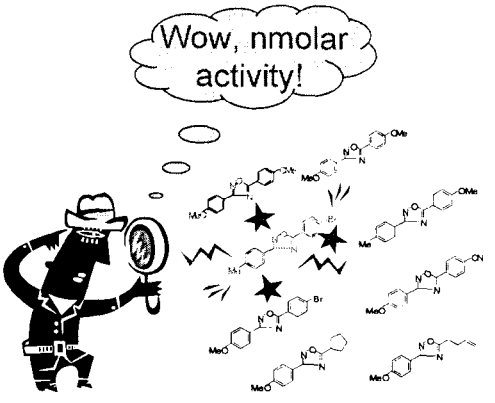
Applying Parallel Synthesis From Lead Discovery and Optimization through Process Development



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"

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Our Vision...

To empower you to shorten the time from mmolar to nmolar by 50%

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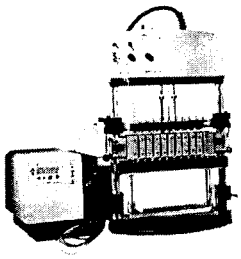
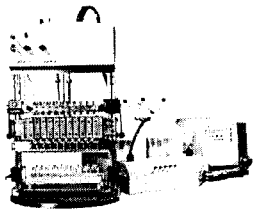
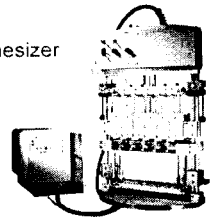
Quest Family of Organic Synthesizers



Quest 210 SLN
Multi-Step Solution Phase Synthesizer

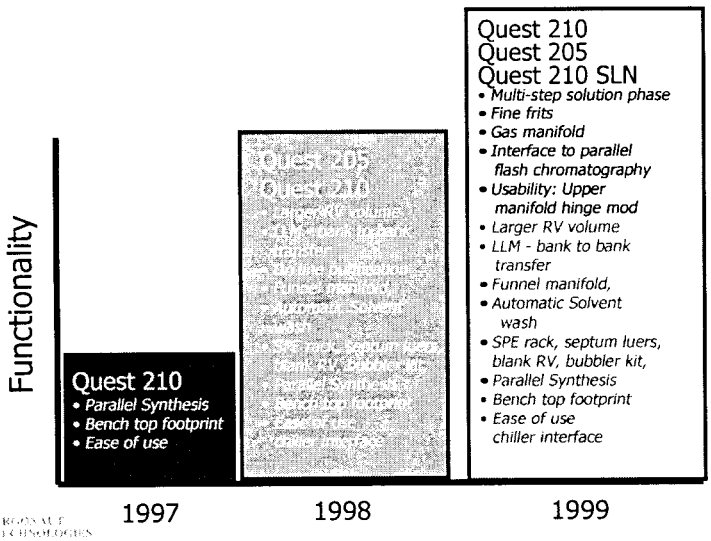


Quest 210 ASW
Easy to Use Solid Phase Synthesizer

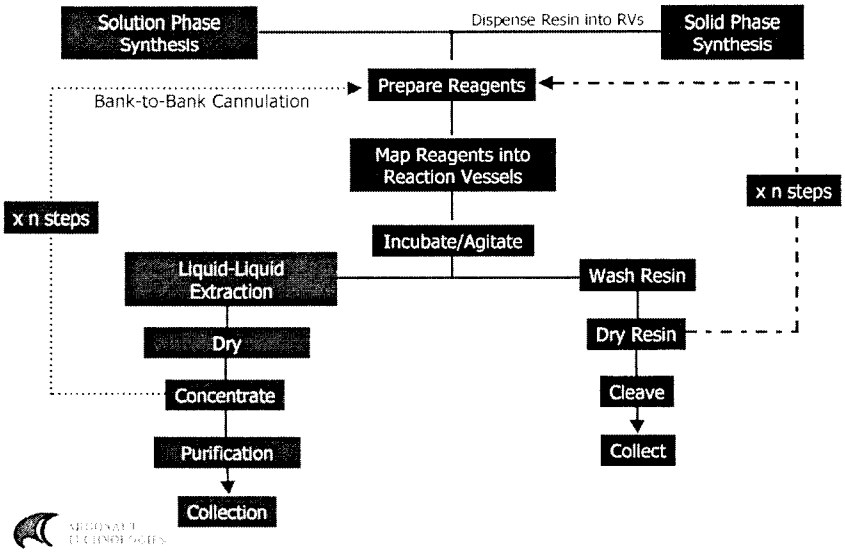


Quest 205
Flexible Large Scale Synthesizer

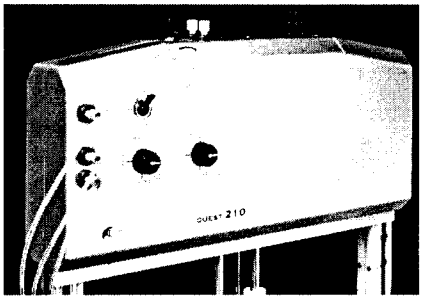
Quest Synthesizer Product History



Solution and Solid Phase Synthesis on the Q210 SLN and Q210 ASW

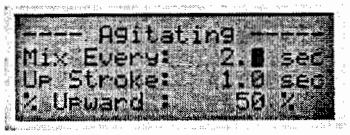


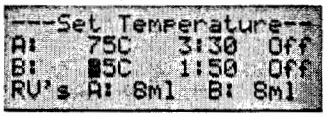
Parallel Solvent and Gas Delivery



- *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*

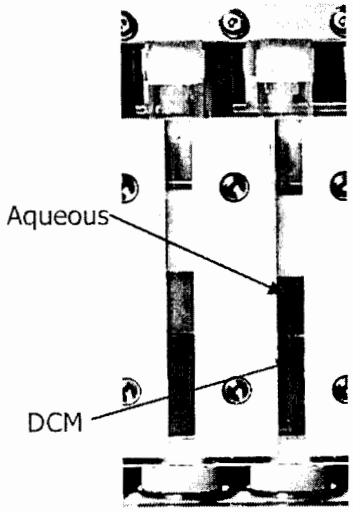
Easy Programming Minimizes Your Learning Curve





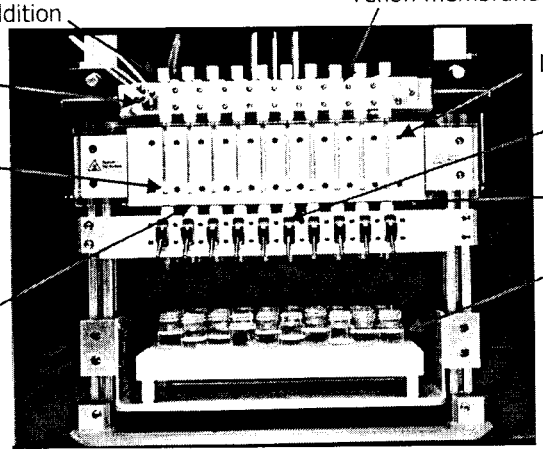
- *Menu driven software for ease of use*
- *Control of agitation frequency and profile*
- *Independent control of reaction bank temperature and heating duration*
- *Temperature program starts once programmed temperature is achieved*

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*

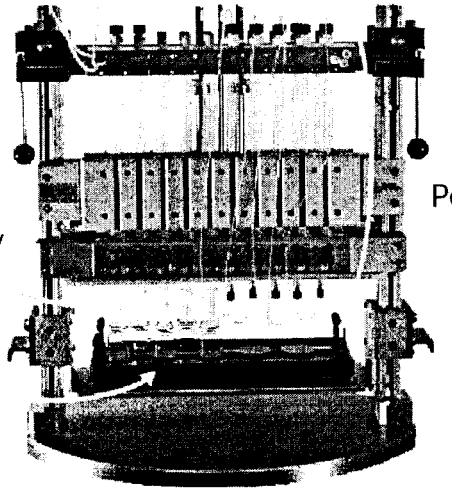
Quest 210 SLN Synthesis Platform



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

Media	Surface chemistry	Mass	Synthesis Application	Product Name	Vendor	Part. No.
Silica	SiO_2	900 mg	Baseline impurity removal	Maxi-Clean	Alltech	20992
Silica	SiO_2	1 g	"	Bond Elut Jr.	Varian	12166008
Florisil	Mg_2SiO_3	900 mg	In-line purification oxadiazoles	Maxi-Clean	Alltech	210059
Alumina-Neutral	Al_2O_3	1800 mg	Baseline impurity removal	Maxi-Clean	Alltech	210098
Alumina-Basic	Al_2O_3	1 g	Separation/Freebasing of acidic cpds.	Bond Elut Jr.	Varian	12166044
SCX	$-ArSO_3H$	1 g (0.8 mmol)	Synthesis of Amino-Biaryls	Bond Elut Jr.	Varian	12166011
SCX	$-ArSO_3H$	500 mg	"Catch and Release"of amines	Whatman SCX	Whatman	6804-2605
C18	octadecyl	900 mg	"	Maxi-Clean	Alltech	20944
Aminopropyl	$-NH_2$	1 g	Removal of electrophiles	Bond Elut Jr.	Varian	12166012
Carboxylic acid	-COOH	x	Removal of amine/bases	MiniSpeed Plus	Applied Sep.	24020
Diethylamino	Diethyl amine	x	Removal of acidic cpds.	MiniSpeed Plus	Applied Sep.	24024

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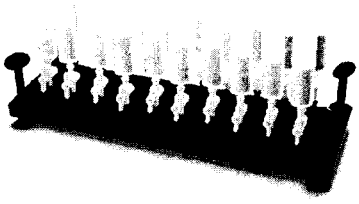
... And Off-Line Purification for Flexibility



- *Purify more compounds faster with parallel purification*
- *Purification solutions*
  - *Silica*
  - *Florisil*
  - *Alumina (neutral, basic and acidic)*
  - *SCX*
  - *C18*
  - *Aminopropyl*
  - *Carboxylic acid*
  - *Diethylamino*

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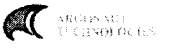
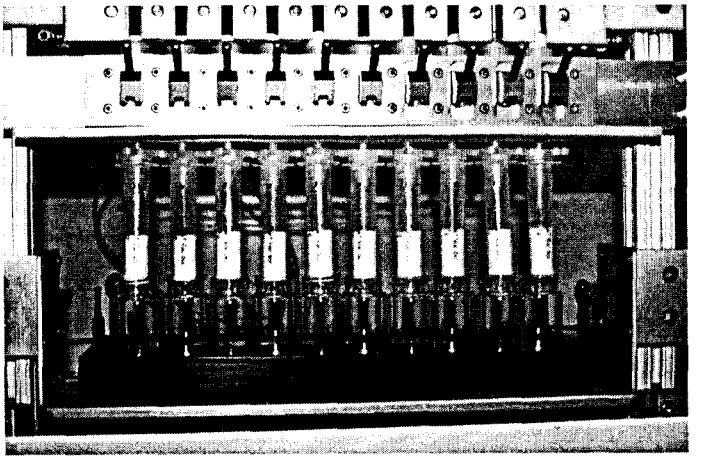
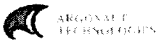
Menu of SPE Columns for the Quest 210/SLN

Media	Surface chemistry	Mass	Synthesis Application	Product Name	Vendor	Part. No.
Silica	SiO_2	2 g	Baseline impurity removal	Isolute Si	Jones Chromat.	460-0200-C
Silica	SiO_2	2 g	ADD oxidation (in-line purification)	Extract Clean	Alltech	209202
Florisil	Mg_2SiO_3	2 g	Baseline impurity removal; polar solvent retention	Spe-ed Cart.	Applied Sep.	2118
Alumina-N	Al_2O_3	2 g	Baseline impurity removal	Isolute AL-N	Jones Chromat.	714-0200-C
Alumina-B	Al_2O_3	2 g	Freebasing; extraction of acidic cpds.	Spe-ed Cart.	Applied Sep.	2148
Alumina-B	Al_2O_3	1 g	"	MegaBond Elut	Varian	12256044
C18	octadecyl	2 g	Adsorption non-polar compounds	Spe-ed Cart.	Applied Sep.	2008
C18	octadecyl	2 g	"	Isolute C18	Jones Chromat.	220-0200-C
SCX	$-ArSO_3H$	1 g	"Catch and Release"of amines	MegaBond Elut	Varian	12256011
SCX	$-ArSO_3H$	2 g	"	Spe-ed Cart.	Applied Sep.	2328
Carboxylic acid	COOH	2 g	Removal of amine/bases	Spe-ed Cart.	Applied Sep.	2318
Aminopropyl	NH_2	2 g	Removal of electrophiles	Spe-ed Cart.	Applied Sep.	2218
Diethylamino	$-NEt_2$	2 g	Removal of acidic cpds.	Spe-ed Cart.	Applied Sep.	2338



Attachment of SPE columns





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

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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*

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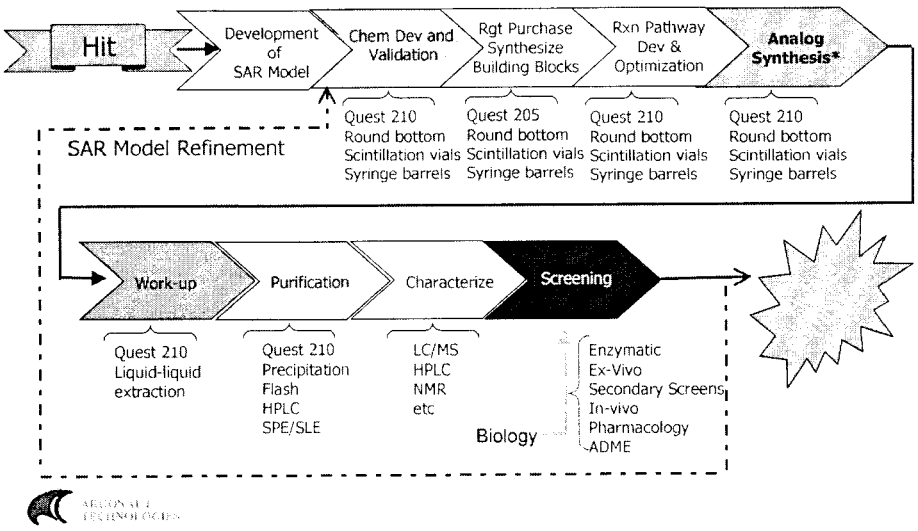
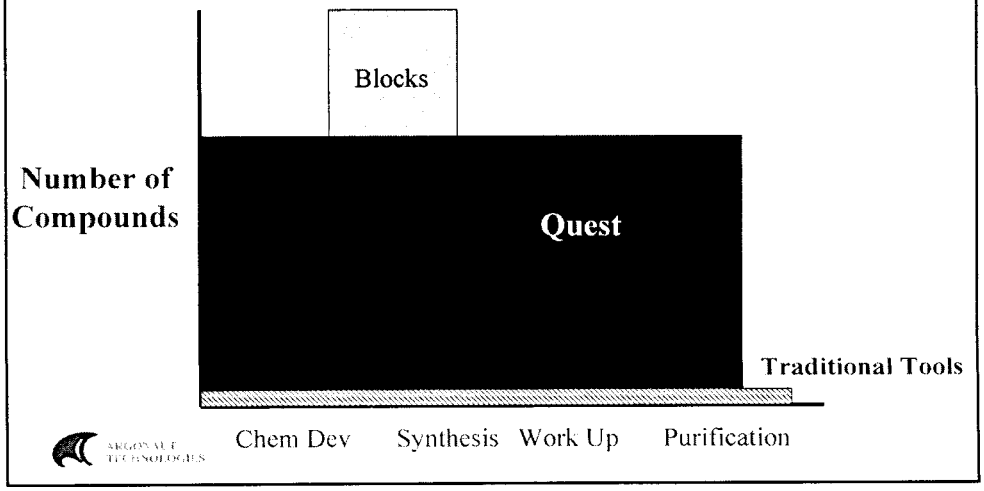
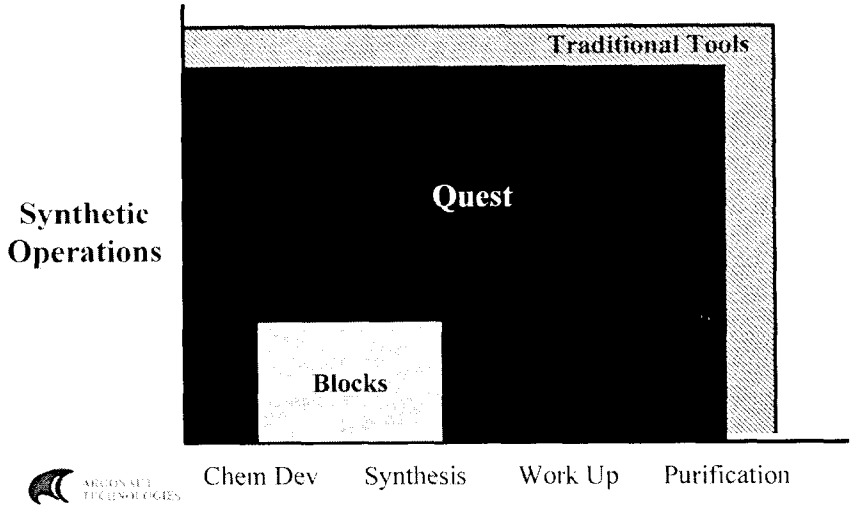
Application of Quest Synthesizers in Lead Optimization



Multidimensional Organic Synthesizer



Perform 90% of All Synthetic Operations



Medicinal Chem Operations

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

- *Quest*
  - *Heat - 130C*
    - *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*

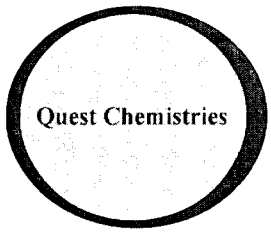
90% of all Medicinal Chemistries & Work up

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

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

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

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



Medicinal Chemistries

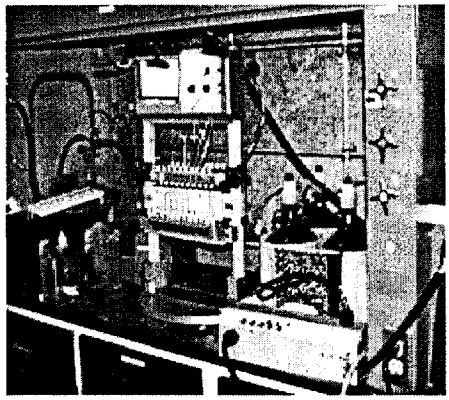
90% of all Medicinal Chemistries & Work up

Elimination
- *Shapiro*
- *Hoffman*
- *Dehydrohalagenation*

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

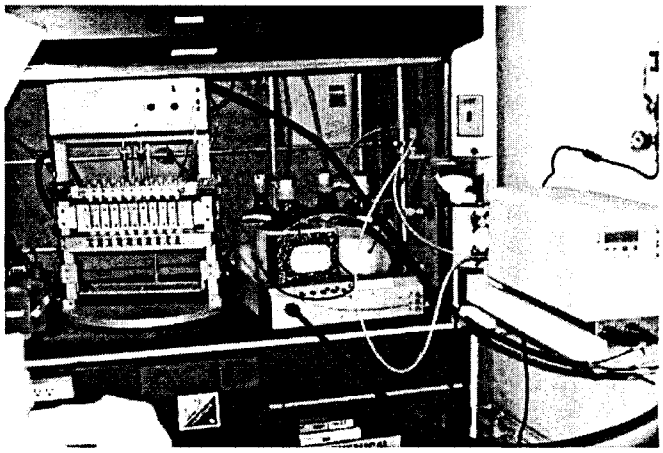
Heterocycle Formation
- *Thiazoles*
- *Oxadiazoles*
- *Benzimidazoles*
- *Fisher Indole Synthesis*
- *Quinoxalines*
- *Hydantoins*
- *Ugi*
- *Pictet-Spengler*

Set Up and Install



ARGONAUT TECHNOLOGIES

Set up and Install

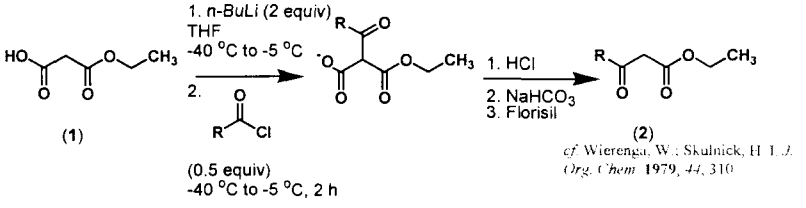


ARGONAUT TECHNOLOGIES

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*

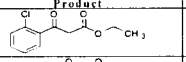
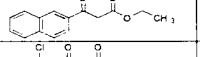
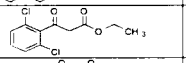
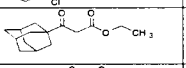
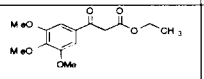
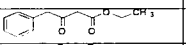
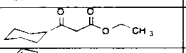
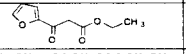
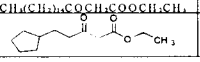
Parallel synthesis of β-Ketoester analogs n-Butyllithium followed by on-line post synthesis work-up



cf. Wierenga, W.; Skulnick, H. I. *J. Org. Chem.* **1979**, *44*, 310

- *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_20 on-line*

Characterization of β-Ketoester Products

Reaction Vessel	Acyl Chloride	β-Ketoester Product	Recovery (%)	GC % Purity
RV 01			89%	82%
RV 02			85%	100%
RV 03			80%	84%
RV 04			67%	31%
RV 05			94%	93%
RV 06			83%	94%
RV 07			79%	89%
RV 08			86%	100%
RV 09	$CH_3(CH_2)_{16}COCl$	$CH_3(CH_2)_{16}COCH_2COOCH_2CH_3$	76%	80%
RV 10			85%	88%

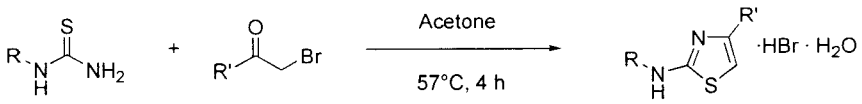
ARGONAUT TECHNOLOGIES

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*

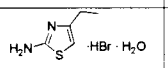
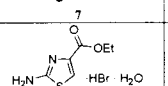
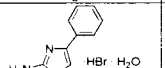
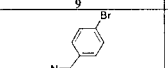
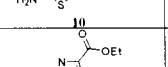
ARGONAUT TECHNOLOGIES

Preparation of Starting Materials on the Quest 205

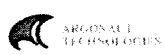


- *Reactions were performed on the Quest 205 using fine frit reaction vessels to prepare gram quantities of 2-aminothiazole hydrobromide monohydrates as bulk starting materials.*
- cf. *Joshua, C.P.; Nambisan, P.N.K.* Indian J. Chem. ***1973***, 11, *118.*

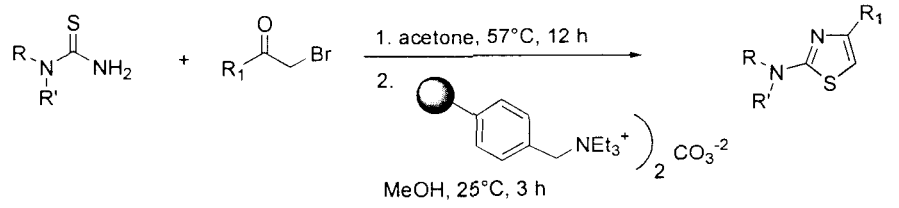
Results of Aminothiazole synthesis

Entry	Thioureas	α-Bromoketones	Products	Amount Prepared	Yield*
1	 1	 3	 7	0.91 g	70%
2	 1	 4	 8	1.34 g	86%
3	 1	 5	 9	1.24 g	78%
4	 1	 6	 10	1.98 g	97%
5	 2	 4	 11	0.50 g	32%

[1]Based on NMR, purity of the products is over 95%.



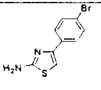
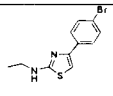
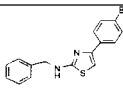
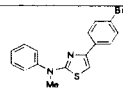
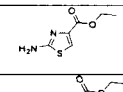
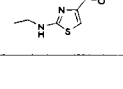
Multistep Synthesis of Free-based Aminothiazoles



- *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.*

ARGONAUT TECHNOLOGIES

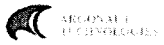
Results of Multistep Aminothiazole Synthesis

Entry	Thioureas	α-Bromoketones	Products	Yield	HPLC Purity
1				81%	100%
2				100%	100%
3				68%	100%
4				63%	100%
5				87%	95%
6				31%	91%

ARGONAUT TECHNOLOGIES

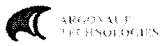
New Products

- *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*

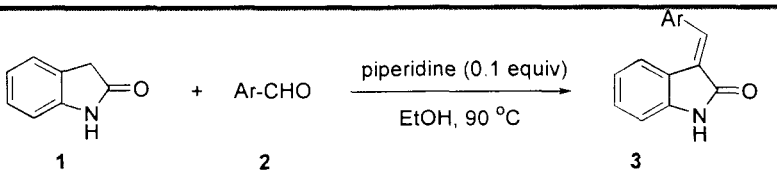


Parallel Product Precipitation on the Quest 210/205

- *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.*

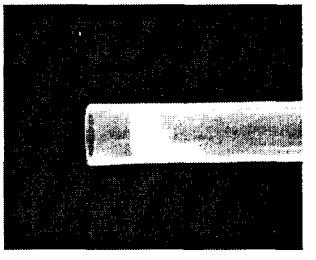


Parallel Precipitation of 3-Substituted Indolin-2-ones on the Quest 210:



1 **2** **3**

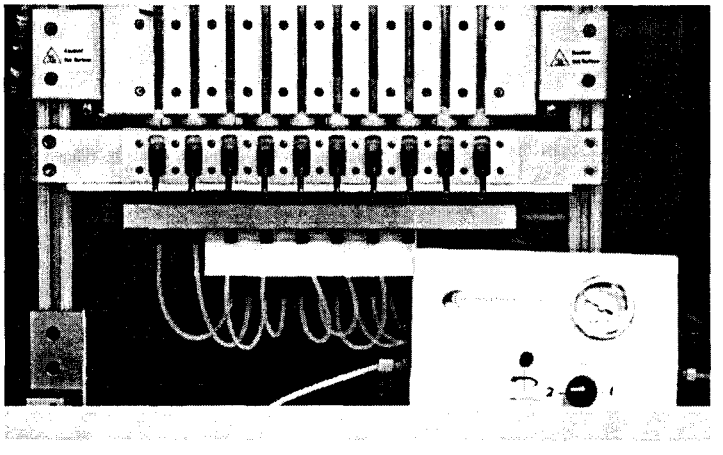
Aldehyde	Yield (Solid) (%)	Yield (Dissolution) (%)	HPLC Purity
benzaldehyde	31	32	100
2,5-dimethoxybenzaldehyde	67	74	100
Piperonal	70	86	100
o-anisaldehyde	85	90	100
4-bromobenzaldehyde	42	-	100



Utilizes new "μfrit" reaction vessel

Indolin-2-ones: J. Med. Chem. **1998**, 41, 2588.

Gas Manifold Accesory

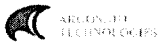


- *Addition of gaseous reagents through lower manifold thru luer ports*

Preliminary Results on Use of Gas Manifold Accesory for Hydrogenation

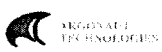
Compound	Hydrogenation time (15 psi)	% Hydrogenated after 6 h (5 psi)	Solvent
4-phenyl-1-butene	2.5 h	100	MeOH
CBz-Trp-OH	<1 h	100	MeOH
CBz-Phe-Osu	<1 h	100	EtOAc
m-Nitro xylene	6.5 h (>90%, 4.5 h)	99.5	EtOAc
Trans-5-decene	4.5 h	100	EtOAc
Benzyl benzoate	6.5 h (>90%, 4.5 h)	>97	MeOH
4-nitrobenzyl alcohol	-	100	EtOAc
4-nitrobenzaldehyde	-	84	EtOAc
4-nitrobenzoic acid	-	100	EtOAc
5-Benzyloxy-1-pentanol	6.5 h (>80%, 4.5 h)	99	MeOH

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

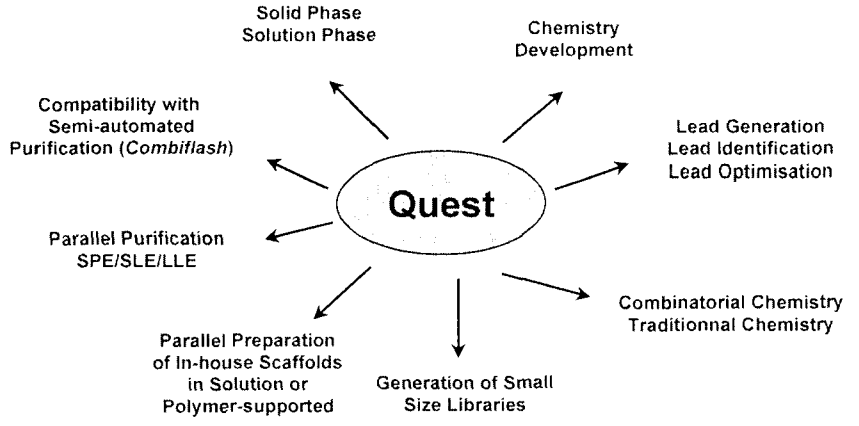


Demonstrated Performance

- *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

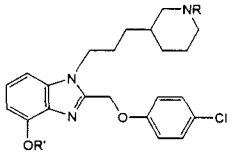


Parallel Multi-step Synthesis of Substituted Benzimidazoles via Hydrogenation of Aromatic Nitro Compounds on the Quest 210 Organic Synthesizer

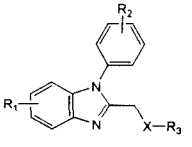
Young K. Yun, John A. Porco, Jr.,
Jeff Labadie

Argonaut Technologies
San Carlos, California
www.argotech.com

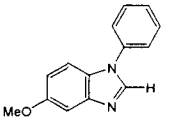
Pharmacologically Active Benzimidazoles



Neuropeptide YY1 Receptor Antagonists
Bioorg. Med. Chem. Lett. **1999**, 647

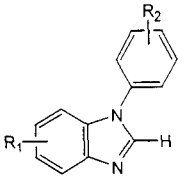


Antiarrhythmatic agents
J. Med. Chem. **1992**, 35, 705



ATP-site Inhibitor of platelet-derived growth factor
J. Med. Chem. **1998**, 41, 5457

Objectives



1-Phenylbenzimidazoles
ATP-site inhibitor of PDGF
J. Med. Chem. **1998**, 41, 5457

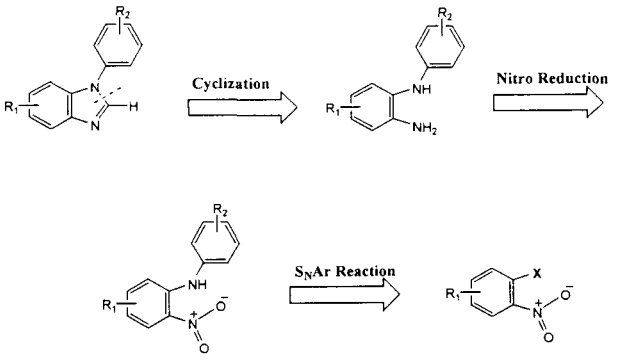
- **Apply the Quest 210 in a Linear synthesis of a target molecule including Reaction Development**
- **Rapid synthesis of target molecule analogs**
- **Demonstration of Parallel Hydrogenation**

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

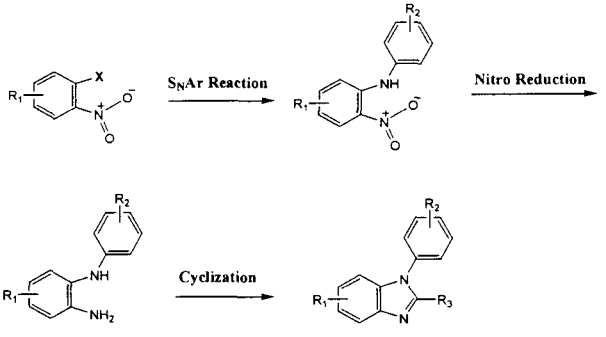
Strategies for Parallel Multi-step Synthesis

- 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_NAr Reaction : Determine Base, Solvent, and Rxn. Temp.

Nitro Reduction : *Validate use of 2-methoxyethanol*

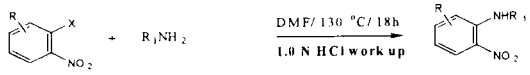
Questions ?

- 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 ?

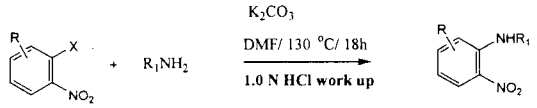
- Nitro Reduction
  - Parallel Nitro Reduction?
  - Possibility of Bank to Bank Transfer
  - Common Solvent for both Nitro reduction and Cyclization
- Formation of Benzimidazoles
  - Utilization of imidate or amidine
  - Any other routes for cyclization

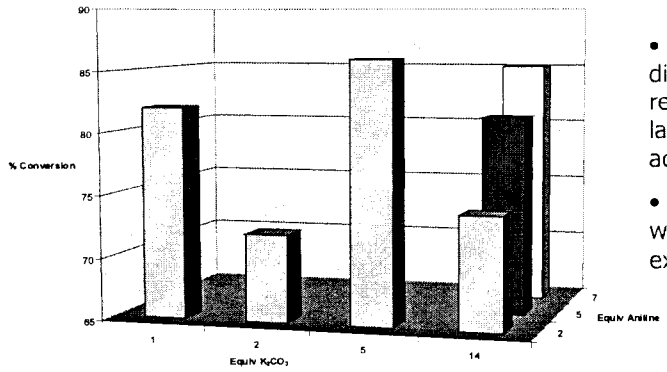
Stoichiometry Screening with K_2CO_3



RV #	Base/ Eqiv.	Aniline/ Eqiv.	Solvent
1	K_2CO_3 / 2.0 eqiv.	 / 2.0 eqiv.	DMF
2	K_2CO_3 / 5.0 eqiv.	 / 2.0 eqiv.	DMF
3	K_2CO_3 / 1.0 eqiv.	 / 2.0 eqiv.	DMF
4	K_2CO_3 / 14.0 eqiv.	 / 2.0 eqiv.	DMF
5	K_2CO_3 / 14.0 eqiv.	 / 7.0 eqiv.	DMF
6	K_2CO_3 / 14.0 eqiv.	 / 5.0 eqiv.	DMF

S_NAr Reaction Optimization



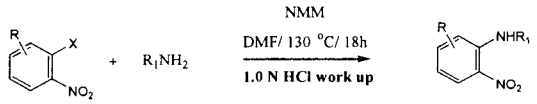


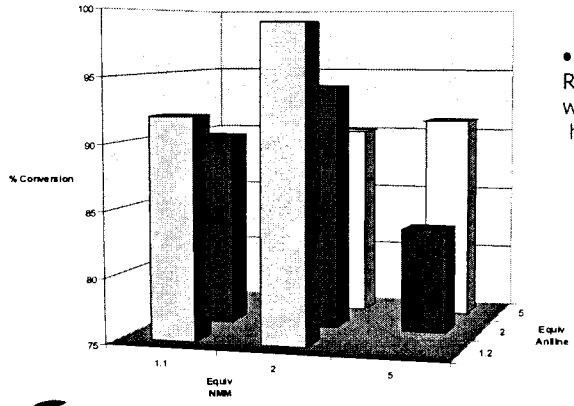
- S_NAr products, diphenylamines remained in organic layer in the aquesous acid workup.
- Aqueous acid workup removed excess anilines.

Base Screening with NMM

RV #	Base/ Eqiv.	Aniline/ Eqiv.	Solvent
1	NMM/ 2.0 eqiv.	 / 1.2 eqiv.	DMF
2	NMM/ 1.1 eqiv.	 / 2.0 eqiv.	DMF
3	NMM/ 1.1 eqiv.	 / 1.2 equiv.	DMF
4	NMM/ 2.0 eqiv.	 / 2.0 equiv.	DMF
5	NMM/ 5.0 eqiv.	 / 5.0 equiv.	DMF
6	NMM/ 2.0 eqiv.	 / 5.0 equiv	DMF
7	NMM/ 5.0 eqiv.	 / 2.0 equiv.	DMF

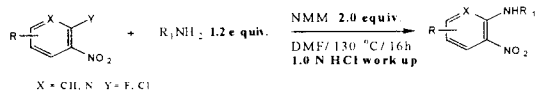
S_NAr Reaction Optimization





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

Screening Substrates



	XArNO2	RArNH2	Yield	Purity
1		R= H, iPr, OMe	> 60 %	> 90%
2		R= H, iPr, OMe	> 60%	> 95%
3		R= H, iPr, OMe	> 90%	> 99%
4		R= H, iPr, OMe	> 85%	> 99%
5		R= H, iPr, OMe	No Reaction	
6		R= H, iPr, OMe	No Reaction	
7		R= H, iPr, OMe	No Reaction	

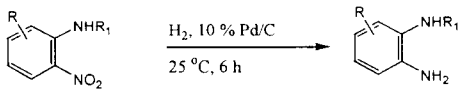
- **Used optimized condition to screen a series of halo-nitrobenzenes**
- **Only chloro-nitropyridine yielded S_NAr product among chloro-nitroaromatic compounds.**

Preliminary Results on Parallel Hydrogenation

Compound	Hydrogenation time (15 psi)	% Hydrogenated after 6 h (5 psi)	Solvent
4-phenyl-1-butene	2.5 h	100	MeOH
CBz-Trp-OH	<1 h	100	MeOH
CBz-Phe-Osu	<1 h	100	EtOAc
m-Nitro xylene	6.5 h (>90% , 4.5 h)	99.5	EtOAc
Trans-5-decene	4.5 h	100	EtOAc
Benzyl benzoate	6.5 h (>90% , 4.5 h)	>97	MeOH
4-nitrobenzyl alcohol	-	100	EtOAc
4-nitrobenzaldehyde	-	84	EtOAc
4-nitrobenzoic acid	-	100	EtOAc
5-Benzyloxy-1-pentanol	6.5 h (>80% , 4.5 h)	99	MeOH

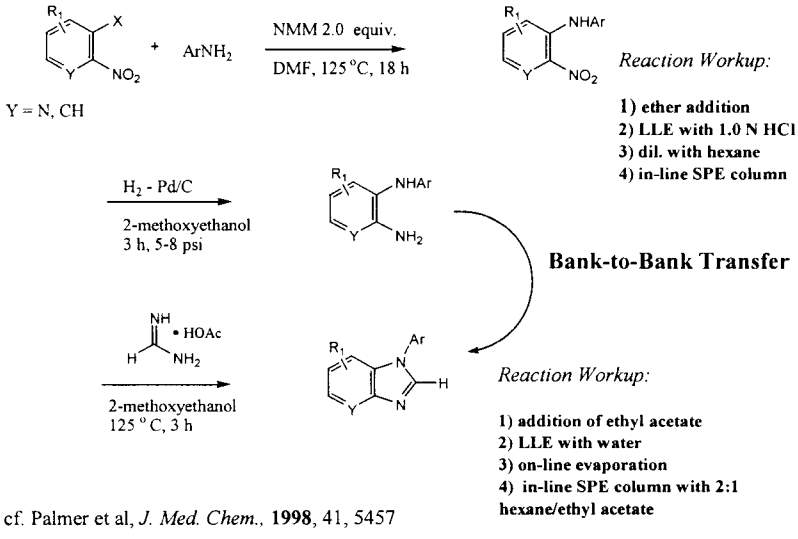
- **Preliminary results indicate that pressures of 5-15 psi are obtainable.**
- **5 psi utilized in 1-Phenylbenzimidazole synthesis**

Parallel Hydrogenation



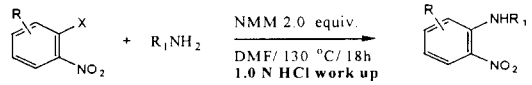
	Catalyst	Solvent	Reaction Time	Results	Remarks
	Pd/C 5 %	MeOH/ EtOAc	3h	100 % Conversion	**Lit. Condition**
	Pd/C 10 %	Methoxyethanol	6h	100% Conversion	**Rxn. Condition adapted from Lit. to offer Bank to Bank Transfer**

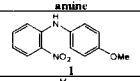
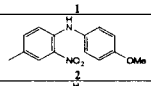
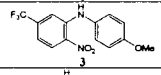
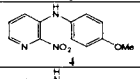
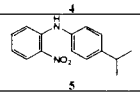
Multistep synthesis of benzimidazoles on the Quest 210

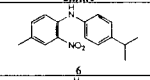
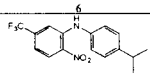
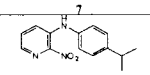
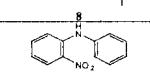
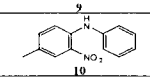


cf. Palmer et al, *J. Med. Chem.*, **1998**, 41, 5457

Results of S_NAr reactions

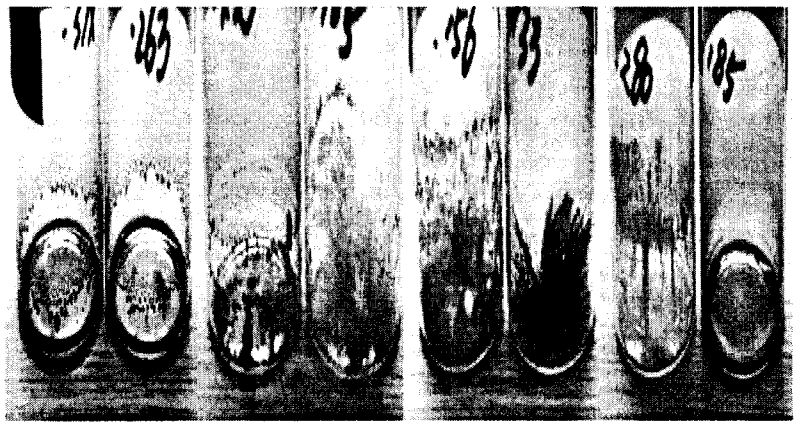


Entry	2-Nitrodiphenyl amine	% Yield (isolated)	GC Purity[1]
1	 1	65%	99%
2	 2	63%	97%
3	 3	98%	100%
4	 4	91%	100%
5	 5	61%	86%

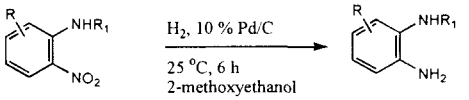
Entry	2-Nitrodiphenyl amine	% Yield (isolated)	GC Purity[1]
6	 6	53%	99%
7	 7	89%	99%
8	 8	84%	99%
9	 9	47%	96%
10	 10	44%	85%

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

O-NitrodiphenylAmines



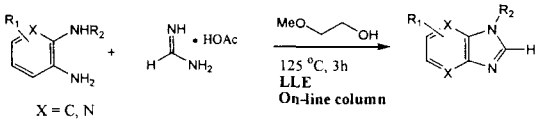
Parallel hydrogenation of nitro anilines



Entry	2-Aminodiphenyl amine	%Yield (isolated)	GC purity
1	13	90%	94%
2	14	100%	98%
3	15	100%	100%
4	16	100%	89%
5	17	91%	93%

Entry	2-Aminodiphenyl amine	%Yield (isolated)	GC purity
6	18	94%	89%
7	19	94%	95%
8	20	96%	92%
9	21	92%	95%
10	22	88%	95%

Parallel Synthesis of 1-Phenyl benzimidazoles



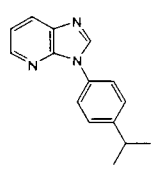
X = C, N

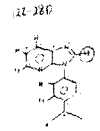
Entry	Benzimidazole	% Yield (isolated)	GC purity
1		82%	97%
2		61%	98%
3		92%	97%
4		63%	98%
5		83%	94%

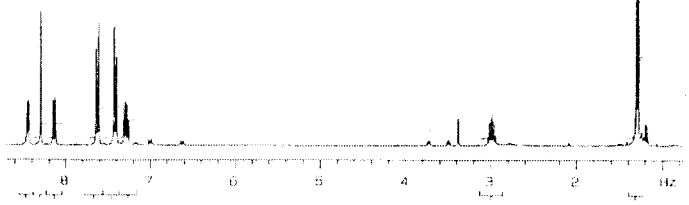
Entry	Benzimidazole	% Yield (isolated)	GC purity
6		73%	94%
7		97%	98%
8		72%	98%
9		67%	92%
10		75%	96%

LLE with EtOAc/water, followed by on-line evaporation

1-(4-Isopropylphenyl)-1H-imidazo[5,4-b]pyridine







Summary

- Benzimidazole derivatives were synthesized in three steps on the Quest 210 using 1) S_NAr Reaction of substituted anilines to o-halo-nitrobenzenes 2) parallel hydrogenation to form aminodiphenyl amines and 3) cyclization of diamines with formimidine acetate.
- Utilization of the Gas Rxn. And Concentration Manifold Accessory permitted the parallel hydrogenation of nitro diphenylamines.
- The Quest 210 synthesizer allows paralle solution phase organic reaction, LLE, on-line concentration, gas reagent addition, and SPE purification to be performed on a common platform.

Quick Answers

ARGONAUT TECHNOLOGIES

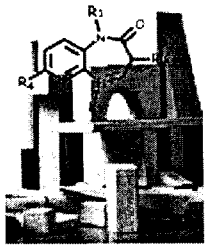
About Argonaut

What's New

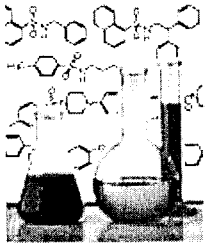
Resources

Our Solutions ...

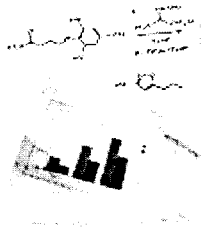
Argonaut's innovative technology enables synthetic organic chemists to benefit from the speed and efficiency of parallel synthesis



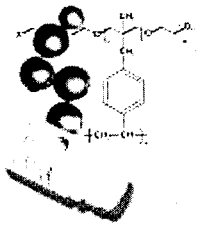
Automated Library Synthesis



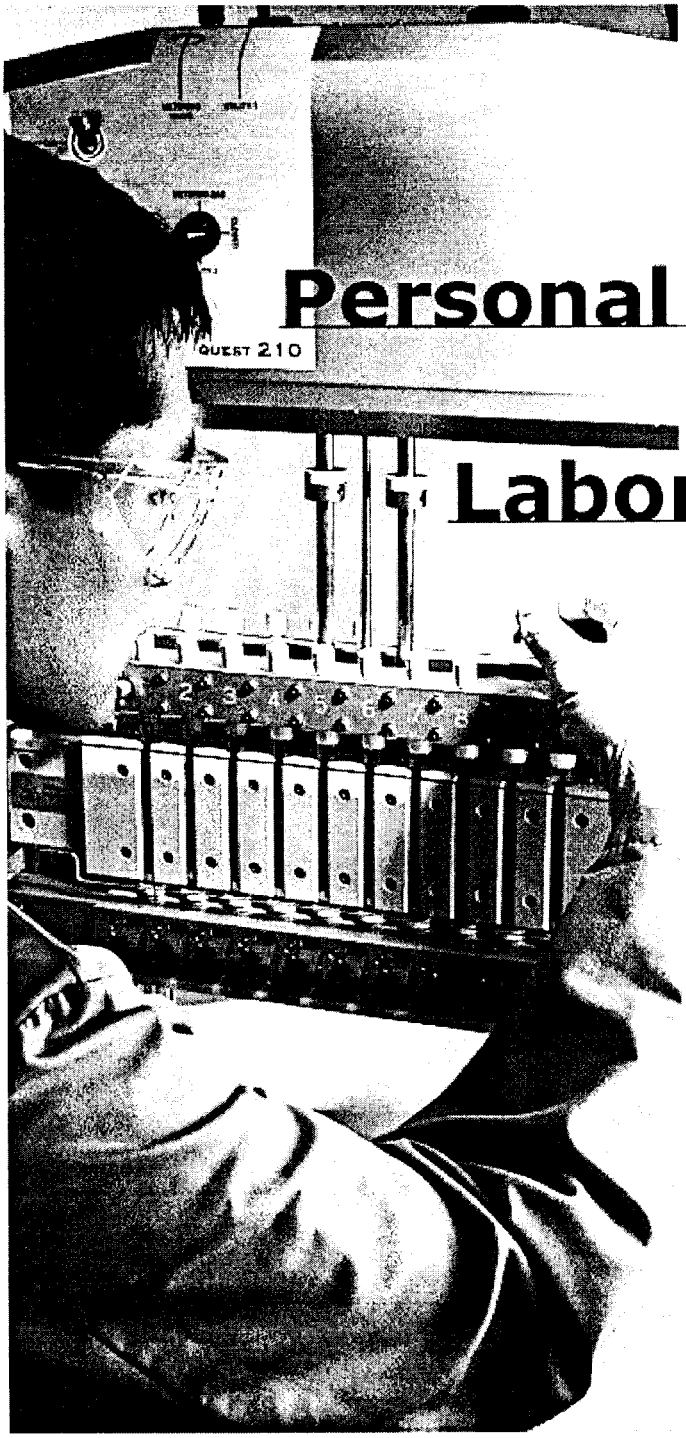
Parallel Organic Synthesis



Chemical Development & Optimization



Resins & Reagents for Parallel Chemistry



Quest™

Personal Productivity *in the* Laboratory

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.

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**

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

ARGONAUT TECHNOLOGIES

Scientific Resources

About Argonaut

What's New

Resources

- Scientific Resources
- Request Information
- Product Part Numbers
- Material Safety Data Sheets

Our Solutions ...

- Automated Library Synthesis
- Parallel Organic Synthesis
- Chemistry Development & Optimization
- Resins & Reagents for Parallel Chemistry

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).

Application Notes

Gel Phase ^{13}C NMR Spectra Using ArgoGel Resin
(78 K, 5 pages)

Automated Solid-Phase Synthesis of Quinazoline-2,4-Diones
(156 K, 5 pages)

Automated Mitsunobu Chemistry I: Performance Validation of the Nautilus 2400
(137 K, 9 pages)

Automated Pictet-Spengler Reaction on Solid Support:

ARGONAUT TECHNOLOGIES

Quest Tips

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Our Solutions ...

- Automated Library Synthesis
- Parallel Organic Synthesis
- Chemistry Development & Optimization
- Resins & Reagents for Parallel Chemistry

These **Quest Operational Tips** are designed to assist users with common instrument operations and synthesis procedures.

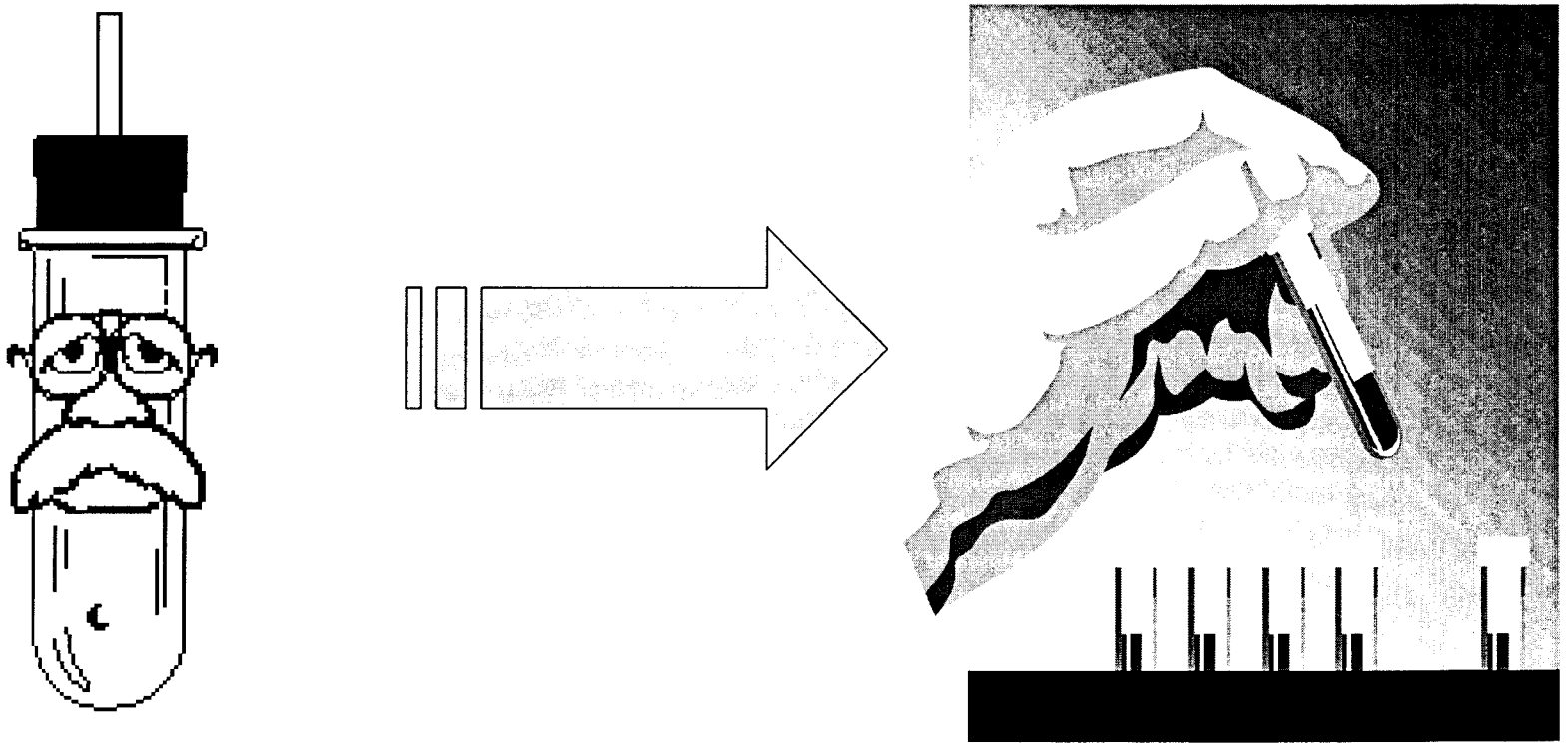
If you would like to contribute a Quest Operational Tip, please contact Dave Yamane.

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

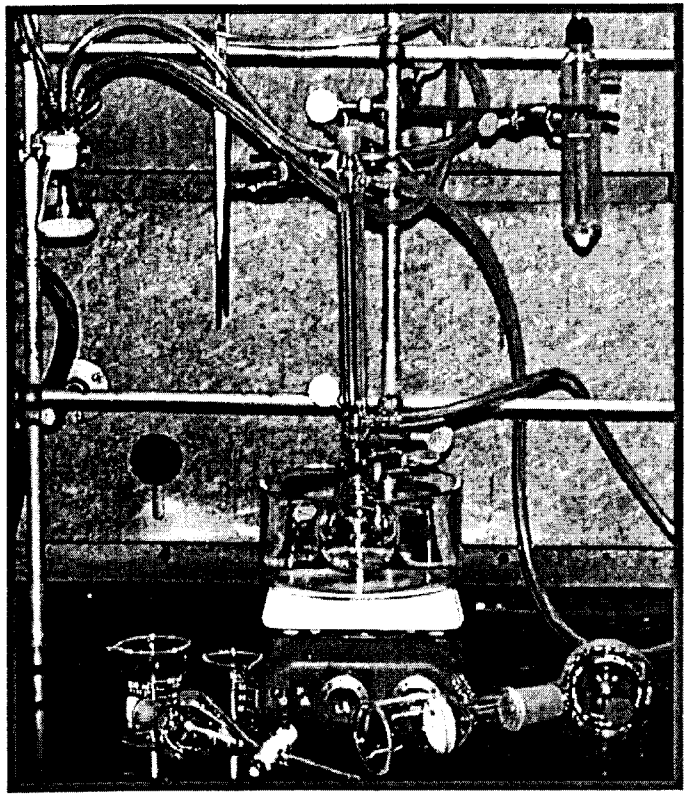
Entering A New Paradigm



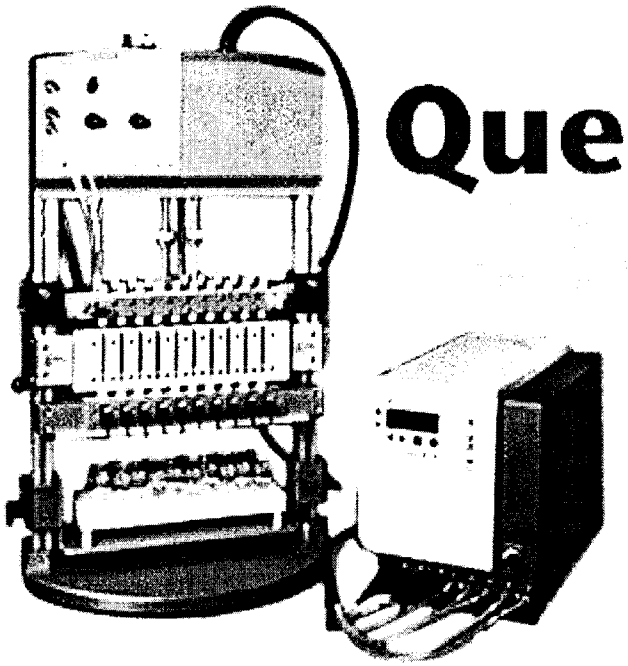
ARGONAUT
TECHNOLOGIES

Operational Integration

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

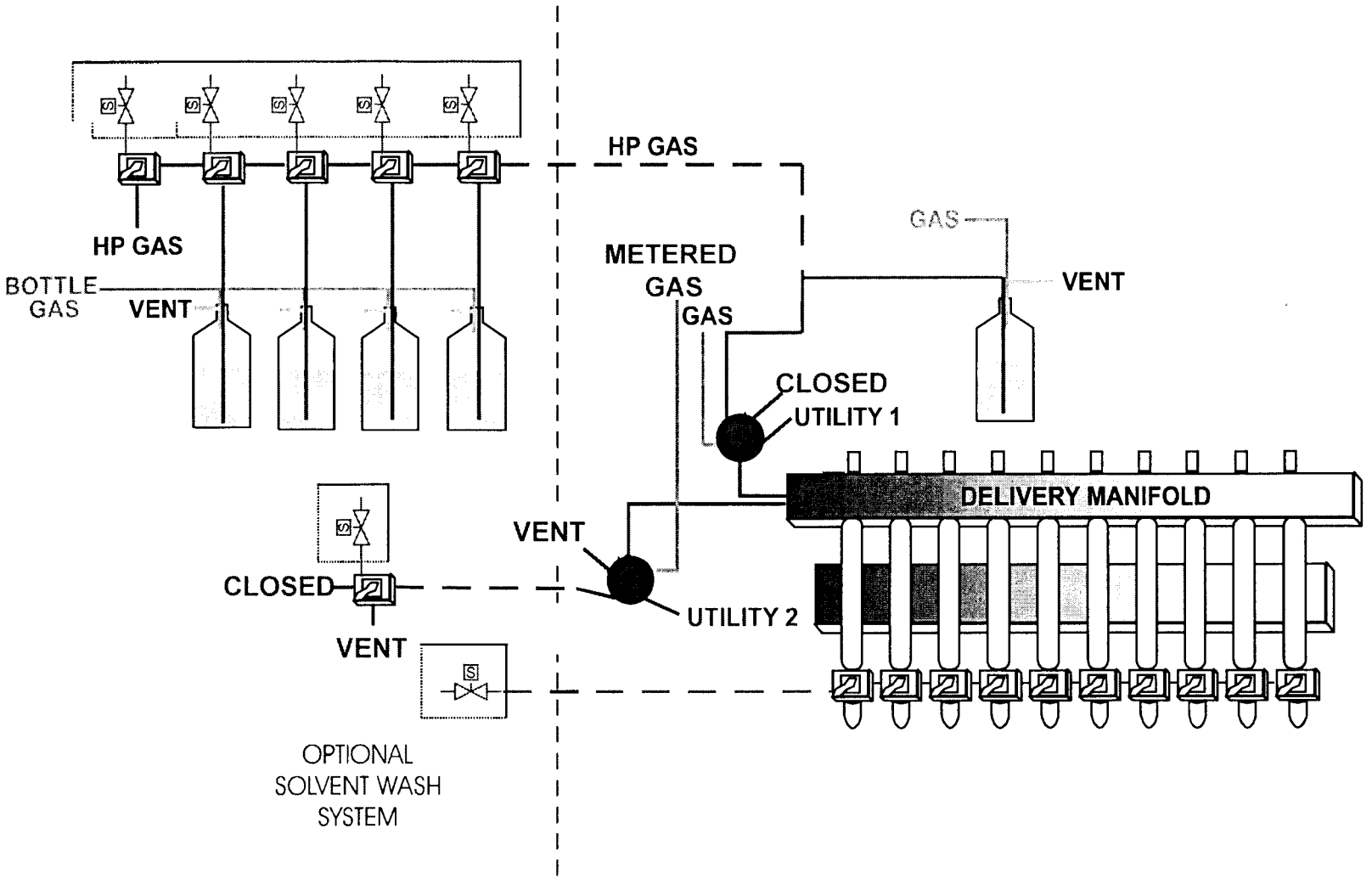


x 20 =



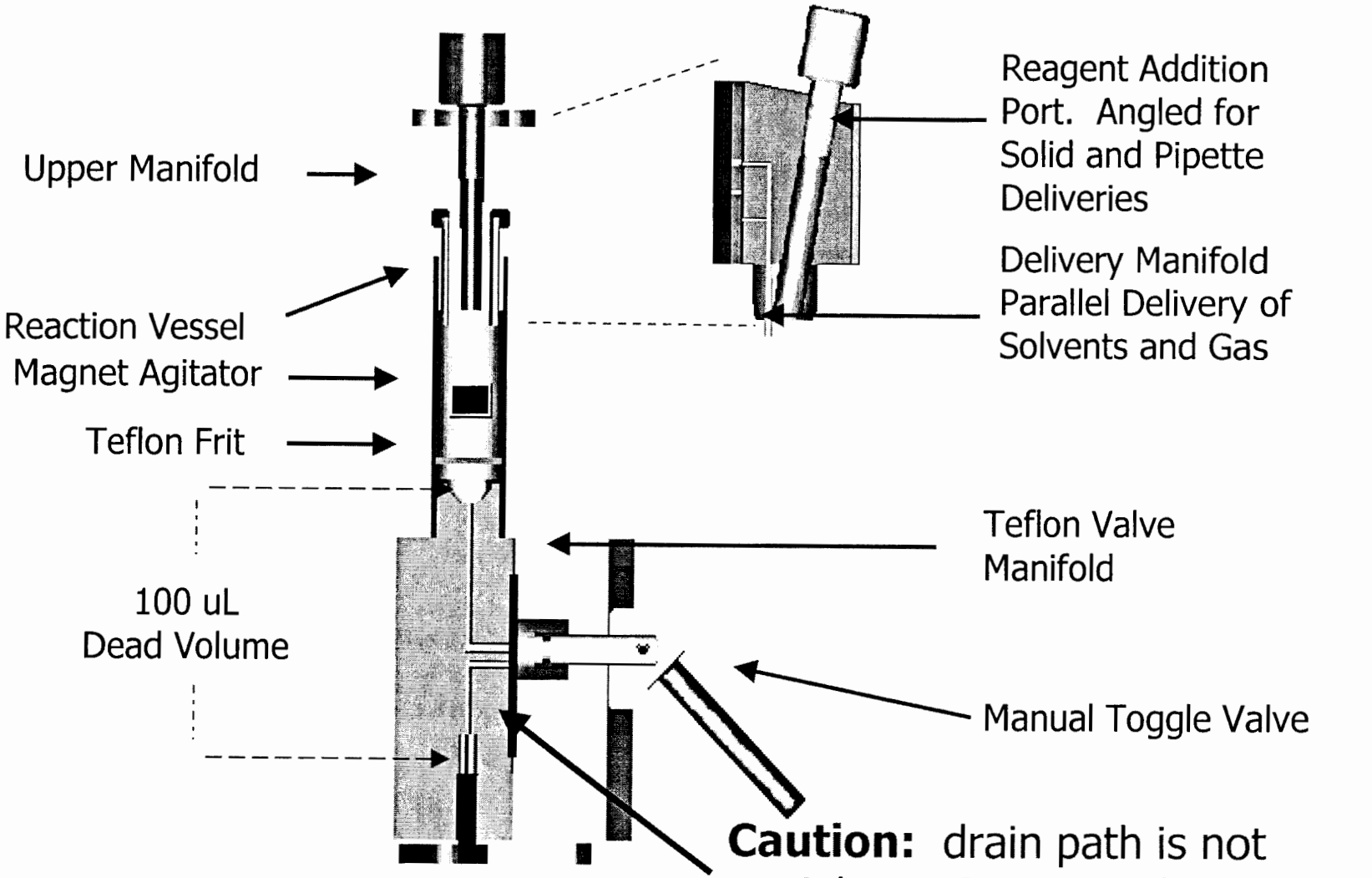
ARGONAUT
TECHNOLOGIES

Quest Plumbing Schematic



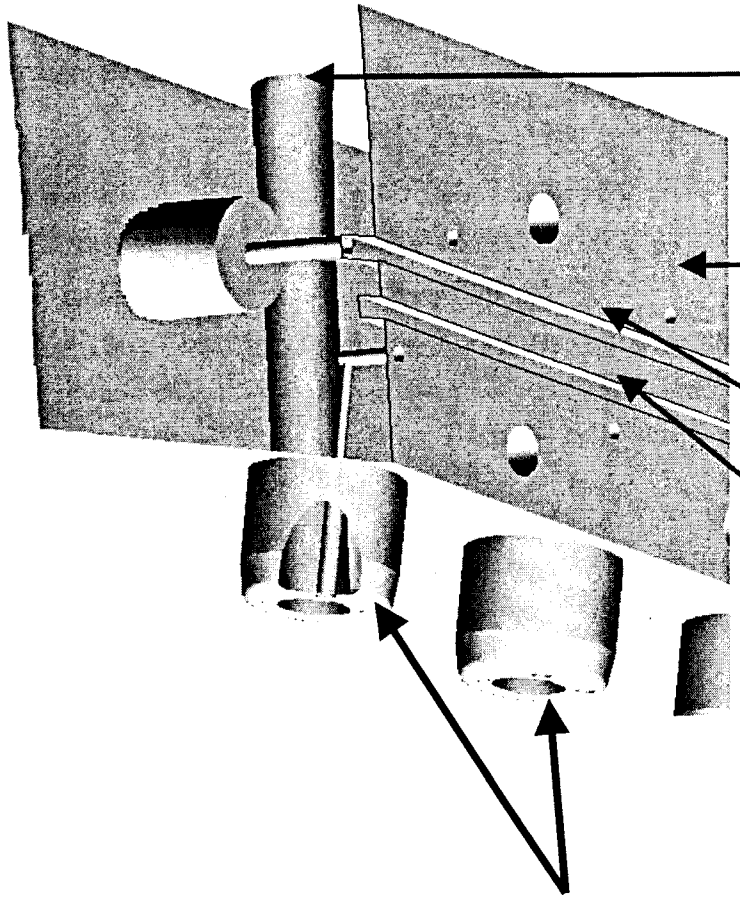
ARGONAUT TECHNOLOGIES

Reactor Unit Cross Sectional View



ARGONAUT TECHNOLOGIES

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.

ARGONAUT
TECHNOLOGIES

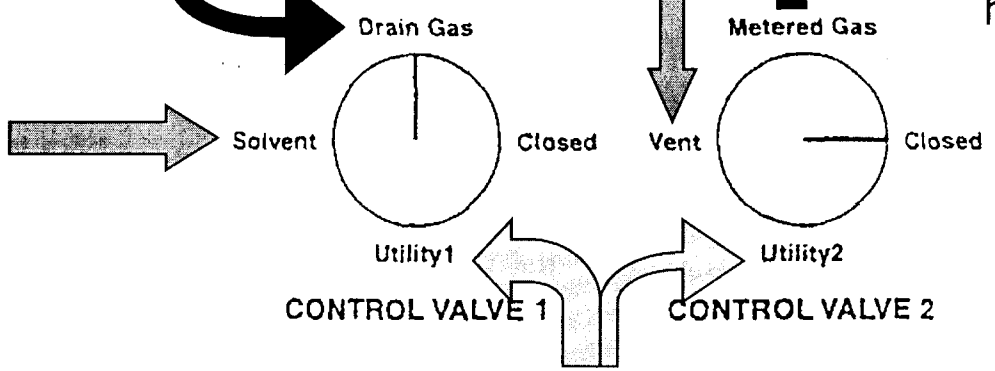
Control Valve Functions

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.)

ARGONAUT TECHNOLOGIES

Overview

A comparison of traditional synthetic operations

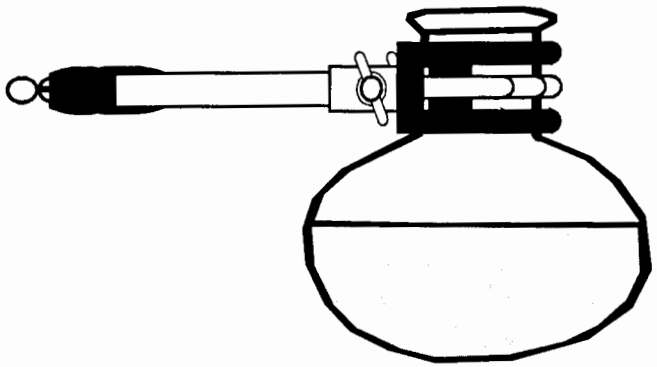
(Left side of slide)

And the comparable operations on the

(Right side of slide)

Reaction Set Up

- *Round bottom*
- *Clamp*

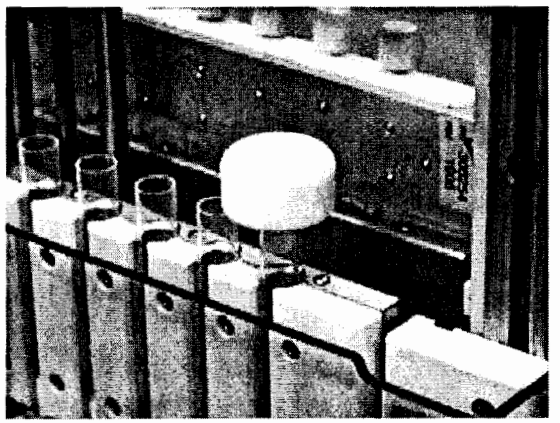


- *Remove reaction vessels (RVs)*

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.

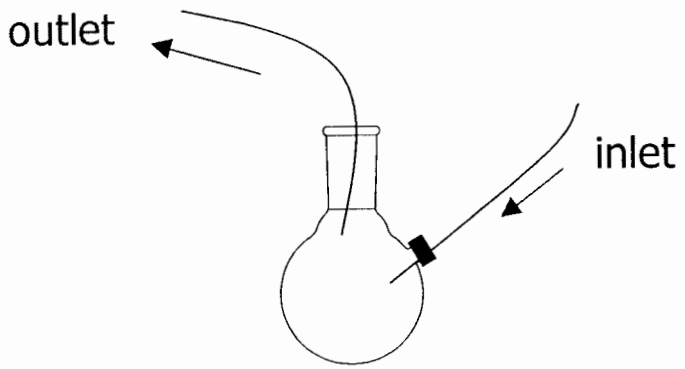
- *Insert new RV*



ARGONAUT TECHNOLOGIES

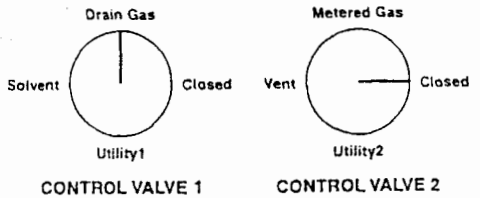
Inerting Reaction Environment

- *Gas purge; septa or stopcock*



- *Solid SM or empty RV*
  - *Straight drain*

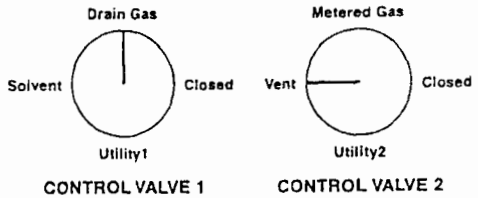
Upper Manifold Membrane Valve: OPEN



Open lower manifold drain valves to empty RVs

- *Liquid SM*
  - *Headspace sweep purges top of RV with 30 PSI gas*

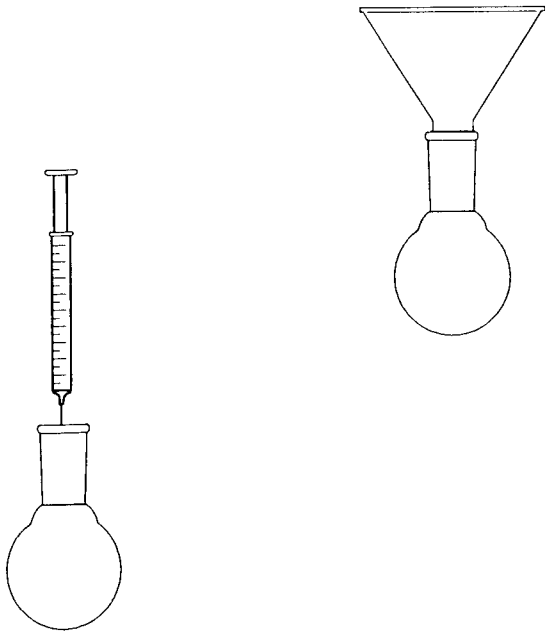
Upper Manifold Membrane Valve: OPEN



ARGONAUT TECHNOLOGIES

Reagent Addition

- *Funnel, needle, pipette, spatula*

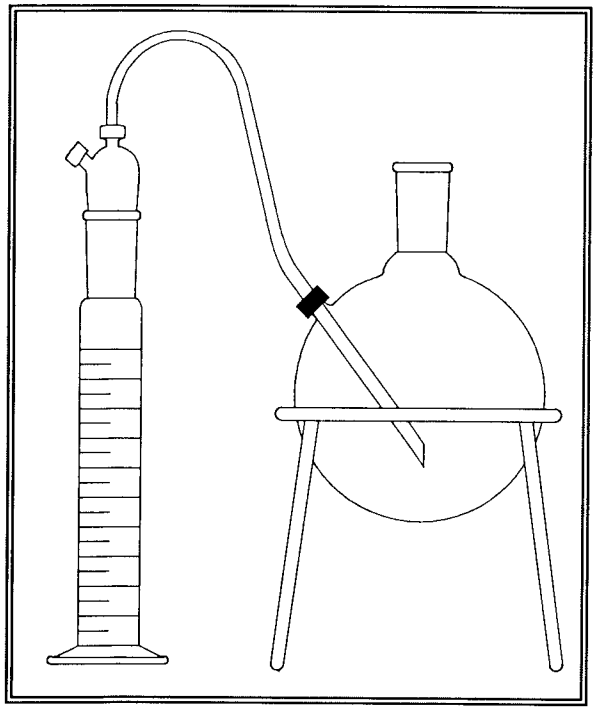


- *Funnel, needle, pipette, micro-spatula*

ARGONAUT TECHNOLOGIES

Addition Under Inert Conditions

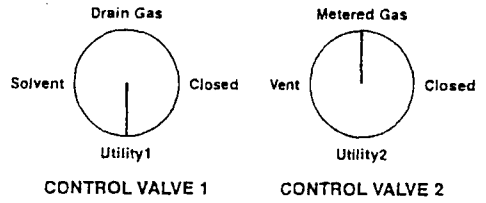
- *Septa*



- *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

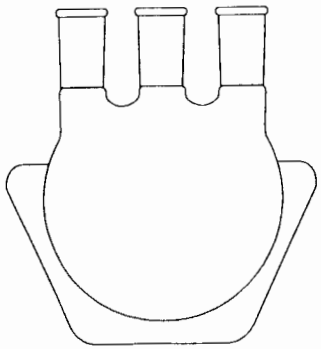
ARGONAUT TECHNOLOGIES

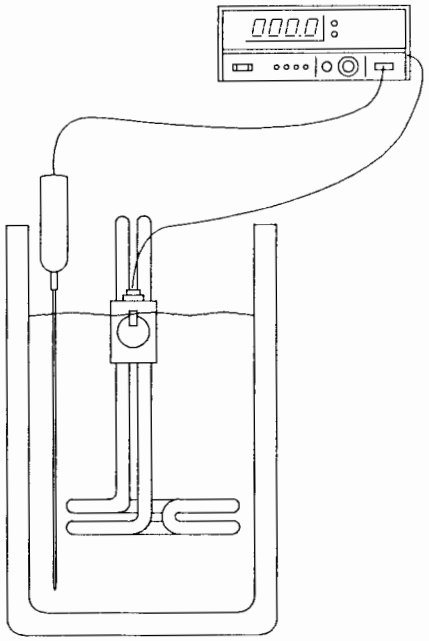
Reagent Addition Tips

- *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.*

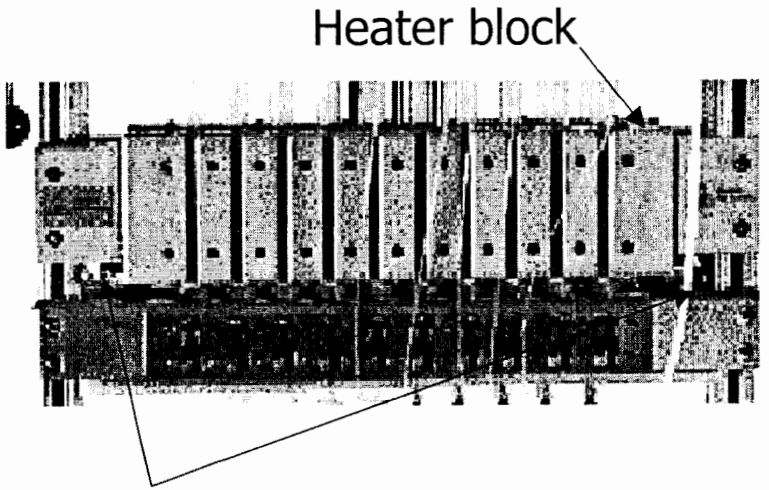
Temperature Regulation: Heat/cool

- *Bath, heating mantle or tape, recirculator*





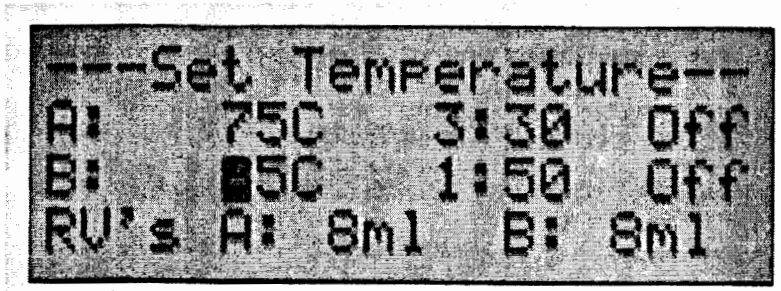
- *Heating block ⇒ 130 °C*
  - *Temperature controlled by controller*
  - *Volume entry in program*
- *Chiller ⇒ -40 °C*
  - *Temperature controlled by chiller*
  - *Remove condensation with towel or acetone*
- *Two temperatures; max Δ = 40 °C*



Connections for chiller; 1/4" MPT

ARGONAUT TECHNOLOGIES

Heating Temperature Programming

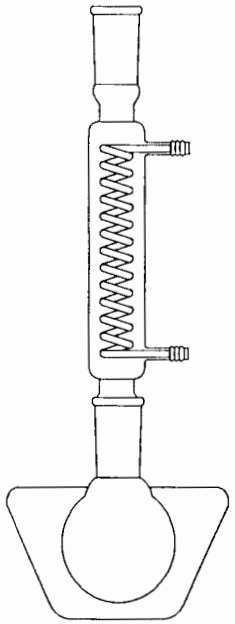


- *Set temperature for bank A or bank B*
- *Input time (hh:mm) to heat*
- *Enter approximate volume to nearest mL*
- *Push start/stop button*
- *Timer counts down when set point is reached*
- *Heaters turn off when time expires*
- *Power failure default; Quest off when power resumes*

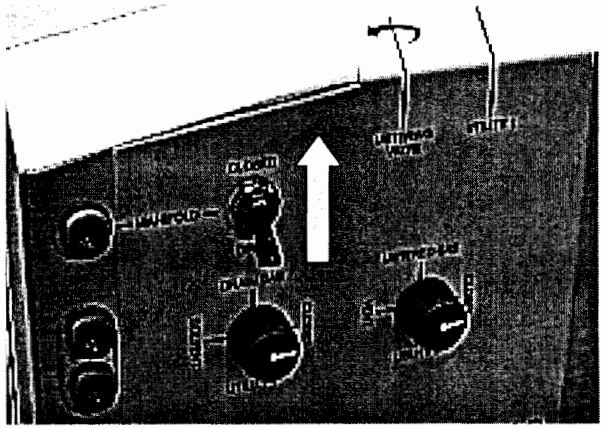
ARGONAUT TECHNOLOGIES

Heating Under Reflux Conditions

- *Condenser at 1 ATM*
- *Condensate regulates rxn temperature*



- ***Seal upper manifold***



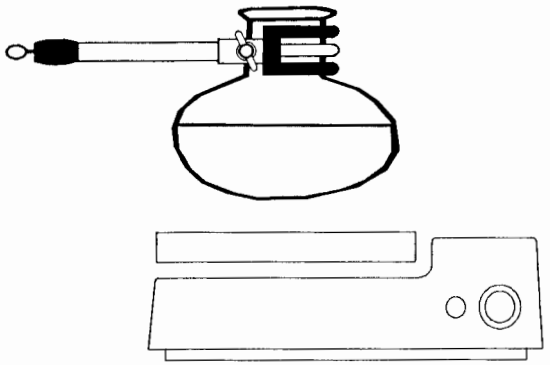
- *Heat to bp of solvent;*

  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!**

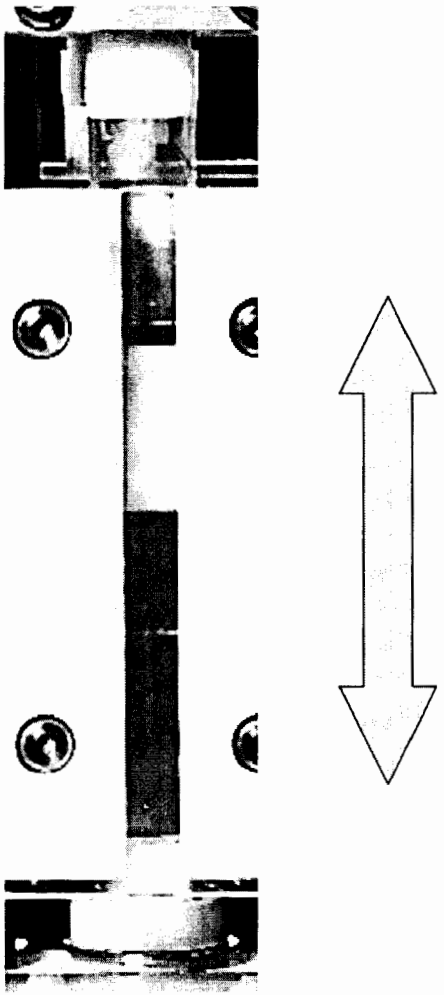
ARGONAUT TECHNOLOGIES

Agitation

- *Shaker*
- *Magnetic stirrer*
- *Overhead stirrer*



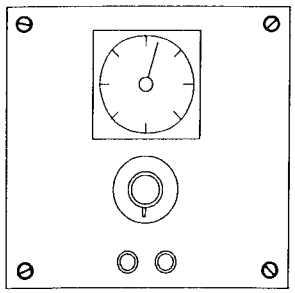
- *Place magnet in RV, dimple down*
- *Mixing via vertical oscillation*



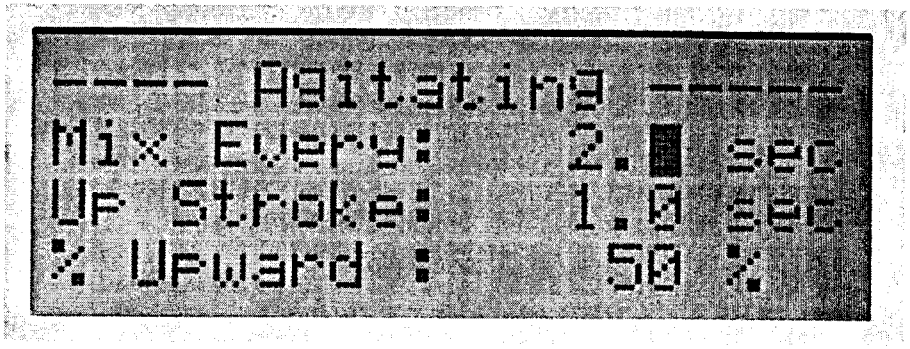
ARGONAUT
TECHNOLOGIES

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***

ARGONAUT TECHNOLOGIES

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)

MixEvery:	3.0-4.0 sec
UpStroke:	1.8-2.6 sec
%Upwards	60%

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:

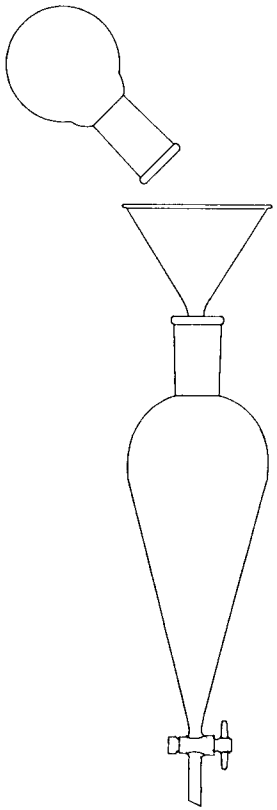
MixEvery:	5.0 sec
UpStroke:	4.8 sec
%Upwards	96%

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.

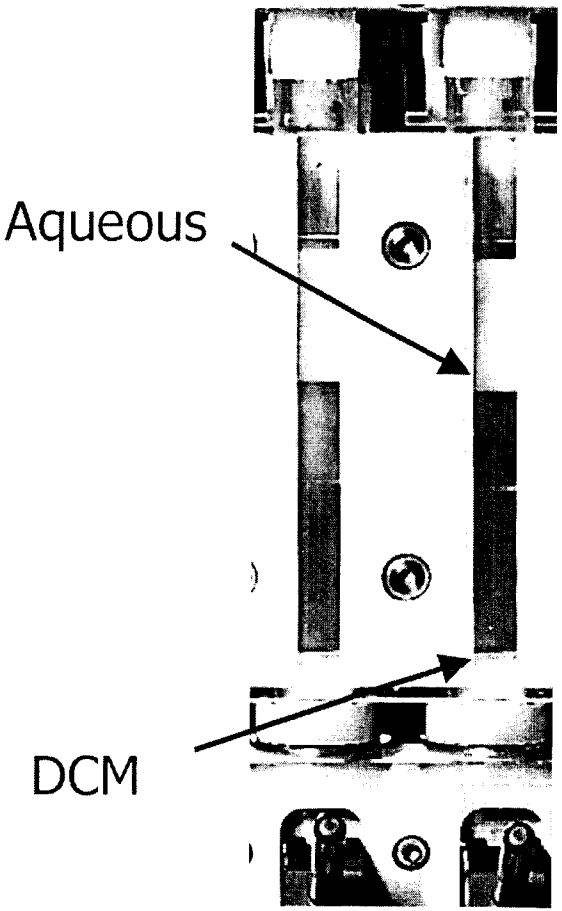
- ■ *Keep magnets ~5 mm below solvent surface*
  - • *Minimize splashing onto upper manifold*
- ■ *Use a large mix every value for viscous solutions (e.g. 4-5 s)*
- ■ *Use external magnet to dislodge stuck magnets*

Reaction Work Up: LLE

- *Pour rxn sol'n into separatory funnel with aqueous sol'n*
- *Split phases*



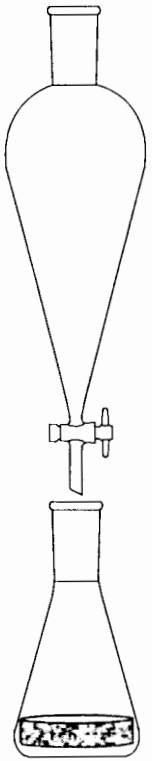
- *All operations combined into Quest RV*



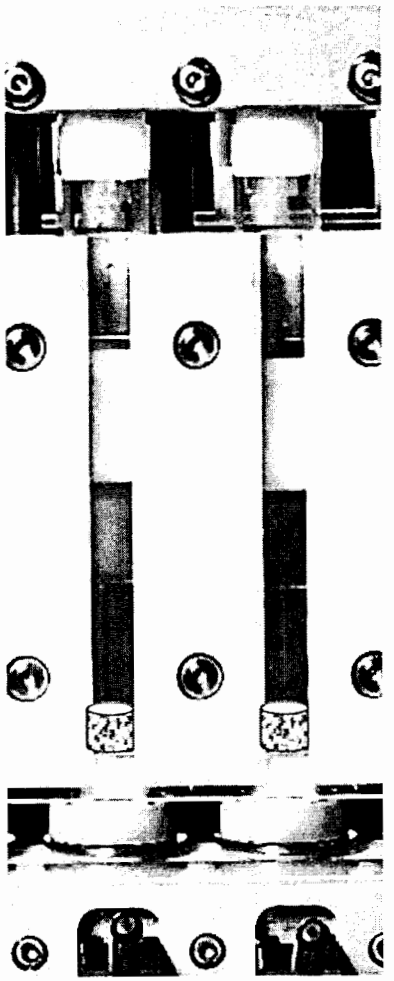
ARGONAUT TECHNOLOGIES

Reaction Work Up: LLE

- *Dry in Erlenmeyer*



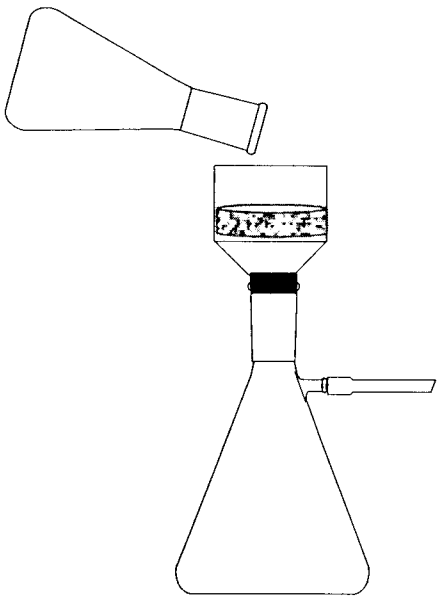
- *Add drying agent to RV*



ARGONAUT TECHNOLOGIES

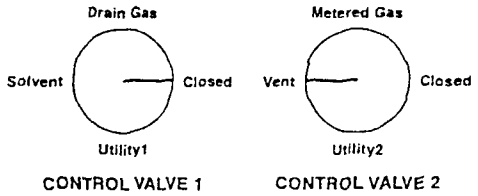
Reaction Work Up: LLE

- *Filter and concentrate*

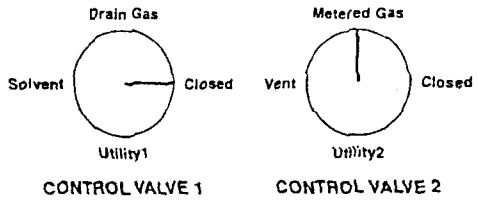


- *Filter and concentrate*
  - *Place collection vessels under lower manifold*

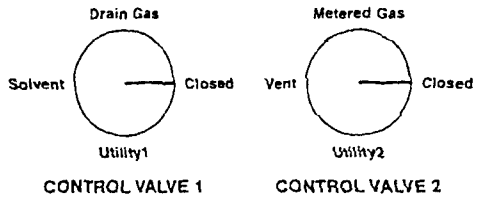
Upper Manifold Membrane Valve: OPEN



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.



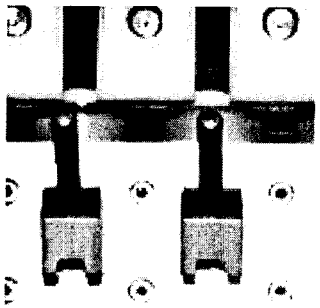
ARGONAUT TECHNOLOGIES

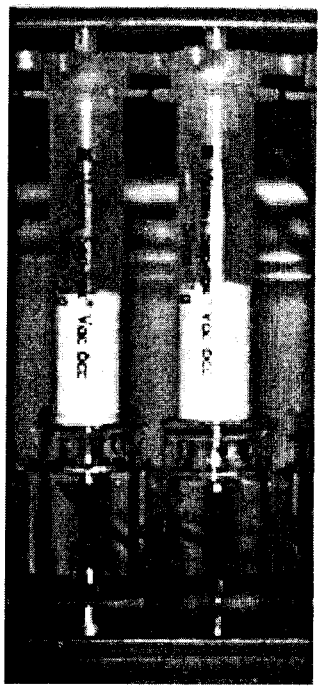
Reaction Work-up: Alternatives

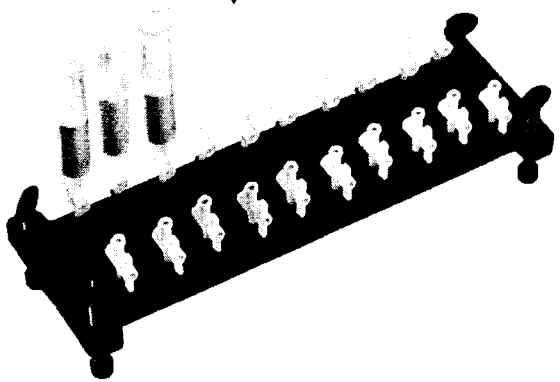
- *Use of resin-bound scavengers and reagents ⇒ RV filter provides purification*
- *Drain through cartridges and SPE*

  Columns: on-line purification
- *Drain into SPE or SLE cartridges:*

  Off-line purification



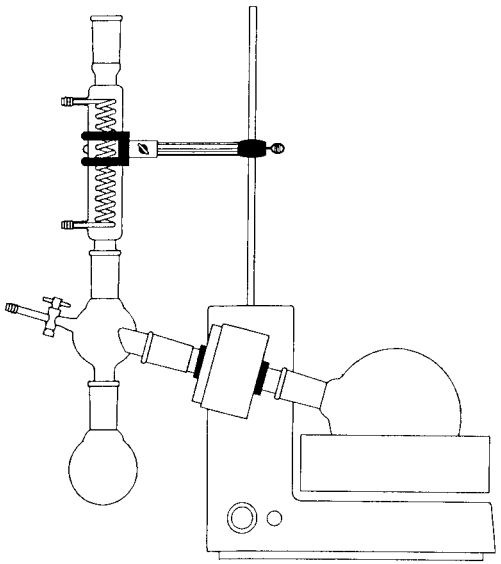


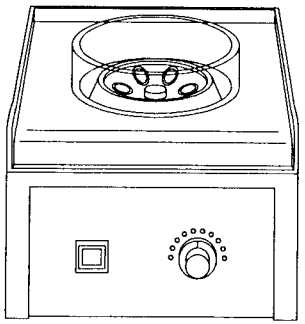


ARGONAUT TECHNOLOGIES

Reaction Concentration

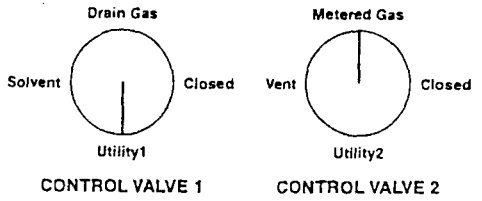
- *Rotary evaporator*
- *Speed-vac/Genevac*
- *Blow-down*





- *Volume reduction in RV*
- *Blow down*

Upper Manifold Membrane Valve: OPEN



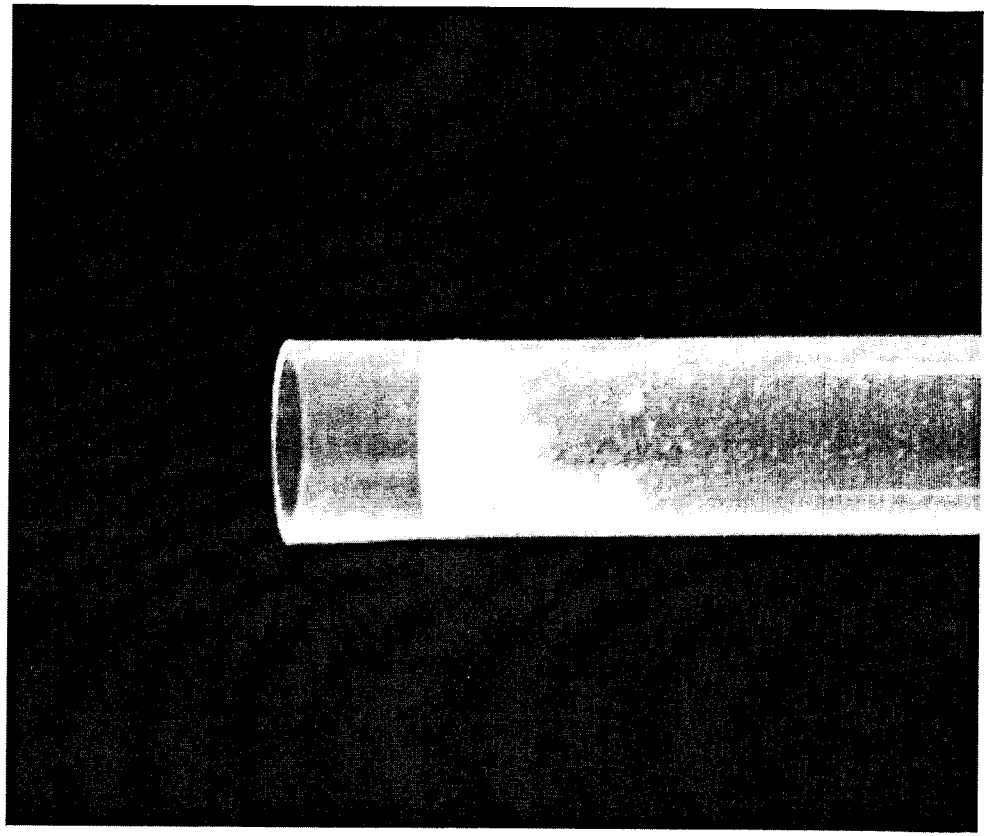
Attach condenser to Utility Port 1
Adjust gas flow with Metered Gas Needle Valve

- *Gas reagent concentration manifold - released later this year*

ARGONAUT TECHNOLOGIES

In-situ *Product Isolation*

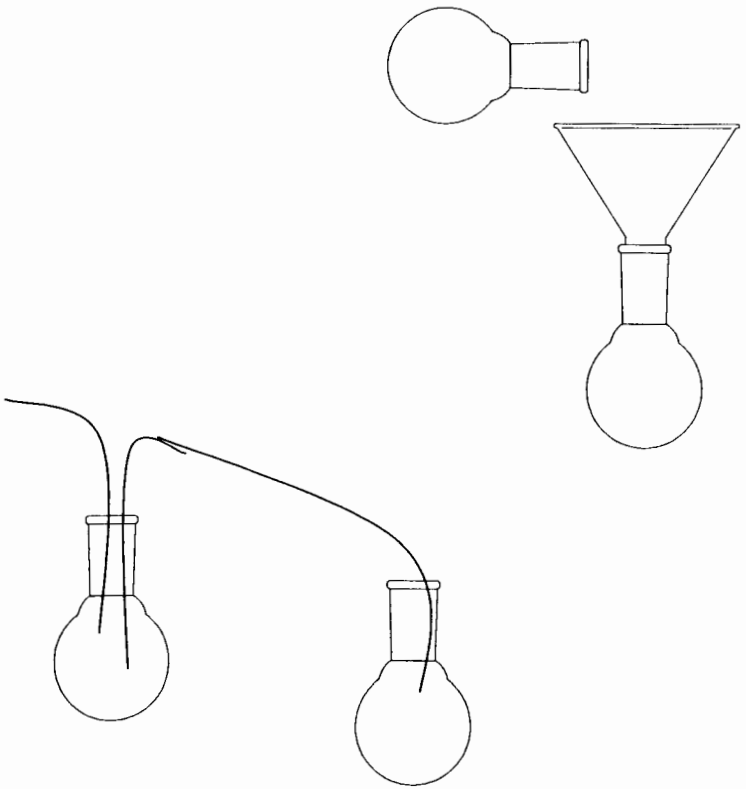
- *Precipitation or crystallization in RV*
- *Re-crystallize in RV*
- *5-7 μm fine frit rvs*



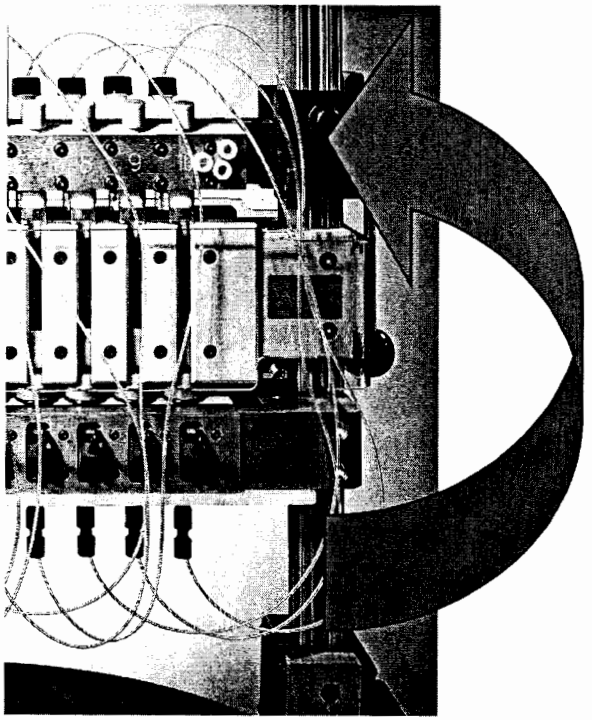
ARGONAUT
TECHNOLOGIES

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*



ARGONAUT TECHNOLOGIES

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*

ARGONAUT
TECHNOLOGIES

QUEST 210/215

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

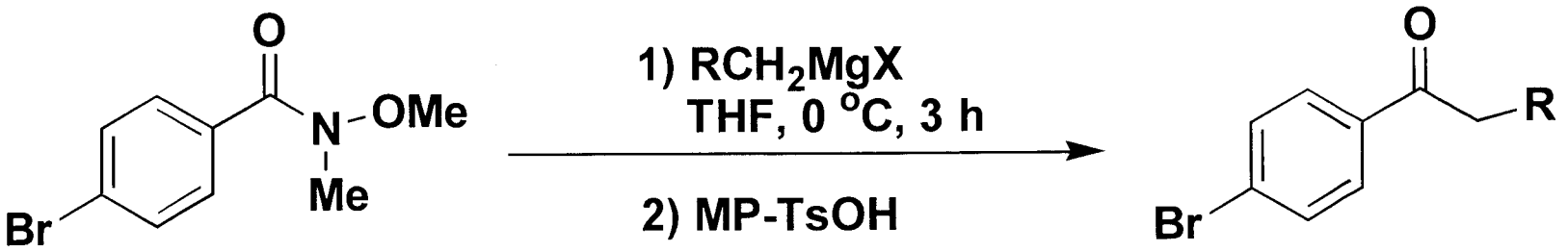
If you encounter any difficulties with your Quest contact your local Argonaut Applications Chemist for assistance. Additionally Bob Horn, Quest Depot Engineer, can assist with diagnosis; ext. 245.

Hands On Experience

Multistep synthesis and purification of 1,2,3-thiadiazoles using 'bank-to-bank' transfer

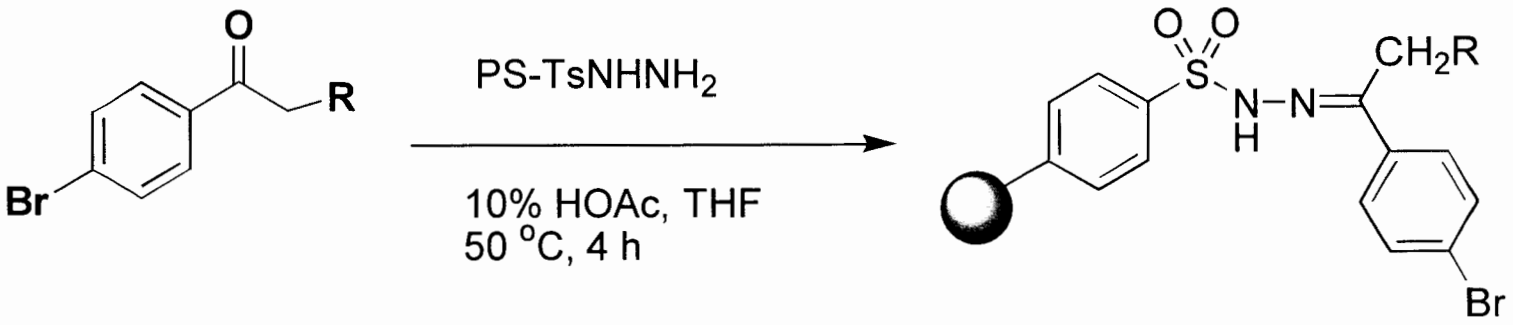
- *Quest SPE rack*
- *Quest lower luer manifold (LLM) and bank-to-bank cannulas*
- *Quest funnel manifold*
- *PS-TsNHNH$_2$ and MP-TsOH resins*

Ketone Synthesis



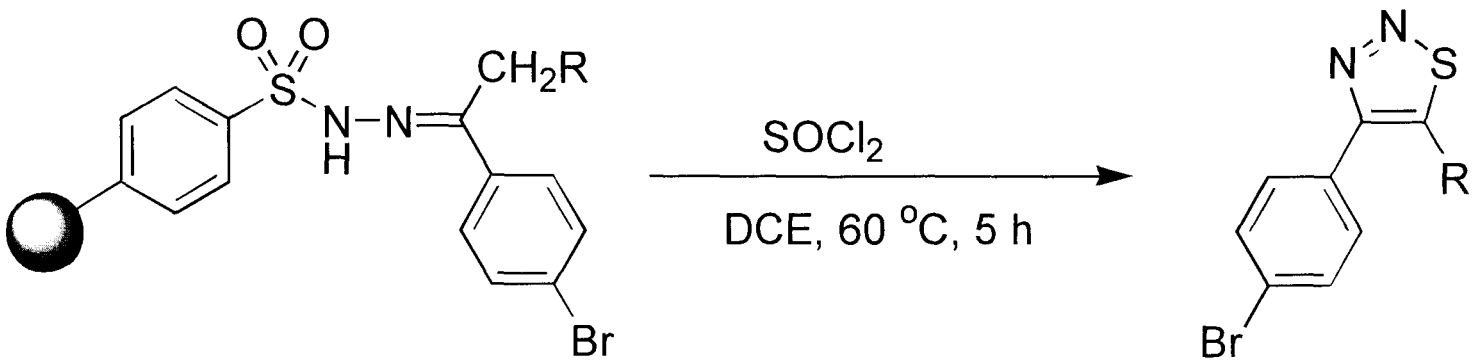
- Instrument pre-run maintenance
- Starting material loading into RVs and inerting of RV environment
- Chilling RVs to 0 °C
- Addition of Grignard reagent through septa cap ports
- Reaction work-up with addition of MP-TsOH
- Addition of HOAc for next step
- Transfer of contents to other side of Quest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

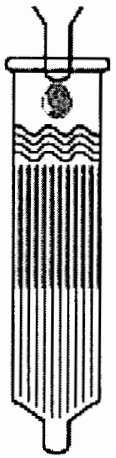


- Release and cyclization affected by addition of $socl_2$
- Product work-up using SLE. SLE cartridges held in SPE cartridge rack
- Post-reaction maintenance

Parallel Solid Liquid Extraction (SLE) using ChemElut Plus Cartridges

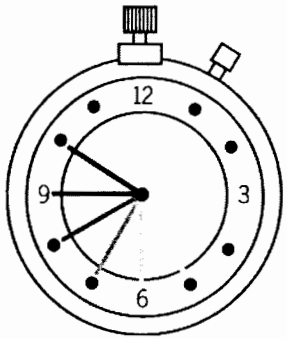
Step 1:
Prep Cartridge

Add aqueous solution (*e.g.*, 2N HCl)

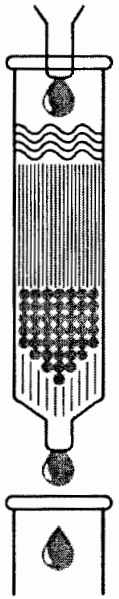


Aqueous buffer coats hydrophilic support and is immobilized on stationary phase

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

ARGONAUT TECHNOLOGIES

PART NO. 103047

Synthesis & Purification LETTERS

Multistep Synthesis and Purification of 1,2,3-Thiadiazoles Using "Bank-to-Bank" Transfer

The ability to run multi-step syntheses on a parallel organic synthesizer greatly enhances its capability. Addition of the Lower Luer Manifold Upgrade to the Quest 210 allows the connection of a variety of accessories with luer fittings to the reaction vessel outlets. By using a Teflon® transfer cannula with a luer fitting on one end and a septum luer on the other, reaction mixtures can be transferred from one bank of reaction vessels to the other, allowing multi-step syntheses on the Quest 210. To demonstrate this, we synthesized 1,2,3-thiadiazoles. The ketones required were prepared in reaction bank A. The reaction mixtures were quenched with MP-TsOH resin and the ketone solutions transferred to reaction vessels containing sulfonylhydrazine resin in bank B. After Hurd-Mori cleavage, 1,2,3-thiadiazoles products were purified using liquid-liquid extraction cartridges. Using this technique we were able to perform the parallel multi-step synthesis of 1,2,3-thiadiazoles on the Quest 210.

- ☑ Quest™ 210
- ☑ Quest Solid-Phase Extraction Rack
- ☑ Quest Lower Luer Manifold and Bank-to-Bank Transfer Cannulas
- ☑ Quest Funnel Manifold
- ☑ PS-TsNHNH$_2$ Resin
- ☑ MP-TsOH Resin

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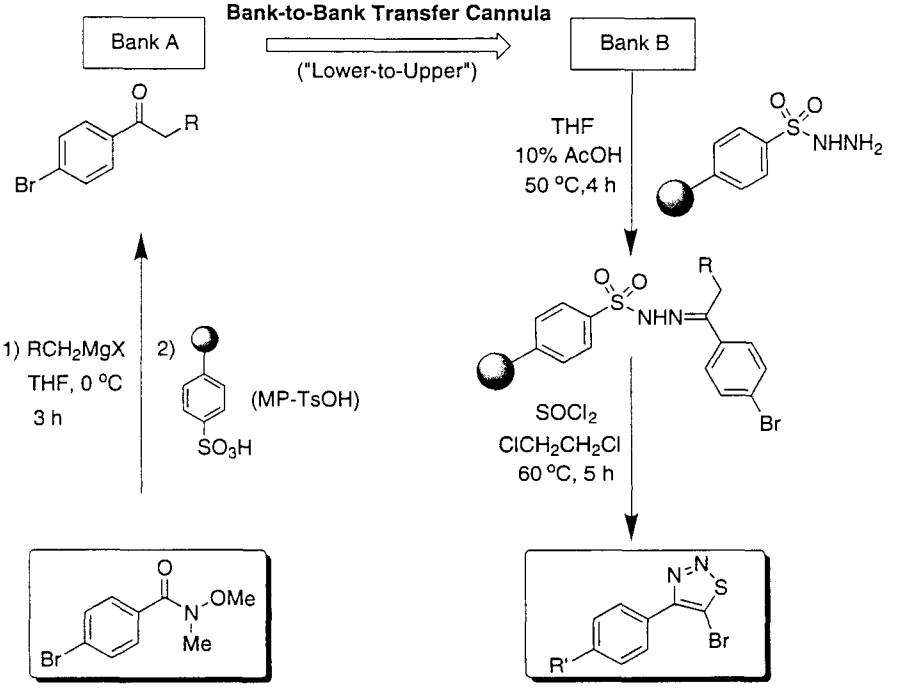
INTRODUCTION

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.[5a] Many methods have been developed for the synthesis of 1,2,3-thiadiazoles,[5d,5e] including the Hurd-Mori cyclization of α-methylene ketones employing *p*-toluene-sulfonyl hydrazone intermediates.[7,8]

Argonaut Technologies supplies a gel-type polystyrene-sulfonylhydrazide resin (PS-Ts-NHNH$_2$) originally designed for carbonyl scavenging applications.[9,10] We felt



RCH_2MgX: CH_3MgCl, n-BuMgCl, EtMgBr, iso-BuMgCl, $PhCH_2MgCl$.

Scheme 1. Synthesis of 1,2,3-Thiadiazoles

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 capabilties 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-$TsNHNH_2$ 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,[12,13] preloaded with saturated Na_2CO_3 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-$TsNHNH_2$ 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.): CH_3MgCl (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), $PhCH_2MgCl$ (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 luers were removed and the funnel manifold mounted. To each

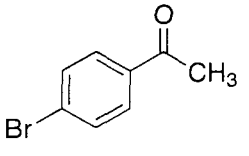
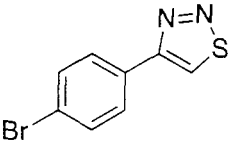
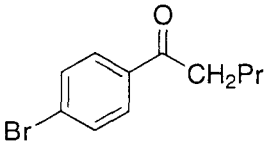
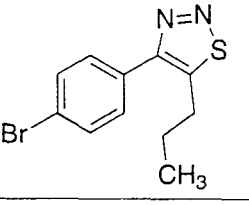
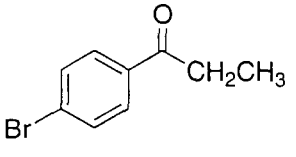
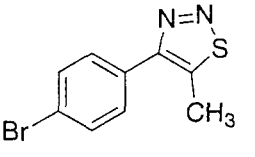
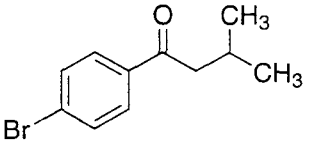
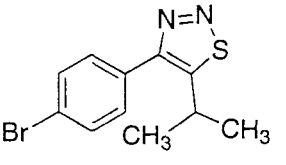
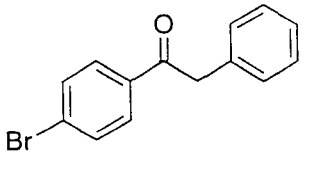
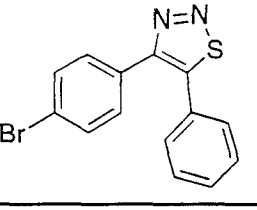
Table 1. Materials Required

MATERIAL	SOURCE	PROPERTY	AMOUNT
PS-$TsNHNH_2$ resin	Argonaut	2.4 mmol/g	1.0 g
MP-TsOH resin	Argonaut	1.45 mmol/g	10 g
N-Methoxy-N-methyl-*p*-bromobenzamide	Prepared[11]	FW 244.09 d 1.434	1.08 mL
CH_3MgCl	Aldrich	3.0 M	465 µL
n-BuMgCl	Aldrich	2.0 M	695 µL
EtMgBr	Alfa Aesar	3.14 M	442 µL
iso-BuMgCl	Aldrich	2.0 M	695 µL
$PhCH_2MgCl$	Aldrich	2.0 M	695 µL
CH_3COOH	Fisher Scientific	FW 60.05 d 1.049	1.5 mL
$SOCl_2$	Aldrich	FW 118.97 d 1.631	3.5 mL

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 luers 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 $SOCl_2$ (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)[13] were mounted on the SPE rack. To each cartridge was added 2.5 mL saturated Na_2CO_3 and the cartridges were allowed to soak for 10 min. The

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

Entry	Ketone	Thiadiazole	Yield (%)	GC Purity (%)
1			98	100
2			82	94
3			77	97
4			59	97
5			67	98

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.[14] 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). Bis-aryl 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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-), 1.01 (t, 3 H, J = 7.4 Hz, -CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{11}H_{11}N_2SBr$: 282.1).

Entry **3**, 4-(4'-bromophenyl)-5-methyl-1,2,3-thiadiazole: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 4 H, Ar-H), 2.71 (s, 3 H, -CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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-), 1.39 (d, 6 H, J = 6.6 Hz, -(CH_3)2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 7.51 (m, 5 H, Ph-H), 7.44-7.33 (m, 4 H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{14}H_9N_2SBr$: 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.

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9. PS-TsNHNH$_2$ resin (1.8-2.5 mmol/g, 1% crosslinked polystyrene-co-divinylbenzene) is commercially available from Argonaut Technologies.
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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 Na_2CO_3 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.

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1,2,3-Thiadiazole Synthesis

Table of Reagents

Black = Input
Red = Limiting reagent, mmoles
Blue = Calculated values

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

Workup Reagent	Loading (mmole/g)	Equiv. (EQ)	Mmols per RV (mmol)	Weight/Vol g or mL	Total # of RVs	Total Req Am't (mL)
MP-TsOH	1.45	1.16	1.45	1.0	10	10.00
Acetic Acid				0.3	10	3.00
THF				9.0	10	90.00
hexane				9.0	10	90.00
dichloromethane				9.0	10	90.00

Resin Catch Reagent	Loading (mmole/g)	Equiv. (EQ)	Mmols per RV (mmol)	Weight g	Total # of RVs	Total Req Am't (mL or g)
PS-TsNHNH$_2$	2.4	0.384	0.48	0.2	10	2.00
THF				9.0	10	90.00
hexane				9.0	10	90.00
dichloromethane				9.0	10	90.00

Cleavage	Molarity (M)	Equiv. (EQ)	Mmols per RV (mmol)	Weight/Vol g or mL	Total # of RVs	Total Req Am't (mL or g)
Thionyl Chloride	2.00	20	9.60	4.8	10	48.00

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

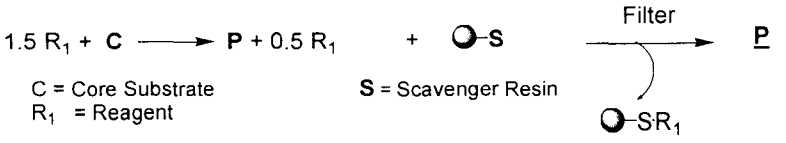
Parallel Solution Phase Synthesis: Improved Purification Techniques

- ***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)

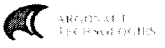
Polymer Assisted Solution Phase Synthesis: Scavengers

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

Solution Phase Reaction | **Scavenger Resin** | **Product**

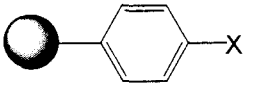


- Technique relies on a chemically-driven separation
- Polymers added *after* reaction is complete in *solution*
- Multiple Scavengers can be used in a single step
  - Mixtures of "incompatible" functionality possible
- Purified reaction solution is isolated by filtration

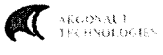


Polymer Scavengers: Functional Polymers

- 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:

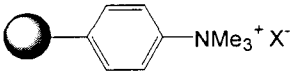


X = - CHO, - CH_2NCO, -SO_2NHNH_2



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

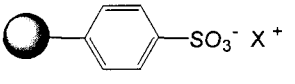


X = OH, $(CO_3)_{1/2}$, $(S_2O_3)_{1/2}$

- 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

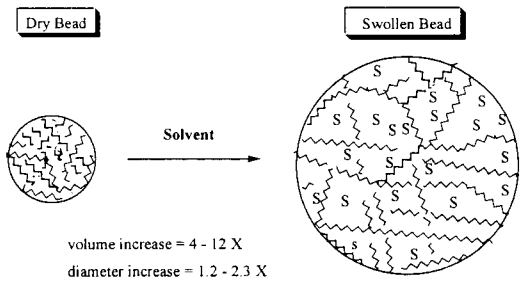


X = H, Ca

- Macroporous and lightly crosslinked forms available
- Amberlsyt A-15 (macroporous) has been most often used
  - Organic leachable polysulfonated impurities present

Functional Polymers:
Resin Swelling

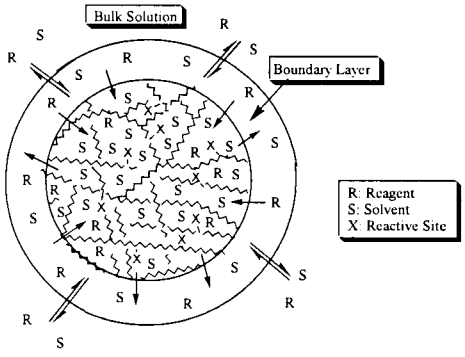
- Swelling is the uptake of solvent by dry resin
- Swelling solvents enlarge beads by 4 - 12 X
- Swelling solvents interact well with the polymer
- Swelling solvents for polystrene are THF, DMF, dichoromethane



- 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

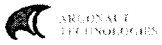
Functional Polymers:
Chemistry Considerations

- 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



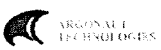
Polymer Scavengers: Considerations for Use

- 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

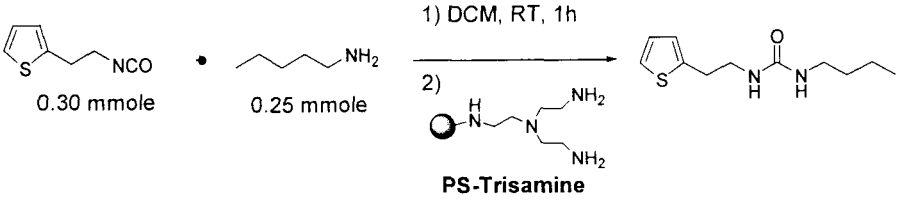


Polymer Scavengers: Critical Requirements

- 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



Resin	Mmole/g	Weight (mg)	Mmole	Equiv.	Time (h)
PS-Trisamine	3.2	50	0.16	3	2

- R.J. Booth and J.C. Hodges J.Am. Chem. Soc. 1997, 119, 4882-6

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

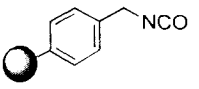
Polymer Scavengers

Reagent Sequestered	Polymer Functionality	Type	Argonaut Product	Reference
Acid Chloride, anhydrides	Amine	F	PS-Trisamine	
Sulfonyl Chloride	Amine	F	PS-Trisamine	
Isocyanate, Isothiocyanate	Amine	F	PS-Trisamine	
Alkyl halide	Thiol	F	PS-Thiophenol	
	Phosphine	F	PS-triphenylphosphine	
Acidic OH	Amine	F	PS-Trisamine	
	Carbonate	IE	MP-Carbonate	
Carboxylic Acid	Carbonate	IE	MP-Carbonate	
Inorganic Acid	Carbonate	IE	MP-Carbonate	
	Amine	F	PS-DIEA, PS-NMM	
Aldehyde	tosyl hydrazide	F		
Ketone	tosyl hydrazide	F		
activated olefin	amine	F		
Alcohol	Sulfonyl chloride	F		
Alkyl Amine	isocyanate	F		
	Isotoni	F		
Aniline	Sulfonic Acid	IE		

Polymer Scavengers

Reagent Sequestered	Polymer Functionality	Type	Argonaut Product	Reference
1° Amine	Aldehyde	F		
Thiols	Thiol	F		
Hydrazines	isocyanate	F		
	Aldehyde	F		
Fluoride	Calcium Sulfonate	IE		
Grignard, alkyllithium	Aldehyde	F	PS-CHO	
Dess-Martin Periodinane	Thiosulfate	F		
DDQ	Citrate, Carbonate	IE		
Fluoride	Calcium Sulfonate	IE		

Scavenger Resins: PS-Isocyanate



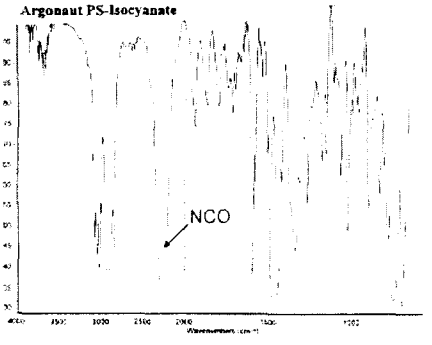
1.2 - 1.5 mmole/g

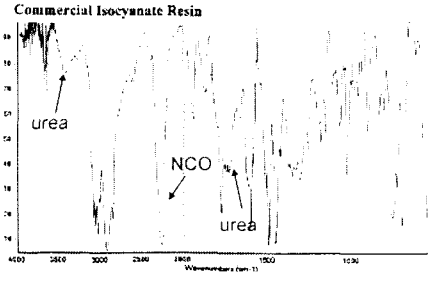
Nucleophile	Nucl Conc M	Ps- Isocyanate (eq)	Time 100% Scavenged (h)
Diisopropyl-amine	0.05	2	0.5
Piperidine	0.015	3	0.5
Methylphenethylamine	0.015	3	1.5
Aniline	0.05	2 3	16h, 20 °C - 89% 16h, 60 °C - 99%
2-Amino Benzophenone	0.05	2 3	16h - 8% 16 h - 81%

- *Readily scavenges alkylamines*
- *Anilines more sluggish*
- *S.W. Kaldor and M.G. Siegel,* ,et.al Tetrahedron Letters ***1996***, 37, *7193. R.J. Booth and J.C. Hodges* J.Am.Chem. Soc, ***1997***, 119, *4882.*

ARGONAUT TECHNOLOGIES

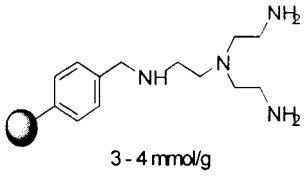
Isocyanate Resins: Comparison of IR spectra





- *Low levels of urea crosslinking present by **IR** in Argonaut resin*

Scavenger Resins: PS-Trisamine



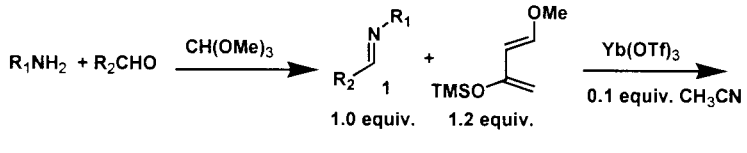
3 - 4 mmol/g

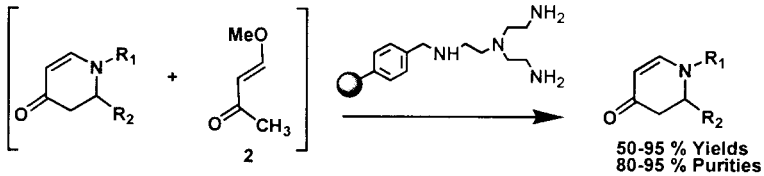
Electrophile	Ps- Trisamine (equiv)	Time 100% Scavenged (h)
4-ClBzCl (0.05 M)	3.5	0.5
2-PhBuCOCl	3.5	0.5
2,6-MeOPhCOCl	3.5	0.5
$PhSO_2Cl$	4	0.5
4-MeOPhNCO	2	0.5

- *Two equivalents of PS-Trisamine per acid or sulfonyl chloride is required when tertiary amine resin is not present*
- *R.J. Booth and J.C. Hodges* J.Am.Chem. Soc, ***1997***, 119, *4882.*

ARGONAUT TECHNOLOGIES

Use of PS-Trisamine: Dihydropyridone Synthesis

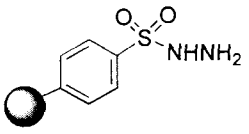




50-95 % Yields
80-95 % Purities

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

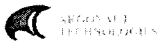
Scavenger Resins: PS-TsNHNH$_2$



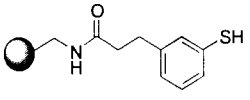
1.8 - 2.8 mmole/g

Carbonyl Compound (DCM solvent)	AcOH added	Ps-TsNHNH$_2$ (equiv)	Time 100% Scavenged (h)
PhCHO (0.05 M)	no	3	1
Hexanal	no	3	1
2,6-MeOPhCHO	no	2.5	1
Cyclohexanone	10 %	3	1
Acetophenone	10 %	3	8
2,6-Me-Cyclohexanone	10 %	3/DCE 70 °C	10

- *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)*

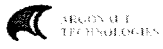


Scavenger Resins: PS-Thiophenol

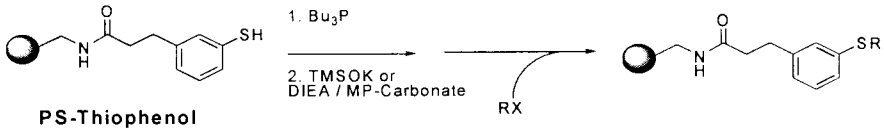


PS-Thiophenol

- *General scavenger for alkylating agents*
- *Capacity = 1.0 - 1.3 mmole/g*
- *"Wash and Ready" Disulfide Reduction*
  - *Bu$_3$P in THF/water, 30 min*
  - *Storable for several weeks*
- *Possible linker for SPOS*
  - cf. *Masquelin* et. al. *Helvetica Chim. Acta.* ***1998***, 81, *646. (oxidation/nucleophilic displacement of resin-bound thiopyrimidines)*



Scavenger Resins: PS-Thiophenol

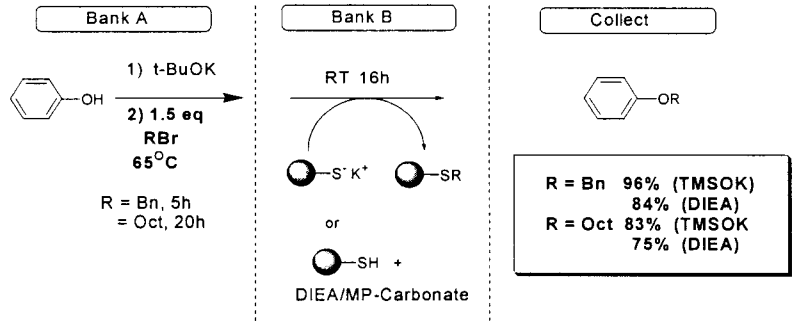


PS-Thiophenol

RX	PS-Thiophenol (eq)	Base	% Scavenged in DMF		% Scavenged in THF:EtOH	
			1 h	16 h	1 h	16 h
BnBr	1.9	TMSOK	-	93	100	-
	2.3	DIEA/MP-Carbonate	-	-	92	100
Cinnamyl Cl	2.2	TMSOK	100	-	100	-
	2.2	DIEA/MP-Carbonate	-	100	-	-
OctBr	1.9	TMSOK	-	92	79	100
	1.9	DIEA/MP-Carbonate	-	86	-	-

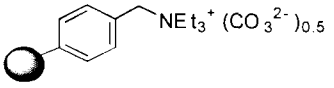
- *2 equiv. DIEA and MP-Carbonate relative to PS-Thiophenol*
- *Scavenging more effective in EtOH/THF than DMF*

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

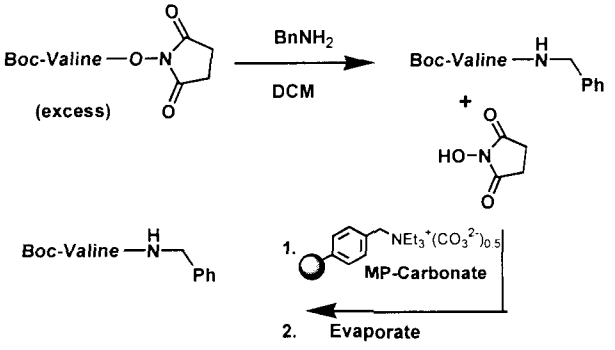


MP-Carbonate

- *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*

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

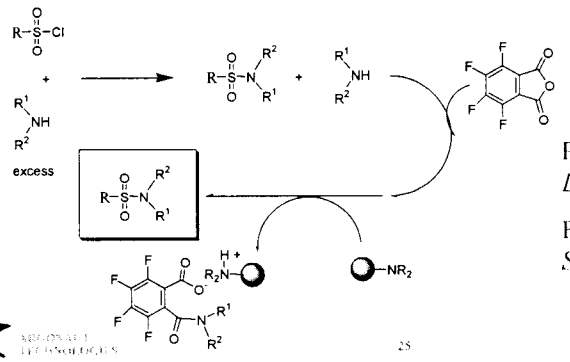
MP-Carbonate: Use in Purification of Solution-Phase Libraries



- *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



Parlow et.al. *Tetrahedron Letters* **1997**, *38*, 7959-62

Flynn et.al. *J. Am. Chem. Soc.* **1997**, *62*, 4874-4881

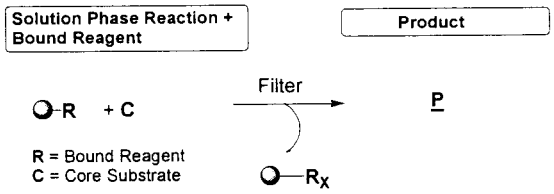
Bound Reagents and Scavengers

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

Scavenger Resin	Reagents Sequestered	Bound Reagent	Application
PS-Trisamine	Electrophiles	Ps-TsCl	Catch & Release
PS-NCO	Nucleophiles	PS-DIEA	Amine Base
PS-TsNHNH$_2$	Aldehydes, Ketones	PS-NMM	Non-Benzylic Amine Base
PS-Thiophenol	Alkylating Agents	PS-DMAP	Catalyst, Catch & Release
PS-benzaldehyde	Nucleophiles	MP-Carbonate	Base, Catch & Release
PS-TsCl (HL)	Nucleophiles	MP-TsOH	Acid
		PS-HOBT	Coupling
		PS-Carbodiimide	Coupling
		PS-Triphenylphosphine	Mitsunobu/Wittig/etc.

Polymer Assisted Solution Phase Synthesis: Polymeric Reagents

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

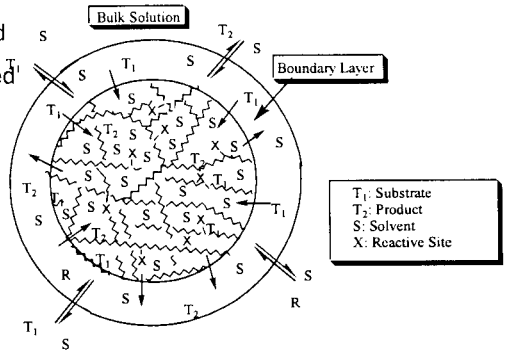


- Simplifies purification by filtration to remove spent and excess reagent
- One-Pot Multistep reactions possible
  - Mixtures of "incompatible" functionality possible
- Reagent performance is affected by polymer

ARGONAUT TECHNOLOGIES

Functional Polymers: Chemistry Considerations

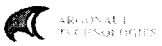
- Chemical reactions at polymer bound reactive sites requires diffusion of substrate into the bead
- The "Microenvironment" associated with the neighboring polymer can effect the course of reactions
- Conversion of functionality on the polymer can affect the microenvironment and swelling properties



- Generally polymer reagents are prepared in "modest loading" (~ 1 mmole/g)
- Agitation serves to refresh reagent concentration around the boundary layer

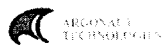
Polymer Reagents and Scavengers: Critical Requirements

- 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"*



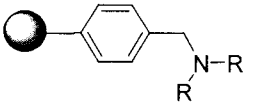
Argonaut Polymeric Reagents

Bound Reagent	Solution Analog	Application
Ps-TsCl	p-toluenesulfonyl chloride	Catch & Release via tosylate
PS-DIEA	hindered tertiary amine	Amine Base
PS-NMM	N-methylmorpholine	Non-Benzylic Amine Base
PS-DMAP	DMAP	Catalyst, Catch & Release
MP-Carbonate	Ammonium Carbonate	Base, Catch & Release
MP-TsOH	p-toluenesulfonic Acid	Acid
PS-HOBt	HOBt	Coupling, protecting group transfer
PS-Carbodiimide	DCC	Coupling
PS-Triphenylphosphine	Triphenylphosphine	Mitsunobu/Wittig/halogenations

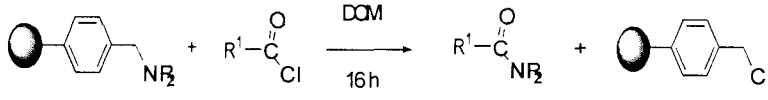
Tertiary Amine Bases

- *Amine base resins in literature are typically are 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



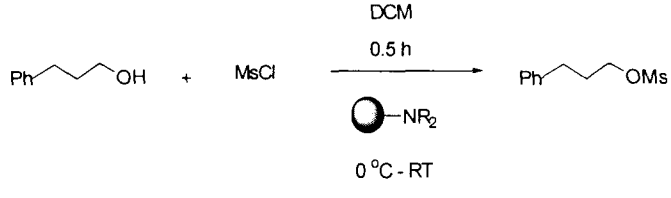
Tertiary Amine Bases
Stability to Electrophiles



R	Loading (mmole/g)	% Cleavage R_1 = Ph	% Cleavage R_1 = MeO
Me	4.8	9	-
Morpholine	3.6	0	90
i-Pr	3.8	-	2.5

- *Benzylic 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*

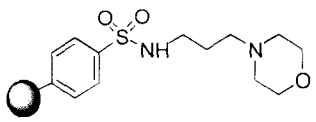
PS-DIEA:
Mesylate Formation



Base	Equiv	ROH M	Conv	Yield
TEA	2	0.5	100%	
PS-DIEA	3	0.4	100%	95%
P-Morpholine	3	0.3	30%	

- *PS-DIEA afforded high purity mesylate under analogous conditions to the solution phase reaction. (Gooding,* et.al. *Synth Commun* ***1995****, 25, 1155)*

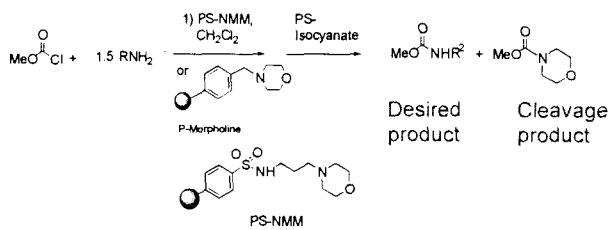
Tertiary Amine Bases: Sulfonamide-Linked Bases



PS-NMM

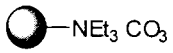
- PS-NMM is a bound non-benzylic analogue of N-methylmorpholine
- Stability studies with methyl chloroformate showed no cleavage under reaction conditions that afford 70% cleavage of a benzylic morpholine resin.

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



Resin	RNH_2	% Yield	% Desired Product	% Cleavage Product
PS-NMM	$BnNH_2$	99.3	100	0
P-Morpholine	$BnNH_2$	76.5	95.8	4.2
PS-NMM	Aniline	67	100	0
P-Morpholine	Aniline	67	83.6	16.4

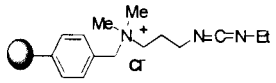
General Acid and Base Resins: MP-Carbonate



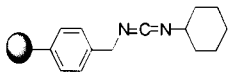
MP-Carbonate

- 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.
  - *J. Parlow* Tetrahedron Lett ***1996***, 37, *5257.*

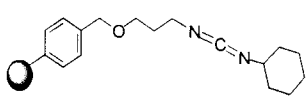
Carbodiimide Resins: Structures and Stability



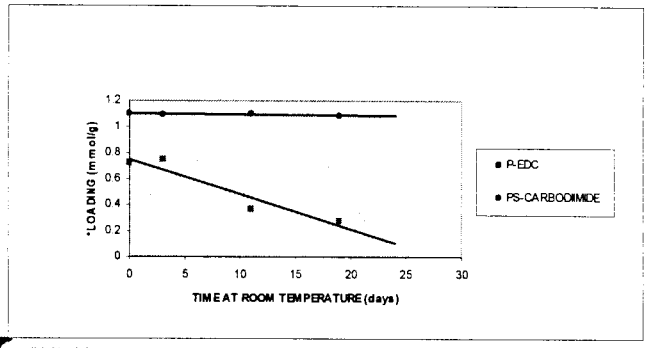
P-EDC

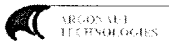


N-Cyclohexylcarbodiimide-N'-Me-PS



PS-Carbodiimide (Argonaut)





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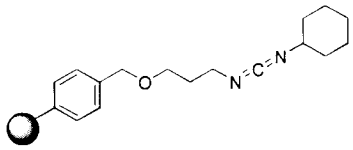
7/29/99

Comparison of Amide Coupling Efficiency

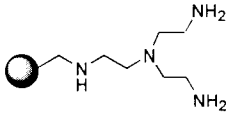
Entry	Resin	Acid	Amine	HPLC Purity[1]	GC Amine[2] Residue %	% Yield
1	PS-Carbodiimide	3,3-Diphenylpropionic	1,2,3,4-tetrahydroisoquinoline	90	0	86
2	Bn-N' Me Carbodiimide	3,3-Diphenylpropionic	1,2,3,4-tetrahydroisoquinoline	90	11	85
3	PS-EDC	3,3-Diphenylpropionic	1,2,3,4-tetrahydroisoquinoline	88	7-20	73
4	PS-Carbodiimide	3,3-Diphenylpropionic	3,3-diphenylpropylamine	100	0	86
5	Bn-N' Me Carbodiimide	3,3-Diphenylpropionic	3,3-diphenylpropylamine	100	10-25	77
6	PS-EDC	3,3-Diphenylpropionic	3,3-diphenylpropylamine	84	30	72
7	PS-Carbodiimide	3-Iodobenzoic acid	1,2,3,4-tetrahydroisoquinoline	98	0	88
8	Bn-N' Me Carbodiimide	3-Iodobenzoic acid	1,2,3,4-tetrahydroisoquinoline	96	18	75
9	PS-EDC	3-Iodobenzoic acid	1,2,3,4-tetrahydroisoquinoline	97	10	73
10	PS-Carbodiimide	Boc-Phe	3,5-dimethylaniline	100	0	89
11	Bn-N' Me Carbodiimide	Boc-Phe	3,5-dimethylaniline	98	0	83
12	PS-EDC	Boc-Phe	3,5-dimethylaniline	96	0	76

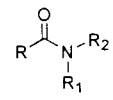
- In general, couplings with PS-Carbodiimide lead to full amine consumption

PS-Carbodiimide Couplings using added HOBt



1. RCO_2H, CH_2Cl_2 or DMF, HOBT
2. R_1R_2NH
3.



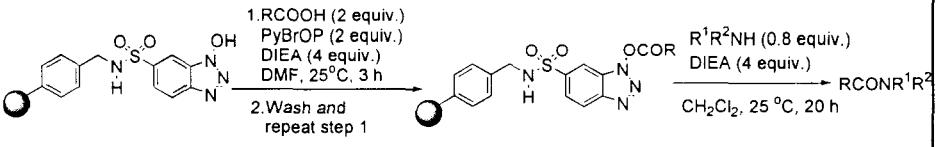


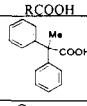
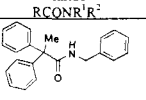
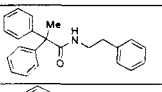
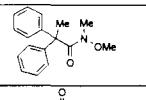
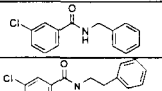
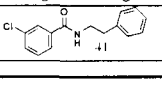
Acid	Amine	% Yield (Isolated)	HPLC Purity	GC Amine %
3,3-Diphenylpropionic	1,2,3,4-tetrahydroisoquinoline	88	85	0
3,3-Diphenylpropionic	Benzylamine	92	85	0
3-Iodobenzoic acid	1,2,3,4-tetrahydroisoquinoline	96	85	0
3-Iodobenzoic acid	Benzylamine	94	98	0

- HOBt scavenged with PS-Trisamine resin

cf. Weidner et. al. Tetrahedron Lett. ***1999****, 40, 239.*

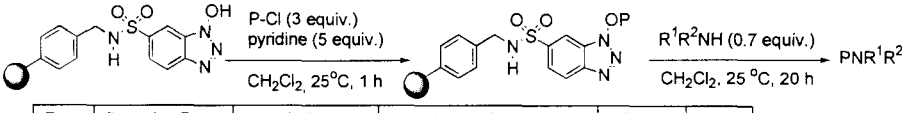
"Catch and Release" Synthesis of Amides Using PS-HOBt

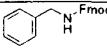
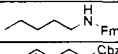
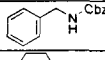
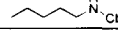


Entry	Acid RCOOH	Amine R^1R^2NH	Amide $RCONR^1R^2$	Yield	GC Purity
1				100% (1st cycle) 100 % (2nd cycle)	96% 100%
2				100%	99%
3				51%	87%
4				89%	95%
				82%	98%

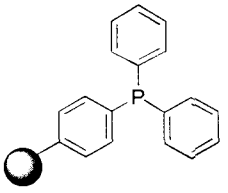
- *Pop* et. al. J. Org. Chem ***1997***, 62, *2594.*
- *Resin is recycleable*

PS-HOBt: Protecting Group Transfer



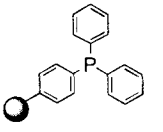
Entry	Protecting Group P-Cl	Amine R^1R^2NH	Protected Amine PNR^1R^2	Yield	HPLC Purity
1	Fmoc-Cl			77% (1st cycle) 100% (2nd cycle)	93% 100%
2	Fmoc-Cl			75%	100%
3	Fmoc-Cl			76%	100%
4	Cbz-Cl			87 %	97%
5	Cbz-Cl			42%	95%
6	Cbz-Cl			70%	95%

PS-Triphenylphosphine resin



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

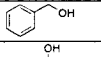
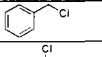
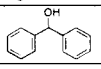
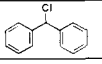
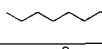
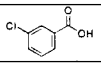
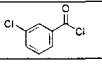
Chlorination of Alcohols and Acids using PS-Triphenylphosphine



(2 equiv.)

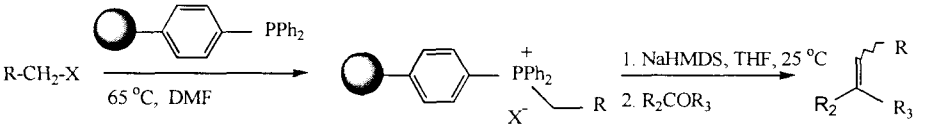
ROH or RCOOH → RCl or RCOCl

CCl_4, 80 °C

Entry	ROH or RCOOH	RCl or RCOCl	Yield	GC Purity
1			100 %	98 %
2			98 %	95 %
3			100 %	100 %
4			73 %	98 %

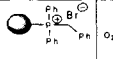
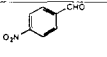
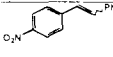
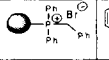
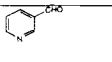
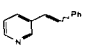
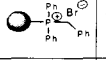
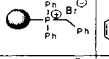
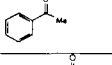
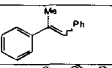
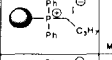
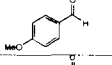
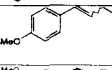
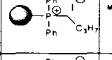
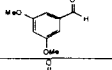
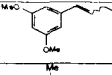
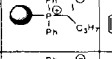
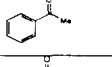
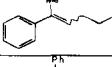
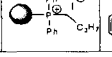
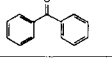
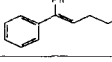
- cf. *Relles, H. M.; Schluenz, R. W.* J. Am. Chem. Soc. ***1974***, 96, *6469. Regen, S. L.; Lee, D. P.* J. Org. Chem. ***1975***, 40, *1669. Landi, J. J. Jr.; Brinkman, H. R.* Synthesis ***1992***, *1093.*

Wittig Reaction using PS-Triphenylphosphine

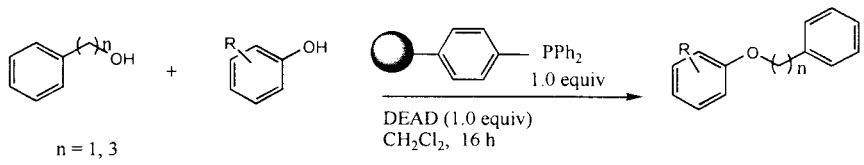


- cf. *Bernard, M.; Ford, W.T.* J. Org. Chem. ***1983***, 48, *326; Bolli, M. H.; Ley, S. V.* J. Chem. Soc., Perkin Trans. 1. ***1998***, 15, *2243.*
- Wittig reactions using a commercial higher crosslinked polymer-bound Triphenylphosphine (2 % DVB), led to recovery of starting materials.

Results of Representative Wittig Reactions

Entry	Wittig Reagent	Carbonyl compound	Olefin	Isolated yield (%) (cis:trans)	GC Purity
1				98 % (3:1)	96 %
2				81 % (5:1)	95 %
3				96 % (1:1)	81 %
4				88 % (2:1)	87 %
5				94 % (2:3)	91 %
6				87 % (1:3)	98 %
7				88 % (2:1)	94 %
8				82 %	99 %

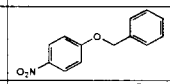
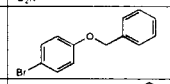
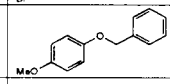
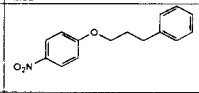
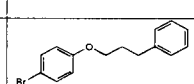
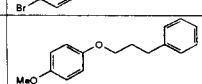
Mitsunobu Reaction using PS-Triphenylphosphine



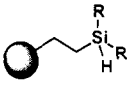
n = 1, 3

- *After the reaction, resin was filtered and washed with CH_2Cl_2*
- *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*
- cf. *Tunoori, A. R.; Dutta, D.; Georg, G. I.* Tetrahedron Lett. ***1998***, 39, *8951.*

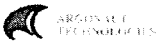
Results of Mitsunobu reactions

Entry	Alcohol	Phenol	Aryl ether	% Yield (isolated)	GC Purity
1				79	98 %
2				80	92 %
3				88	98 %
4				62	100 %
5				68	96 %
6				75	100 %

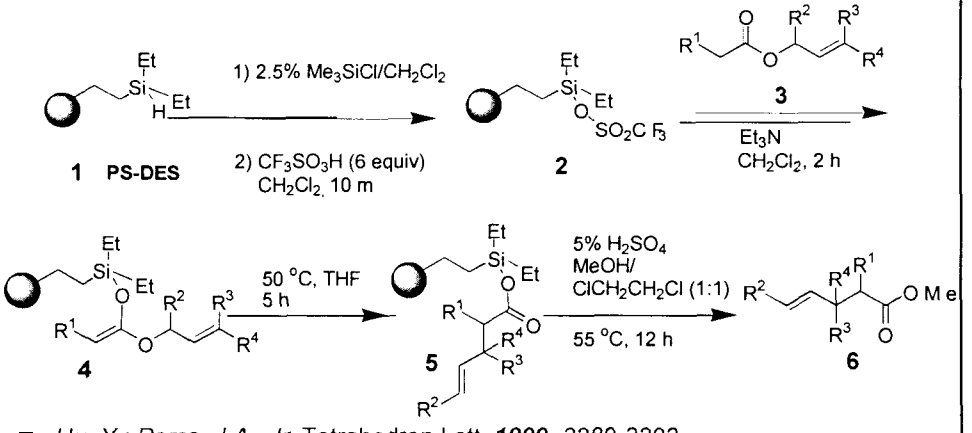
Trialkylsilane Resins



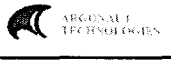
- ***Advantages of Polymer-Supported Trialkylsilanes with Pendant Si-H Functionality***
  - Stability to moisture providing shelf-storable silane resins
  - Potential for direct attachment of various functional groups (e.g. alcohol, carbonyl, aromatic, or unsaturated derivatives) without prior transformation 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

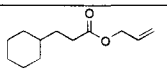
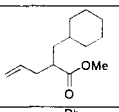
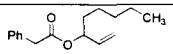
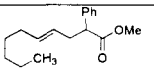
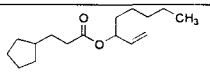
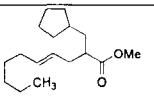
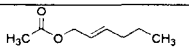
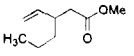


- *Hu, Y.; Porco, J.A., Jr.* Tetrahedron Lett. ***1999***, *3289-3292*
- *Claisen rearrangment monitored by IR microscopy (1710-1720 cm^{-1} for silyl esters)*



Solid-supported Ireland-Claisen Rearrangement:

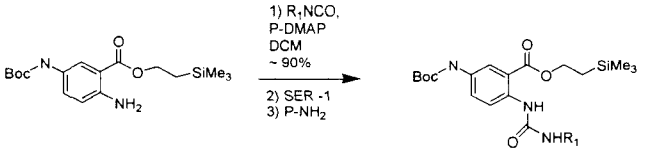
- *Quest 210 provides convenient and necessary inert environment for PS-DES drying (TMS-Cl) and conversion to triflate*

Entry	Allylic Ester (3)	Product (6)	Yield (%)	GC Purity (%)
1			58	92
2			56	95
3			52	97
4			0	NA

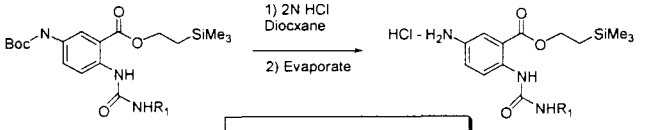
Multi-Step Reaction Sequences Utilizing Quest and PASP

- 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: Benzoxaxinones



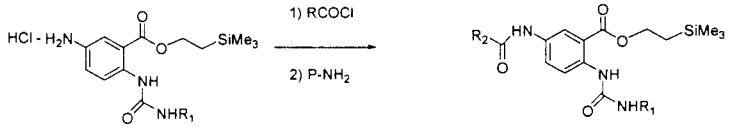
Bank 1: Urea formation, Add SER, Add Scavenger resin
Cannulate to Bank 2
Bank 2: Concentrate



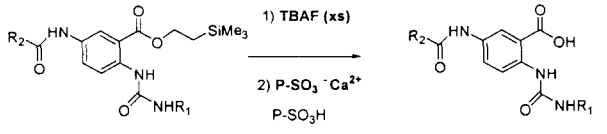
Bank 2: DeBoc, concentrate

Flynn D.L. *et al. Med Chem Res* **1998**, 8, 219-243

Multi-Step Reaction Sequences Utilizing Quest and PASP: Benzoxaxinones



Bank 2: Amide Formation, Acid Chloride Scavenging
Cannulate to Bank 1A
Bank 1A:Concentrate



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

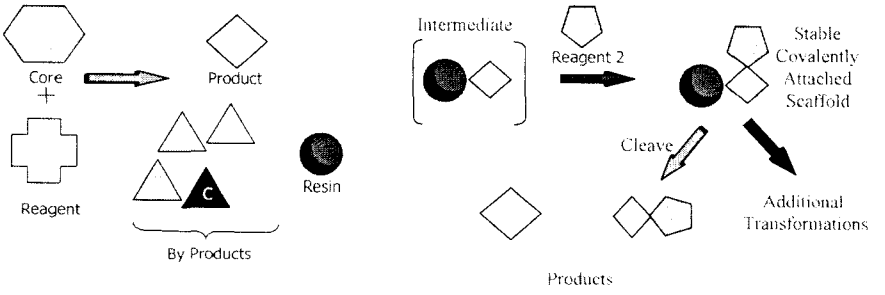
Multi-Step Reaction Sequences Utilizing Quest and PASP: Benzoxaxinones

Bank 2A: Benzoxazinone cyclization
Filter to vials
Concentrate

"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

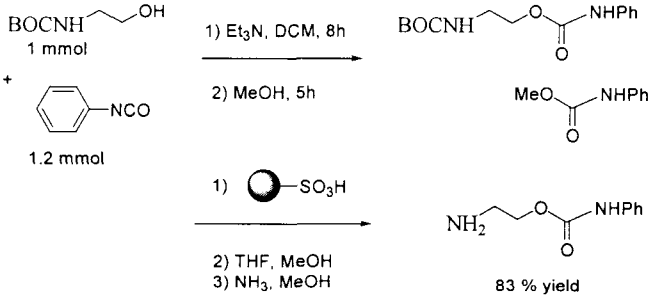


"Catch and Release" resins: a subset of polymer bound reagents

- "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

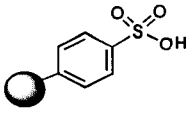
- Sulfonic Acid Resins can be used to bind amines and basic heterocycles
- Release performed with 2 M NH_3/MeOH or 2 M triethylamine/MeOH



Resin concomitantly removed BOC and purified product amine

Liu, Y.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*,

General Acid and Base Resins: MP-TsOH



MP-TsOH

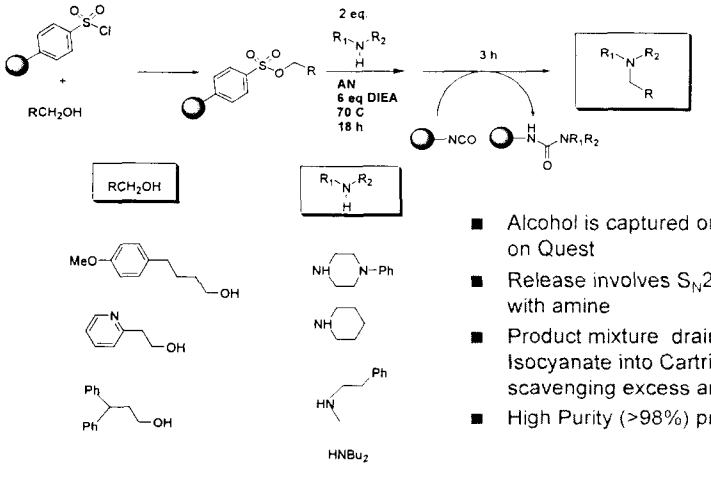
- *Resin-bound toluenesulfonic acid equivalent*
  - *"Clean" Amberlyst A-15 (high purity, low leachables)*
  - *Loading: 1.4 mmol/g*
- *Surface functionalized macroporous resin*
  - *Fast Kinetics*
- *Useful for Amine "Catch and Release" Purification (ion exchange)*
  - *high loading, low particulate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

"Catch and Release": Functional Resins

- *Synthetic Transformations Utilizing "Catch and Release":*

Resin Functionality	Substrate	"Release"	Product	Reference
TsCl	Alchohol	2° amine	3° amine	
$TsNHNH_2$	Carbonyl	Cyclization	Thiadiazole	
PPh_3	Alkyl Bromide	Carbonyl (Wittig)	Olefin	
TBD, OH^-	Phenol	Alkyl Halide	Ethers	
Active Esters	Carboxylic Acids	Amines	Amides	
DMAP	Acid Chloride Sulfonyl Chloride	Amines	Amides Sulfonamides	

"Catch and Release": Tertiary Amine Synthesis via Bound Tosylate

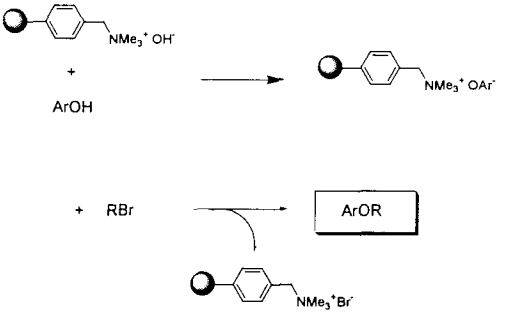


- Alcohol is captured on PS-TsCl Resin on Quest
- Release involves S_N2 displacement with amine
- Product mixture drained into PS-Isocyanate into Cartridges for scavenging excess amine
- High Purity (>98%) products obtained

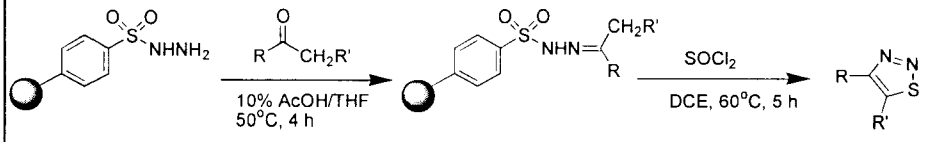
ARGONAUT TECHNOLOGIES

"Catch and Release": Ether Synthesis

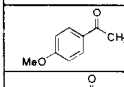
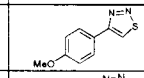
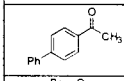
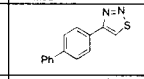
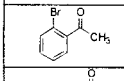
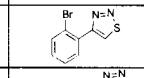
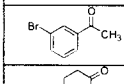
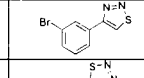
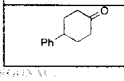
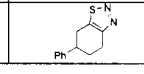
- *Phenols and hydroxyheterocycles caught on a Anion exchange resin*
- *Used in Williamson ether synthesis*
  - Parlow J.J. *Tetrahedron Lett.* **1996**, *37*, 5257.



"Catch and Release" Synthesis of 1,2,3-Thiadiazoles

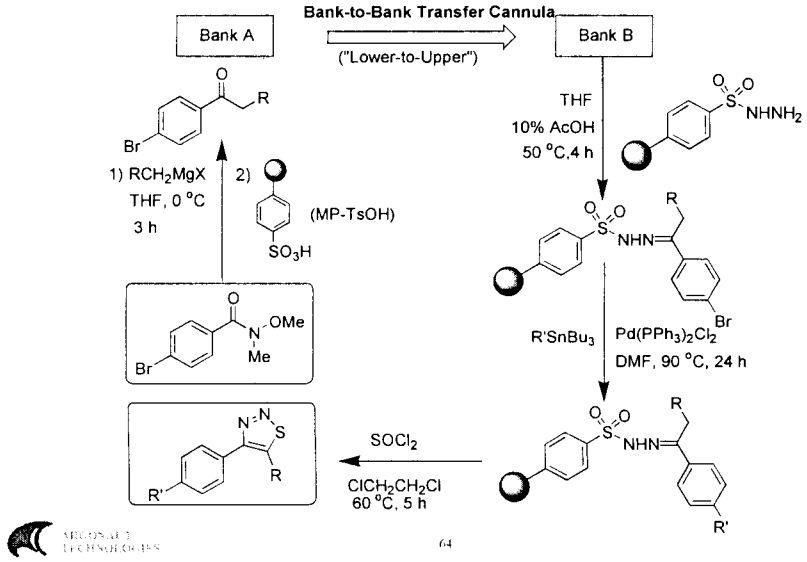


PS-Ts-$NHNH_2$

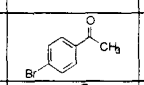
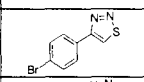
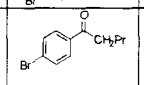
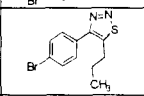
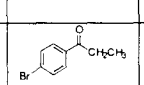
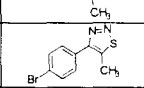
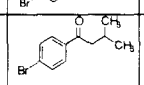
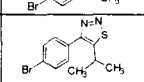
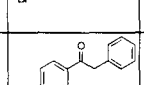
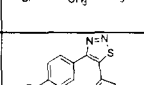
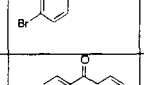
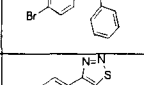
Ketone	Thiadiazole	Yield (%)	GC Purity (Area %)
		100	99
		95	97
		100	98
		100	94
		94	98

- *Hu, Y.; Baudart, S.; Porco, J.A., Jr.* J. Org. Chem. ***1999***, 64, *1049.*
- *Workup reactions using SLE cartridges impregnated with aqueous sodium carbonate*

Multistep Synthesis of 1,2,3-Thiadiazoles: "Catch and Release"



Results of 1,2,3-Thiadiazole Synthesis Employing "Catch and Release"

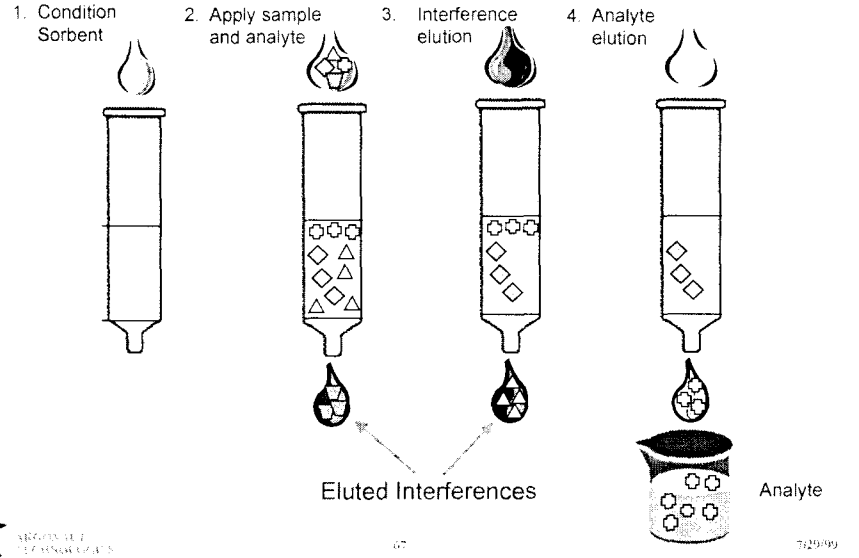
Entry	Ketone	Thiadiazole	Yield (%)	GC Purity (%)
1			98	100
2			82	94
3			77	97
4			59	97
5			67	98
6			48	71

- 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



Solid Phase Extraction Media: Examples

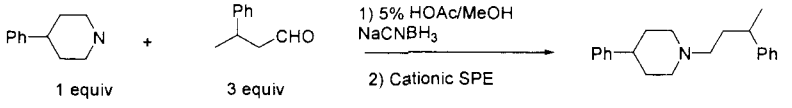
- *Common SPE Media used in Organic Synthesis:*

Type	Media	Loading (mmole/g)	Application
Normal Phase	Silica Alumina Fluorisil		Absorb polar species "plug chromatography"
Reverse Phase	C-18		Absorb nonpolar species
Cation Exchange	Silica-Ar-SO_3H (SCX)	0.6-1.0	-Absorb basic impurities -"catch-release" amines, basic heterocycles
Anion Exchange	Silica-$(CH_2)_3NR_3^+X^-$ (SAX)	0.7	-Absorb acidic species

Synthetic Examples with SPE

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

•Siegel M. et. al. *Tetrahedron Lett* **1997**, *38*, 3357

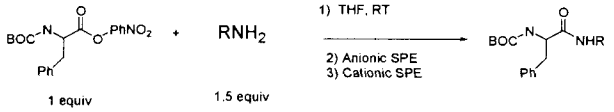


1 equiv 3 equiv

SPE:
1. Precondition methanol
2. Apply sample: 0.5 mL, 0.124 mmole amine, 500mg SCX (0.6mmole/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 xs amine
    - Lawrence, R. M. *et al Synthesis* **1997** , 553.



1 equiv 1.5 equiv

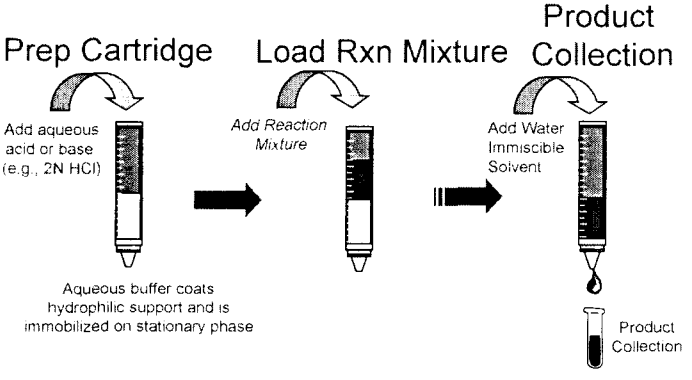
Anionic SPE:
1.Condition KOH(aq)/ MeOH, MeOH, DCM
2. Apply sample: 1 mL, 0.2 mmole amine, 1g SAX (0.7 mmole/g)
3. Rinse 1 mL THF, 2 mL DCM
Cationic SPE:
1. Condition SCX with DCM
2. Pass effleunt from SAX-SPE through 1 g SCX (0.6mmole/g)
3. Rinse with 2 mL DCM, collect

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

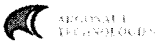
*Johnson, C.R., *et al.*, *Tetrahedron*, **1998**, *54*, 4097

Parallel Solid Supported Liquid Extraction (SLE)



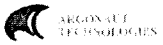
Add Reaction Mixture to Column and Gravity Elute Product with Water Immiscible Solvent

Compound Purification using Parallel Flash Chromatography

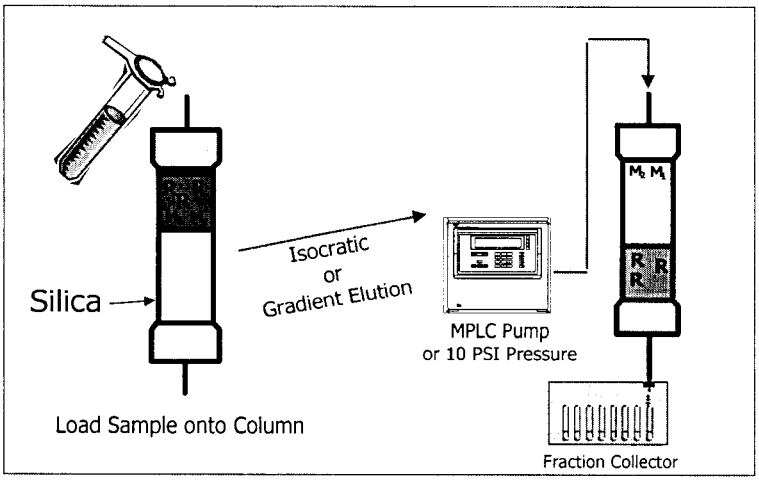


Medicinal Chemistry Bottleneck, Work Up and Purification!

- *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*



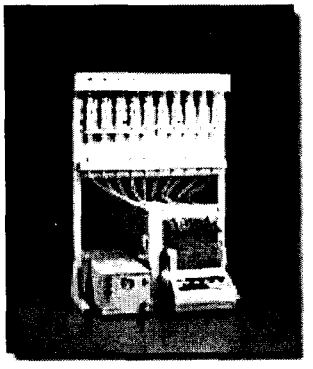
Flash Chromatography



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*

ARGONAUT TECHNOLOGIES

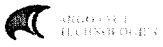
Evaluation of Isco Si1000s

- *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*

ARGONAUT TECHNOLOGIES

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

Mixture II:		Delta Rf	Wt Ratio
	1. 2-Bromo-1-indanol (Rf** = 0.89)		2
	2. 2-Indanol (Rf** = 0.68)	0.21	2
	3. Oxindole (Rf** = 0.49)	0.19	1

** *Rf values obtained from Silica/Hexanes:EtOAc 1:1*

Run #	Sample Wt	Loading Method	Compound	Fraction # 7 8 9 10 11 12 13 14 15 16 17 18 19 20
4	75 mg	Liquid 1.5 mL EtOAc: Hex. 1:1	1 2 3	
5	75 mg	Liquid 1.5 mL EtOAc: Hex. 1:1	1 2 3	
6	75 mg	Liquid 1.5 mL EtOAc: Hex. 1:1	1 2 3	
7	75 mg (1 mL THF soln)	Quest Transfer 3.0 g Silica	1 2 3	
8	75 mg (1 mL THF soln)	Quest Transfer 3.0 g Silica	1 2 3	
9	75 mg (1 mL THF soln)	Quest Transfer 3.0 g Silica	1 2 3	

Condition: Flow rate ~ 9 mL/ min
Gradient: 0 to 2 min: 0% EtOAc; 2 to 15 min: 0 to 100% EtOAc; 15 to 20 min: 100% EtOAc

* *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:		Delta Rf	Wt Ratio
	1. Ethyl-4-bromobenzoate (Rf* = 0.86)		1
	2. Ethyl-N-dimethylaminobenzoate (Rf* = 0.74)	0.12	1
	3. Methyl-4-hydroxybenzoate (Rf* = 0.57)	0.17	1

** Rf values obtained from Silica/Hexanes:EtOAc 2:1*

Run#	Sample Wt.	Loading Method	Compound	Fraction # 7 8 9 10 11 12 13 14 15 16 17 18 19 20
1	50 mg (1 mL soln)	Quest Transfer	1	
		3.0 g Silica	2	
			3	
2	100 mg (2 mL soln)	Quest Transfer	1	
		3.0 g Silica	2	
			3	
3	150 mg (3 mL soln)	Quest Transfer*	1	
		3.0 g Silica	2	
			3	

Condition: Flow rate: ~ 10 mL/ min
Gradient: 0 to 2 min: 0% EtOAc; 2 to 15 min. 0 to 50% EtOAc; 15 to 20 min. 50% EtOAc
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

ARGONAUT TECHNOLOGIES

Separation of Compounds with High Rf and low ΔRf

Mixture III:		Delta Rf	Wt Ratio
	1. 4-Bromobiphenyl (Rf*** = 0.83)		1
	2. Phenanthrene (Rf*** = 0.74)	0.09	1

****Rf values obtained from Silica/Hexanes*

Run#	Sample Wt.	Loading Method	Compound	Fraction # 1 2 3 4 5 6
10	36 mg	Solid Rotavap	1	
			2	
11	110 mg	Liquid Hexanes	1	
			2	

Condition: Flow rate: ~12 mL/ min
Isocratic 100% hexanes

ARGONAUT TECHNOLOGIES

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*