



Integrating Microwave Synthesis with Emerging Chemical Technologies.

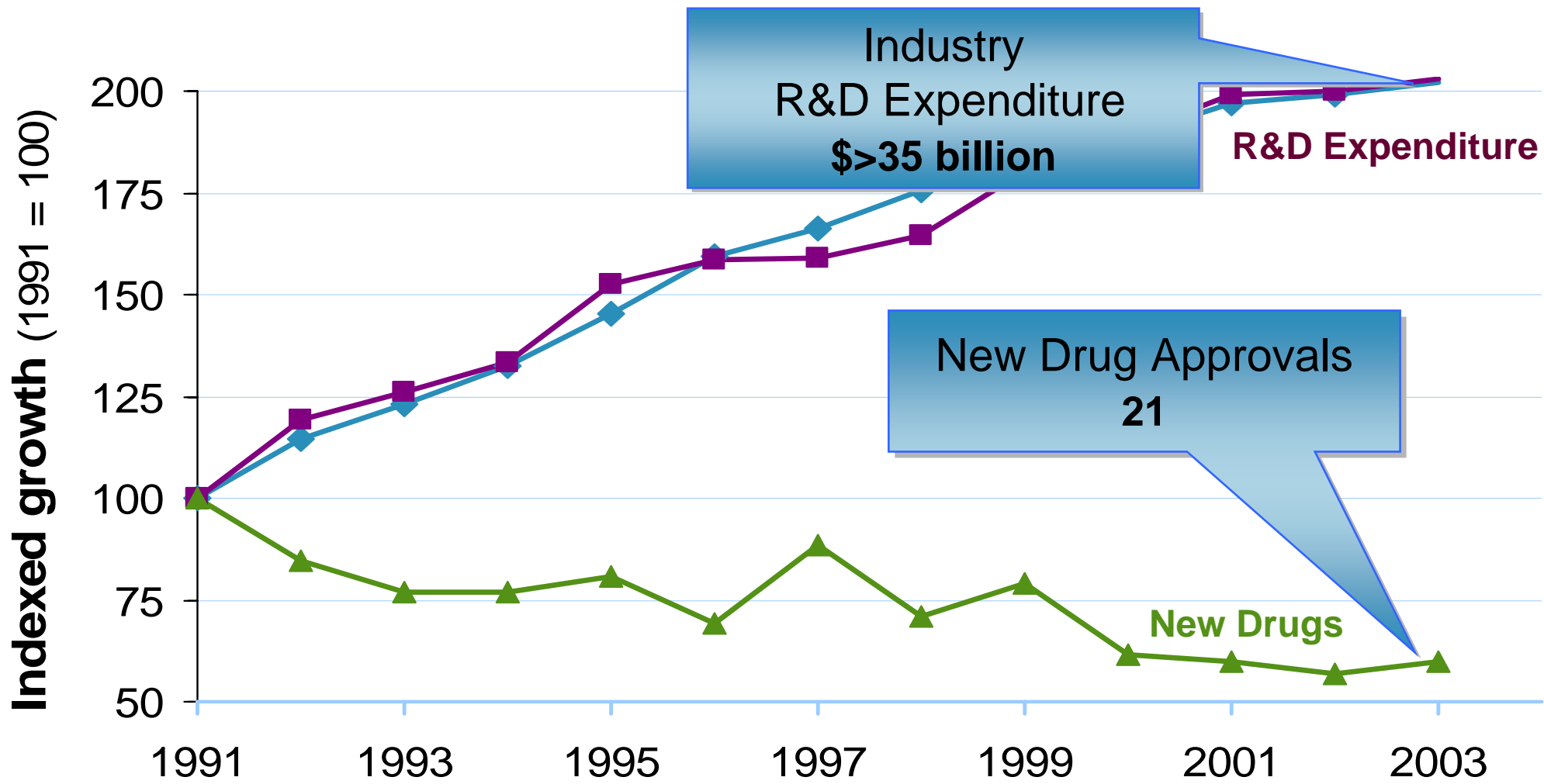
Biotage Summer Program, Richmond July 21-23

Bruce Clapham, Ph.D.

Hit To Lead Chemistry

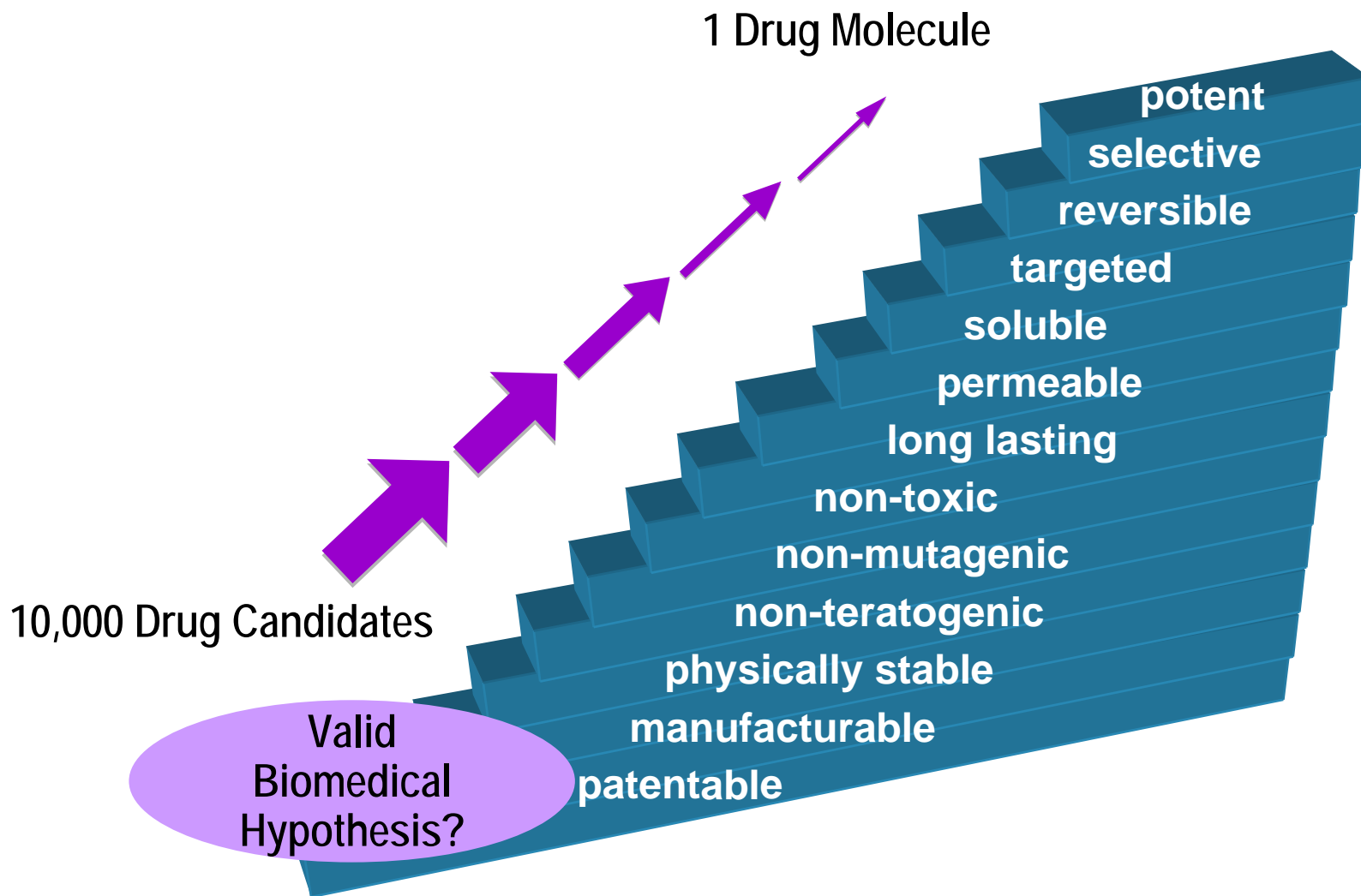
Global Pharmaceutical Research and Development

Rising Research Costs, Fewer Drugs



High-Throughput Organic Synthesis

Challenge of Drug Discovery: Finding a molecule that meets multiple criteria



High-Throughput Organic Synthesis

Goal of Abbott's HTOS Facility

A centralized, highly automated, state-of-the-art, parallel synthesis facility that enables the discovery of more highly optimized biological tools and drug candidates

Emphasis on preparing libraries of analogs designed to rapidly generate structure activity relationships (SAR) and accelerate lead development and optimization

Benefits for Abbott's Discovery Organization:

- More analogs = “more shots on goal”
- Libraries created more efficiently
- Project chemists focus on targets not amenable to parallel synthesis
- Quality and scope of SAR enhanced
- Libraries contribute to file enhancement

High-Throughput Organic Synthesis

Overview of HTOS Libraries

Library Characteristics

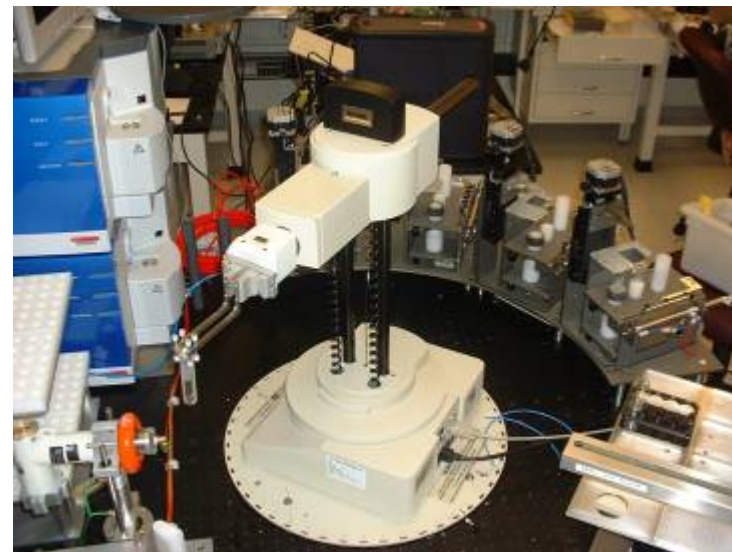
- Solution Phase
- Focused Chemical Space
- 24-96 Member Arrays
- 20-50 mg Scale
- Minimal Development
- High Purities and Yields
- Fully Characterized Products
- File Enhancement
- Hit to Lead
- Lead Optimization

Enabling Tools

- Mass Directed HPLC
- SFC
- Supported Reagents / Scavengers
- Microwave Synthesis
- Standardized Chemistry Protocols
- Multiple Component Reactions
- Fragment Based Screening
- H-Cube flow hydrogenation
- Automation
 - 4,000 analogs/FTE/year
 - Rapid Library Synthesis
 - Cost per Analog Decreased

High-Throughput Organic Synthesis

In our lab, microwave is not the bottleneck!



High-Throughput Organic Synthesis

So what is today's talk about?

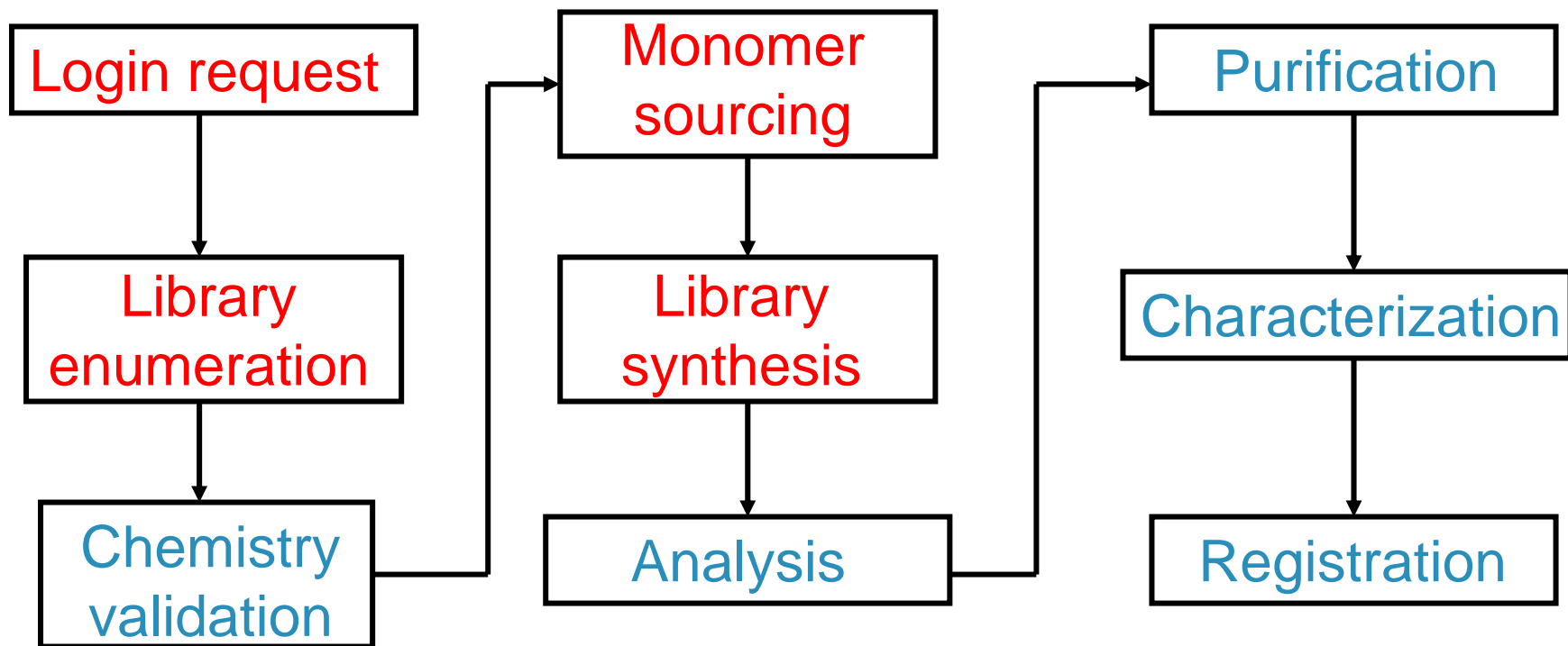
Hint: It's not OBAOS (Oil Bath Assisted....)

- *Improving efficiencies before samples reach the microwave:*
- Address issues with library login, enumeration
- Interface cheminformatics tool; synthesis “selected” compounds
- Provide chemists with standardized monomer sets
- Automated monomer storage, inventory control and re-stocking
- Seamless monomer ordering through LIMS
- Automated monomer dispersal to chemist

- *New technologies for sample processing after the microwave:*
- High-throughput hydrogenation reactions (Thales H-Cube)
- Preliminary investigations to sample drydown (Biotage V-10)

Simplified library production workflow:

Thermo Nautilus: Library information management system



High-Throughput Organic Synthesis

Web based library login portal (Client)

HTOS Library Login - Bruce Clapham - Microsoft Internet Explorer provided by Abbott Laboratories

File Edit View Favorites Tools Help

Address <http://abtap2071dv/abbotthtos/HTOS-WL-UI-LibraryLogin.asp> Go Links

User: claphbx

Add Library **Duplicate Library** **Multi-Step Reaction** **Submit Libraries**

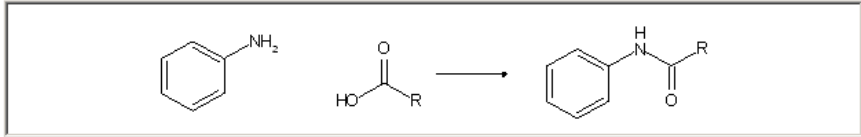
Acylation (1)

Library Purpose: Project: Chemistry Type:


Pharm Class:

Dispersals Information:

Dispersal	Type	Amount	Reaction comments:
<input type="text" value="HTS (mg)"/>	<input type="text" value="All"/>	<input type="text"/>	<input type="text"/>

Reaction Scheme: 

Reactants and Products:

	Reactant 1	ID	Ref #	Amt (mg)	Solub	Reactant 2	ID	Ref #	Amt (mg)
	CORE A	1				DIVERSITY B (acid)	2		
1		1							

Add Reactants
Delete ALL Reactants
(+) Add Row
(-) Delete Last Row
Collapse Rows
Expand Rows

Done Local intranet

Start Bruce Clapham - ... 2 Internet Ex... MAOS2007.ppt Nautilus - Produ... Understanding A... 1S1S/Draw 11:23 AM

High-Throughput Organic Synthesis

Monomer selection (Client)

HTOS Monomer Selection - Microsoft Internet Explorer provided by Abbott Laboratories

Browse Import File Export File Update Select All Unselect All

Available Monomers Selected Monomers Product Properties

Monomer Sets

- Acids
 - Aliphatic Acids 1 - (Rack 1)
 - Aliphatic Acids 2 - (Rack 14)
 - Benzoic Acids 1 - (Rack 2)
 - Benzoic Acids 2 - (Rack 15)
 - Heterocyclic Acids - (Rack 5)
 - Phenylacetic Acids - (Rack 3)
- Alcohols
 - Aliphatic Alcohols 1 - (Rack 26)
 - Aliphatic Alcohols 2 - (Rack 35)
 - Benzyl Alcohols - (Rack 29)
 - Heterocyclic Alcohols - (Rack 31)
 - Phenethyl Alcohols - (Rack 28)
 - Phenols 1 - (Rack 27)
 - Phenols 2 - (Rack 36)
- Aldehydes
 - Aliphatic Aldehydes - (Rack 6)
 - Aromatic Aldehydes 1 - (Rack 7)
 - Aromatic Aldehydes 2 - (Rack 16)
- Amines
 - Anilines 1 - (Rack 21)
 - Anilines 2 - (Rack 33)
 - Benzylamines - (Rack 22)
 - Benzylpiperazines - (Rack 44)
 - Heterocyclic Amines - (Rack 25)
 - Phenethylamines - (Rack 23)
 - Phenylpiperazines - (Rack 42)
 - Diarylamines - (Rack 43)

Monomers loaded. 48 available monomers; 3 selected

High-Throughput Organic Synthesis

Review selected monomers (Client)

Pipeline pilot
Interface
(Cheminformatics
Tool)

High-Throughput Organic Synthesis

Pipeline pilot interface (Client)

Product Properties Selection - Microsoft Internet Explorer provided by Abb...

Please select the properties to be calculated for your list of molecules.

- Select All

- Molecular Weight
- Polar Surface Area
- CLogP
- H-Bond Donor
- H-Bond Acceptor
- Number of Rotatable Bonds

Calculated properties of enumerated product (Client)

HTOS Monomer Selection - Microsoft Internet Explorer provided by Abbott Laboratories

Available Monomers | Selected Monomers | Product Properties

Press SPACEBAR or ENTER to activate and use this control

Product ID	LogP	MW	H_Acceptors	H_Donors	RotBonds	PSA
R01-P16	2.493	191.26948	1	1	3	29.1
R02-P23	2.493	222.242	2	1	2	52.89
R03-P06	2.359	240.30034	2	2	4	55.12
R03-P09	2.407	227.25852	2	2	3	49.33
R03-P42	2.417	255.26862	3	1	3	47.56
R05-P15	1.35	187.19795	2	2	2	57.78

48 available monomers; 16 selected

Version 1:
(Enumerated
products
not shown)

Version 2:
Enter desired property
Traffic light system;
Green = Pass
Red = Fail
Ranking system

High-Throughput Organic Synthesis

Standardized monomer sets

- Rapid Access to 1000's of Monomers and Reagents
- From Chemists Desktop Computer (minutes vs. days)
- Automatically Collect and Format Monomer Sets
- Automatically Generate SD File of Monomer Set
- Standardize vial type, and quantity (4mL vial, 0.6mmol)
- Automatically Re-order and Re-stock Monomers
- Reduce Monomer Cost (\$9-23 per monomer)
- Eliminate Monomer Weighing (1-2 hours, \$3 per monomer)
- Reduce Waste Disposal Cost / Associated Environmental Issues

High-Throughput Organic Synthesis

Monomers grouped by type, subtype:

In stock

- 288 Acids
- 240 Alcohols
- 96 Phenols
- 576 Amines
- 254 Boronic acids/esters
- 48 Aryl halides
- 48 Benzyl halides

On demand (<5 days)

- 144 Aldehydes
- 100 Acid chlorides
- 148 Isocyanates
- 122 Sulfonyl chlorides

Sourcing of monomers (HTOS group)

- Predominantly supplied by Aldrich Discovery CPR
 - All monomers validated for chemistry, long term availability
 - > 1500 individual monomers stored at Abbott, ~10 copies
 - All supplied in 4mL vial, 0.6 mmol quantity
 - Bar coded vial, septa caps
-
- “On Demand”- reactivities, available from Discovery CPR < 5 days
 - Custom monomer orders from Discovery CPR
 - Abbott LIMS interface with Aldrich for seamless ordering

How do we store and manage those 15,000 vials?

- Old sample repository room converted into monomer “I-Store”
- Monomer requests filled by Robot into 24 well Falcon racks
- Computer drives robot, records position of each monomer
- Computer keeps record of monomers in stock
- Currently we manually order monomer replacement when copies <3
- Moving towards an automated ordering system
- Currently 95% of monomers in stock, moving towards 100%

HTOS group LIMS-Monomer ordering

Library Review [Library Processing Inventory Reports]

H2749-1

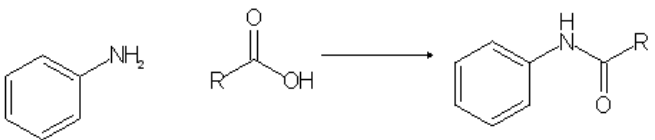
- Order Core
- Order Monomers
- View Orders

Update

Check NMR

Generate SD File

Add/Modify Monomers...



General | Reactants | Products



Submission Information

Submitter: Ethan Hoff | Project: GD099030

Acode Products

Order Monomers

Needs Review

Dispersals:  

Dispersal	Type	Amount (mg)
Project (mg)	All	

Comments

HTOS Comments

Purpose: File Enhancement

Reject Reason:

Pharm Class: ANALGESIC // ION CHANNEL // IMIDAZOLE

Library Information

Library Group: HTOS_3177 | Library Size: 6 | Avg. Yield: | Split From: | Step: |

Chemistry: Acylation | Prod. Run: 0 | Avg. Amt: | Comp From: |

Library Status

Library Received: 8/27/2007 3:12:44 PM

Test Run Completed: |

Production Run Completed: |

Test Run Scheduled: |

Production Run Scheduled: |

Target Completion Date: |


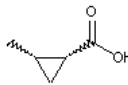
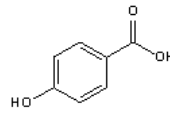
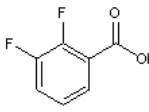
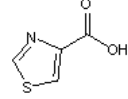
High-Throughput Organic Synthesis

I-store vendor (HTOS)

Reagent Request

File Units

Select All

A	Structure	Amount (mmol)
<input checked="" type="checkbox"/>	 R01-P01 Available	0.6
<input checked="" type="checkbox"/>	DIA  R14-P02 Available	0.6
<input checked="" type="checkbox"/>	 R02-P10 Available	0.6
<input checked="" type="checkbox"/>	 R15-P07 Available	0.6
<input checked="" type="checkbox"/>	 R05-P13 Available	0.6

Inventory Information

Inventory Provider: IStore Fill Not Available

Dropdown menu: Aldrich, IStore, DEV_Provider

Barcode	DEV_Provider	Units	Position
R01-P01	Available	0.6 mmol	1
R14-P02	Available	0.6 mmol	2
R02-P10	Available	0.6 mmol	3
R15-P07	Available	0.6 mmol	4
R05-P13	Available	0.6 mmol	5
R03-P16	Available	0.6 mmol	6

Order Reagents Cancel

High-Throughput Organic Synthesis

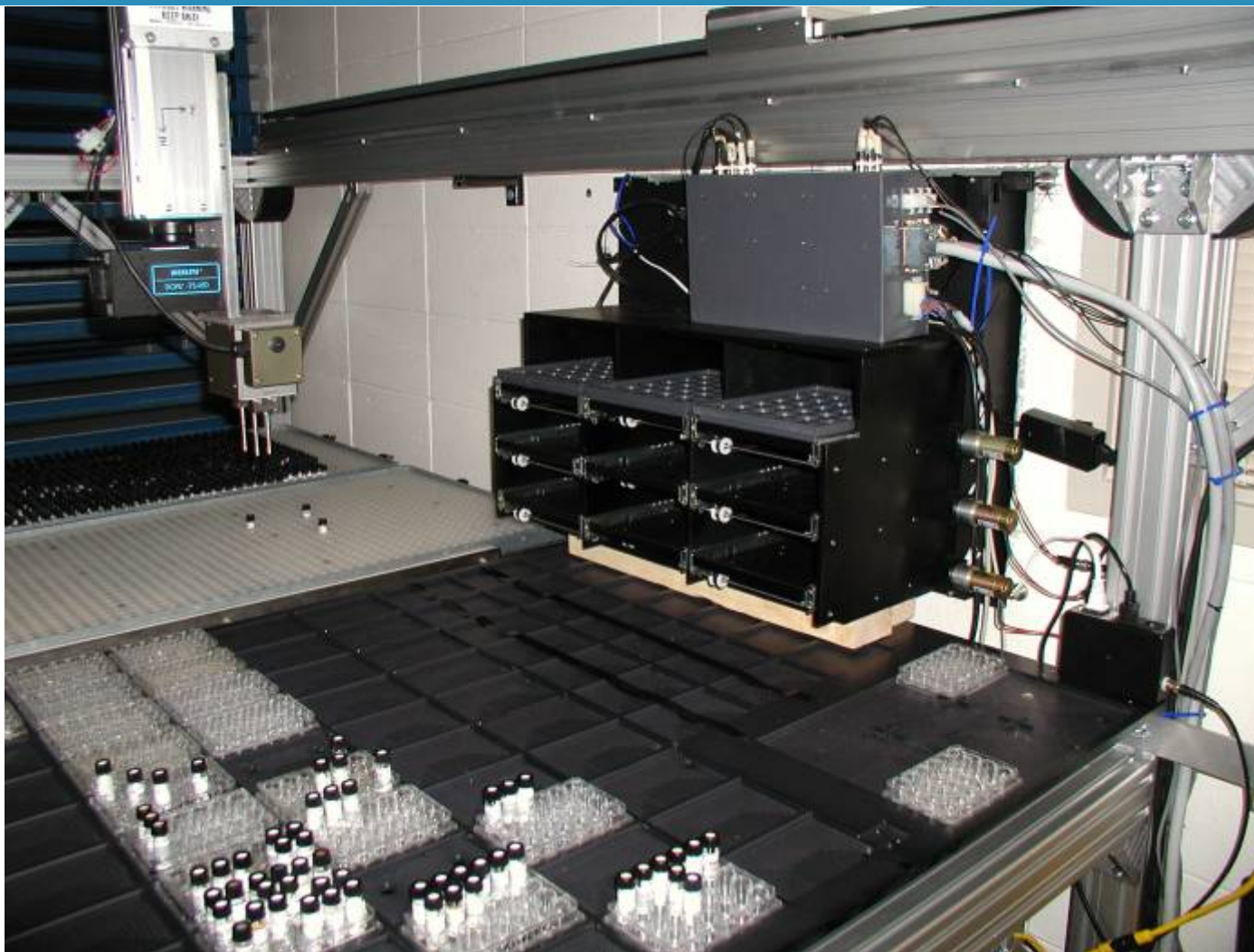
Sample repository converted to “I-Store”



1250 vials per tray
X 360 trays
450,000 capacity!

High-Throughput Organic Synthesis

Robot Deck: Moves vials to and from storage to Falcon rack



High-Throughput Organic Synthesis

I-Store (Shop window)



High-Throughput Organic Synthesis

Chemist receiving monomers



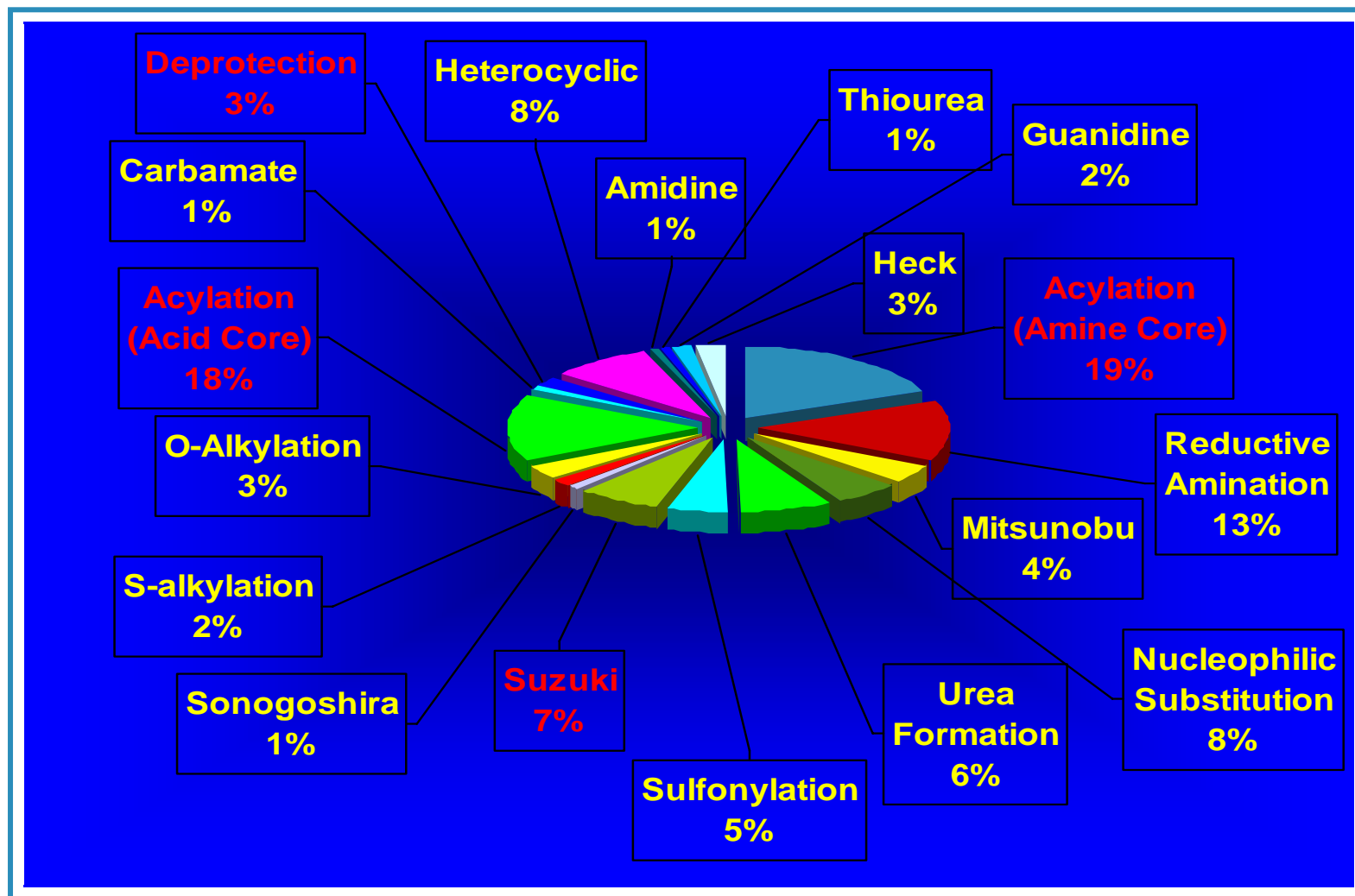
High-Throughput Organic Synthesis

Chemist receiving monomers



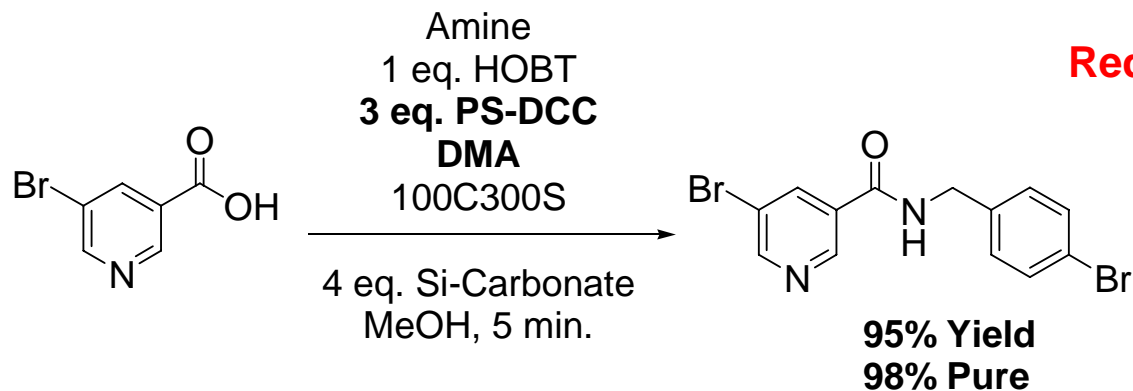
High-Throughput Organic Synthesis

HTOS Reaction Repertoire

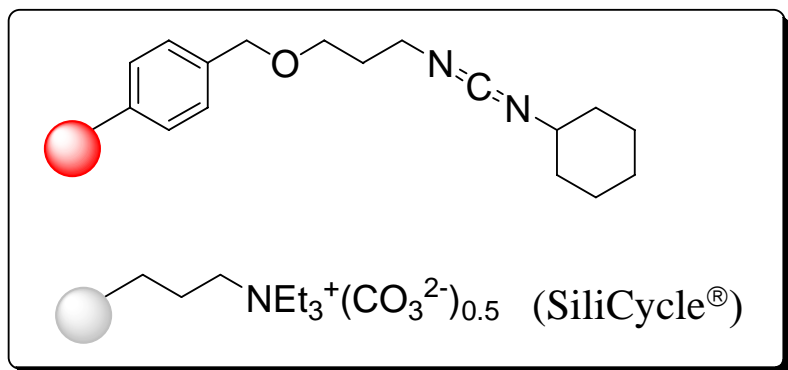


High-Throughput Organic Synthesis

Highly efficient microwave acylation procedure

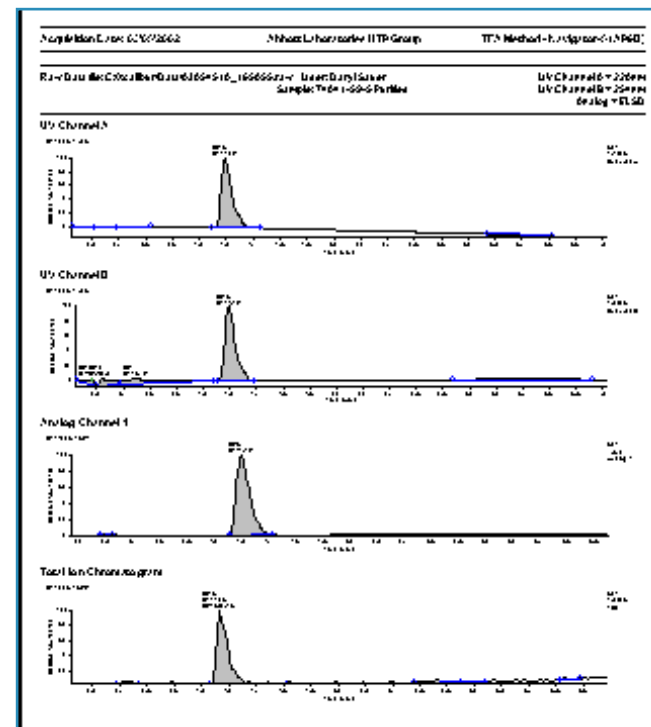


Reduces an 16 hour process to <15 minutes



Initial Microwave Experiments

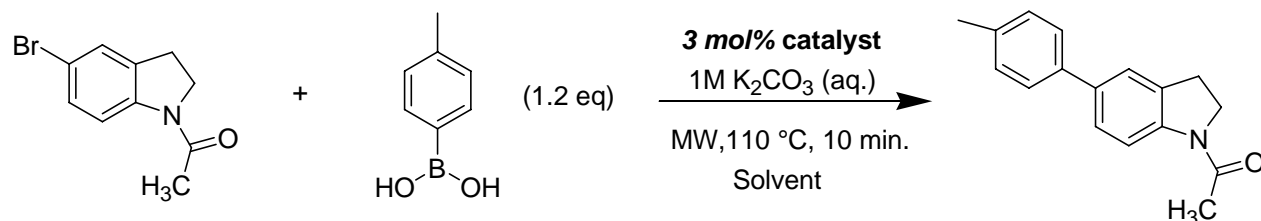
- HOBt adduct precluded use of DCM
- DCC not stable at 150C
- DMA derived by-products > 120C
- No by-products with NMP



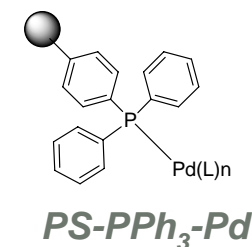
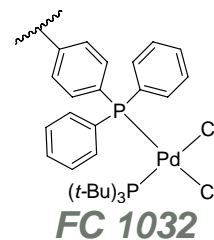
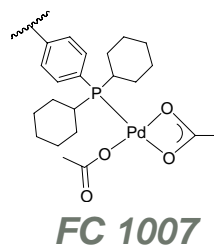
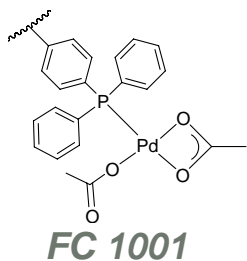
Org. Lett., **2003**, *5*, 4721-4724

High-Throughput Organic Synthesis

Highly efficient microwave Suzuki coupling

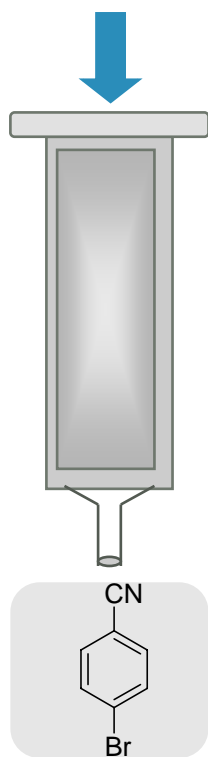
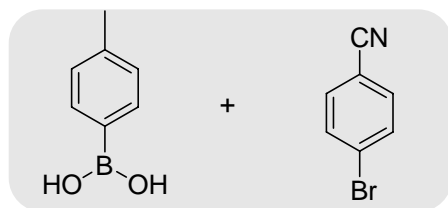


Entry	Catalyst	Solvent	Conversion
1	PS-PPh ₃ -Pd	DME/EtOH (1:1)	81%
2	FC1001	EtOH	97%
3	FC1007	EtOH	100%
4	FC 1032	EtOH	100%
5	PdCl ₂ (PPh ₃) ₂	DME/EtOH (1:1)	88%



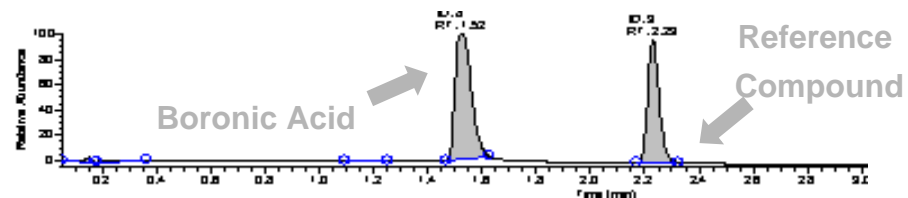
High-Throughput Organic Synthesis

Si-Carbonate — Effective Scavenger For Boronic Acids

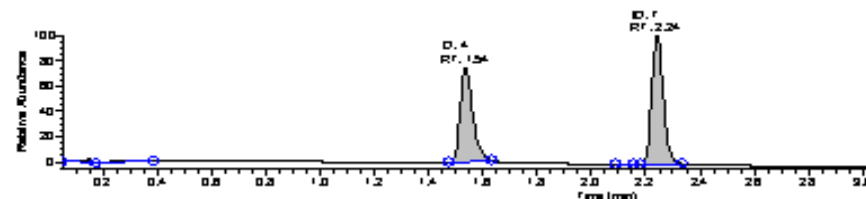


(Reference Compound)

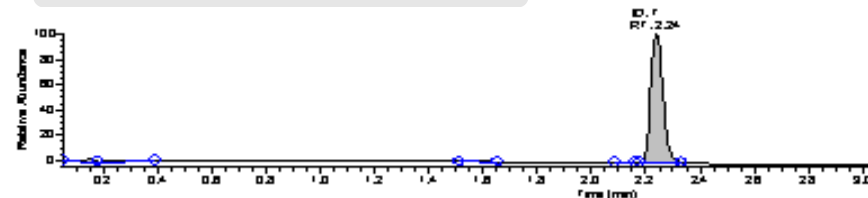
1 equiv. Si-Carbonate



3 equiv. Si-Carbonate

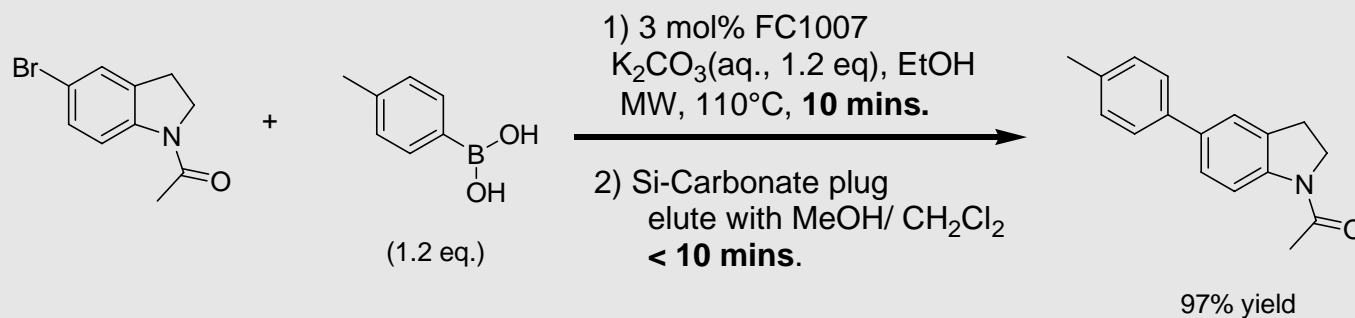


10 equiv. Si-Carbonate



High-Throughput Organic Synthesis

Vessel Rupture Due to Precipitated Pd Virtually Eliminated



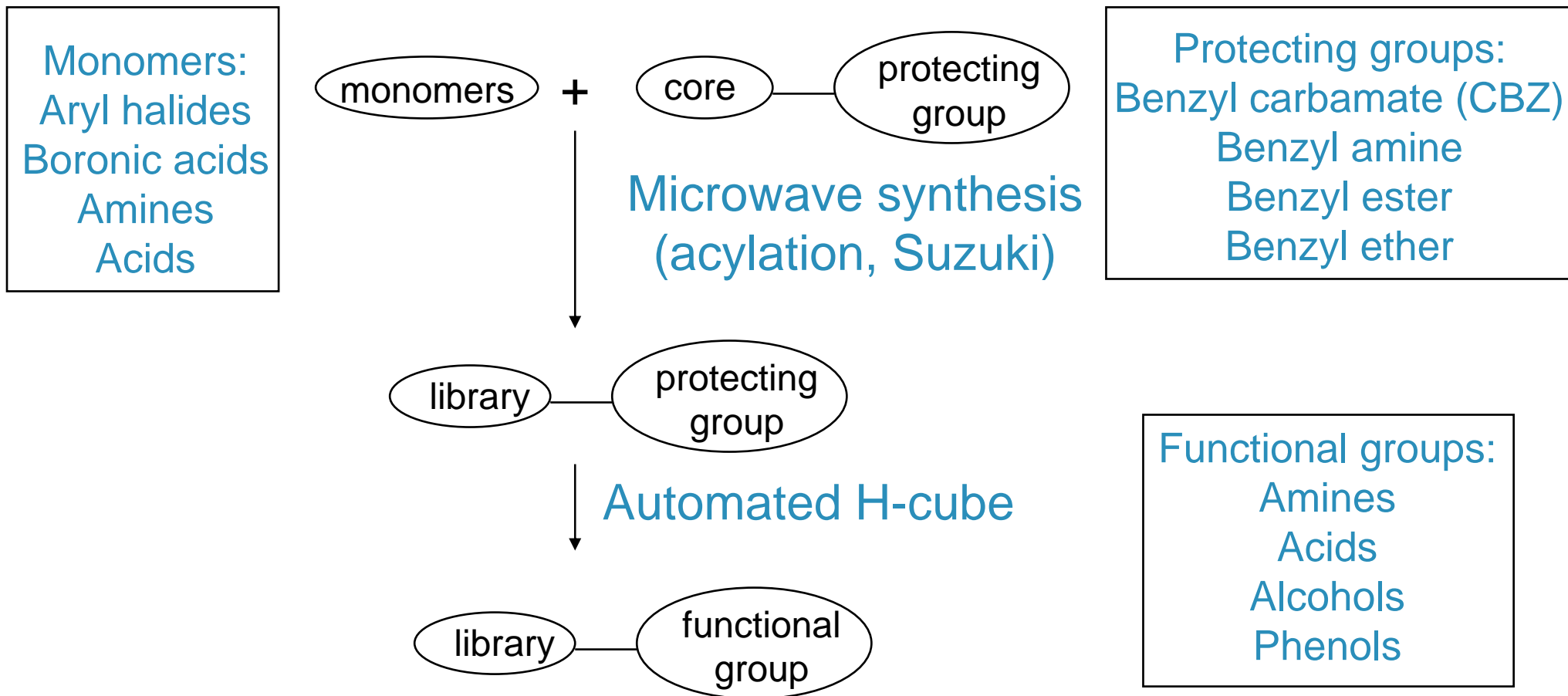
With FibreCat 1007



With $PdCl_2(PPh_3)_2$

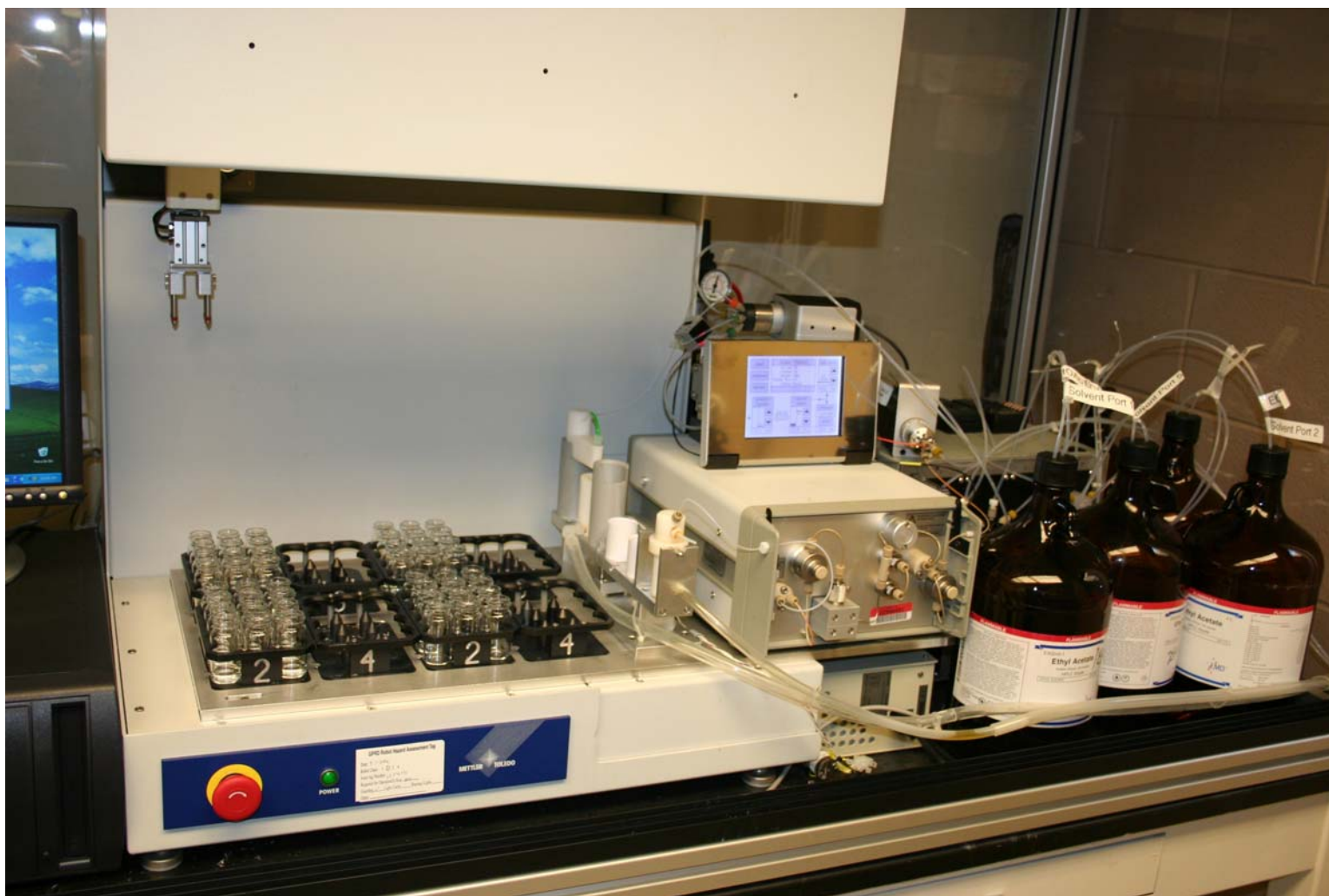
High-Throughput Organic Synthesis

Hydrogenation/Hydrogenolysis of microwave products



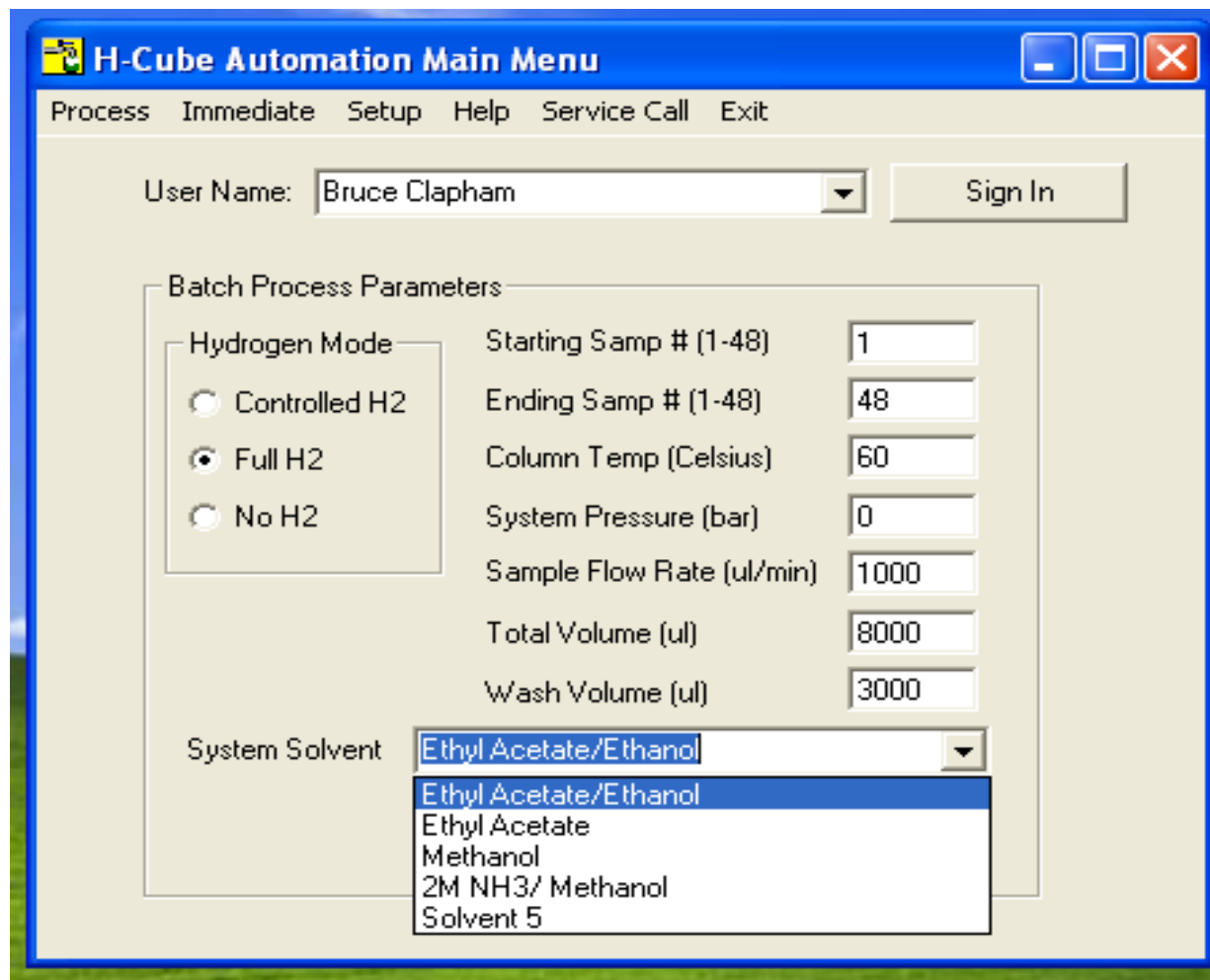
High-Throughput Organic Synthesis

Automated H-Cube platform



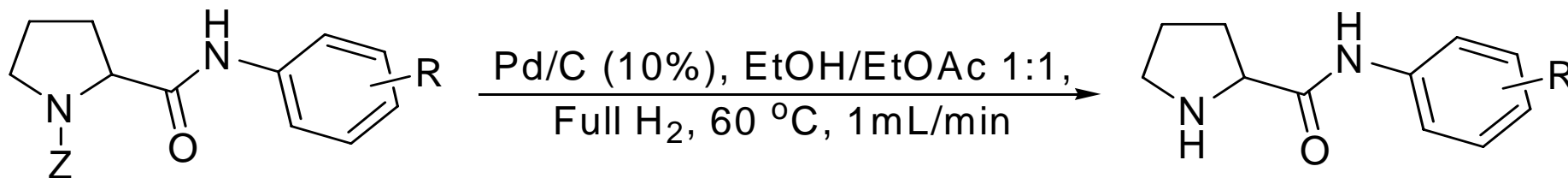
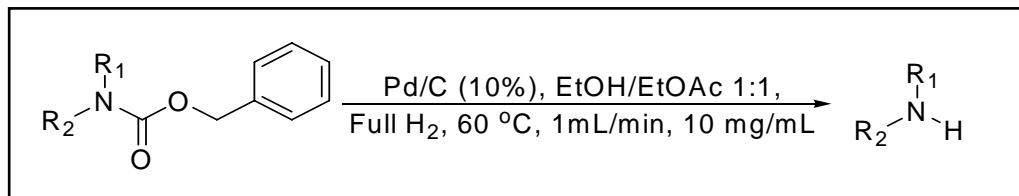
High-Throughput Organic Synthesis

PC interface operation modes



High-Throughput Organic Synthesis

CBZ deprotection:



35 Amides
(Purified by HPLC)

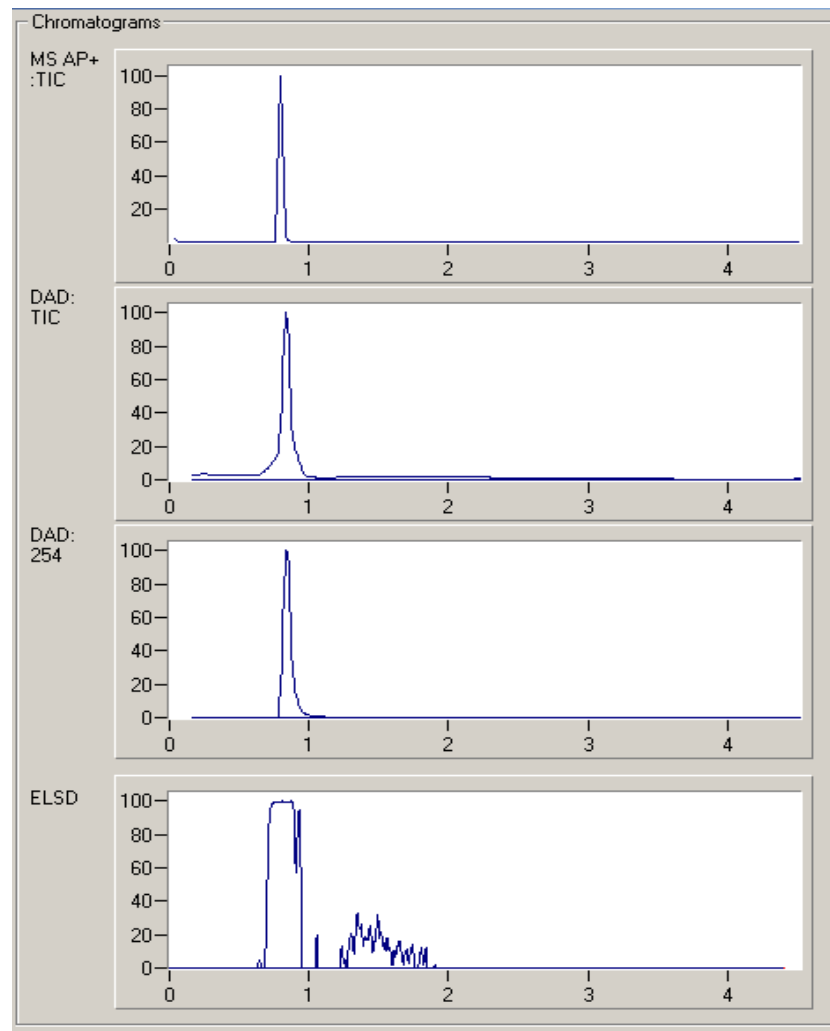
27 from 35 reactions worked

Most products >95% pure, 95% yield

Failures: dehalogenation of aryl halides

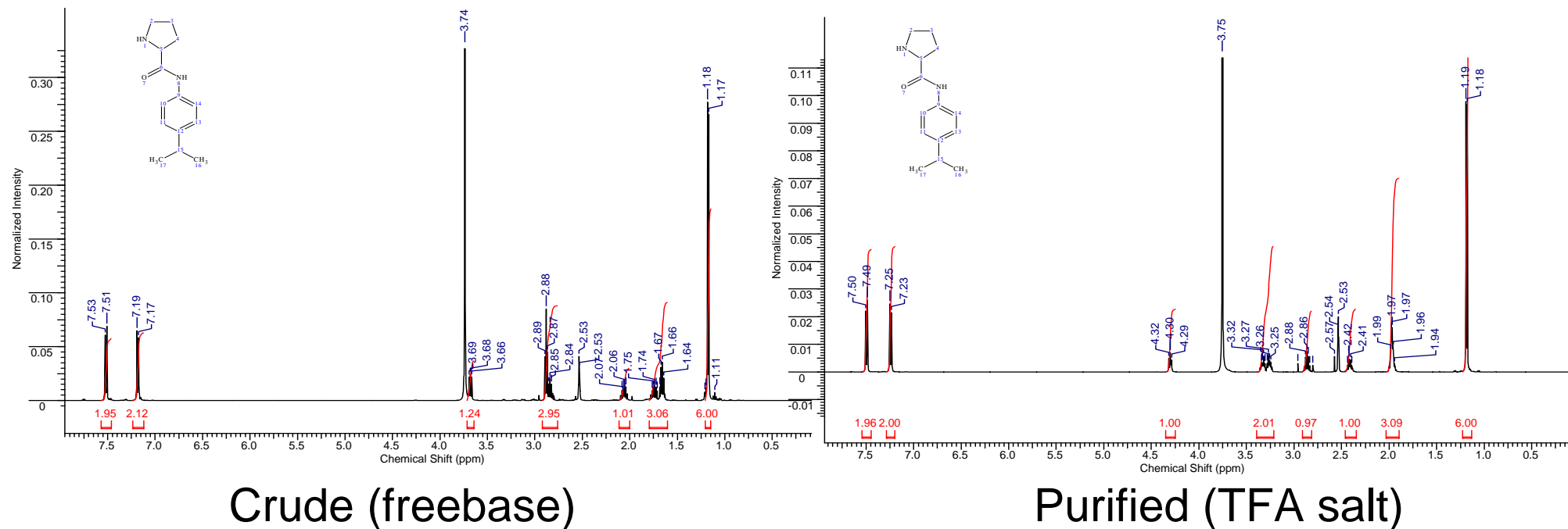
High-Throughput Organic Synthesis

LCMS of Crude CBZ-protected product



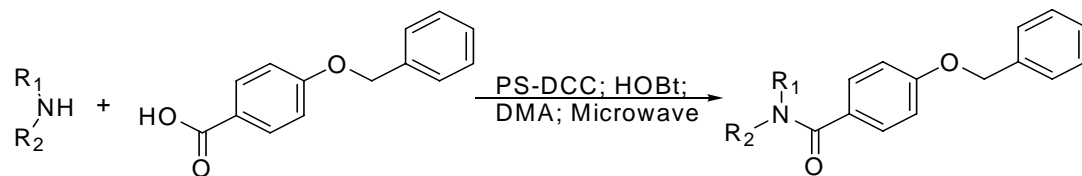
High-Throughput Organic Synthesis

NMR of Crude vs purified product



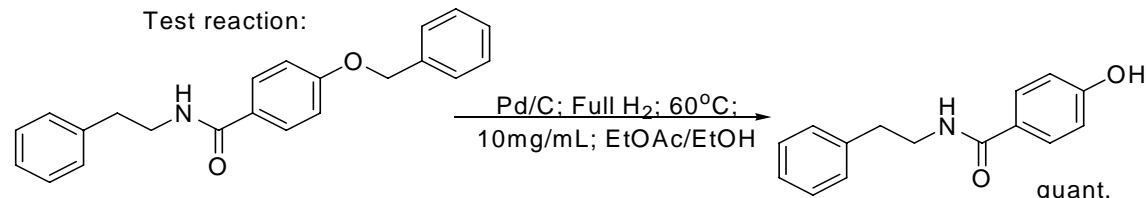
High-Throughput Organic Synthesis

Benzyl ether deprotections:

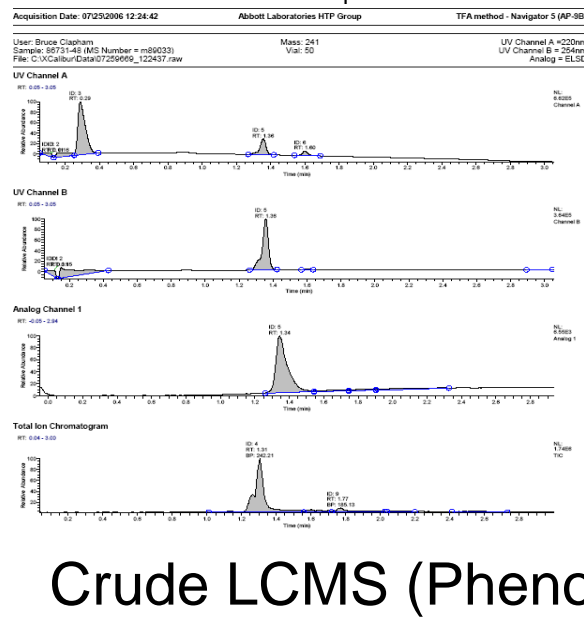
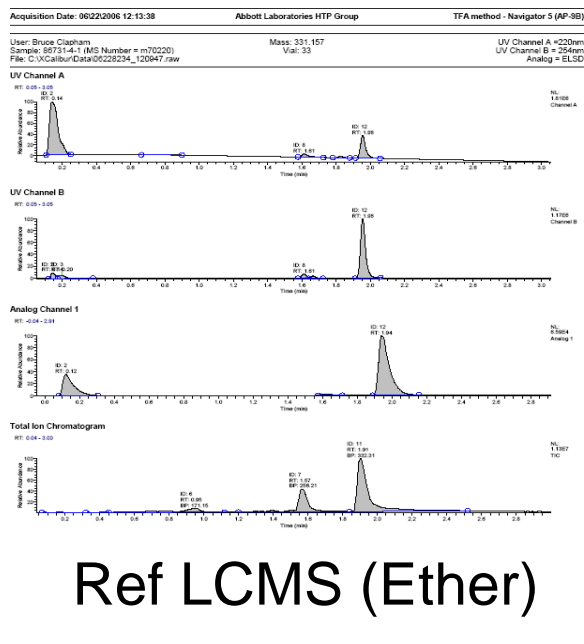


44 from 48
(Purified by HPLC)

Test reaction:



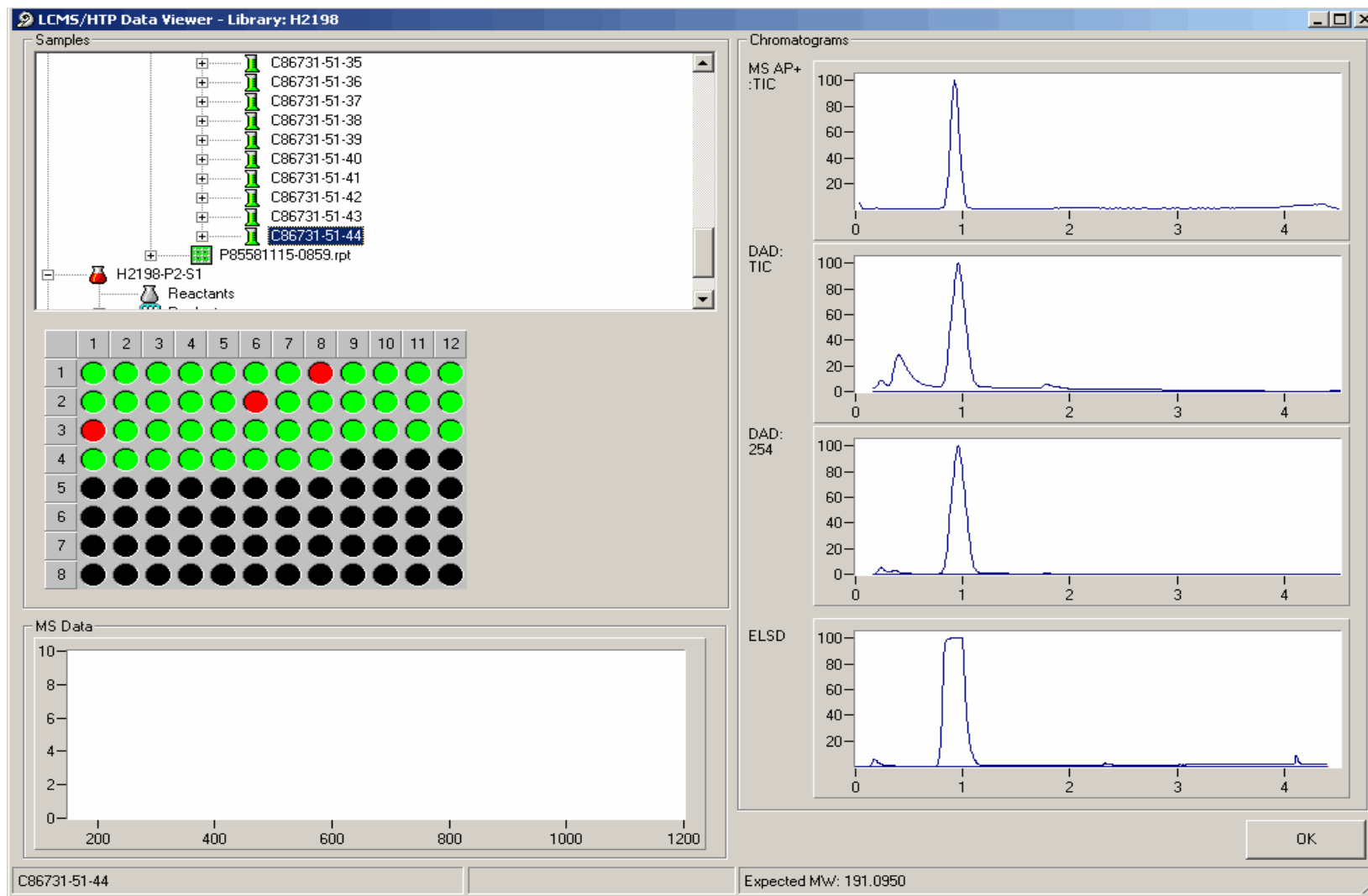
44 from 44- 90%
to quant.



Ref LCMS (Ether)

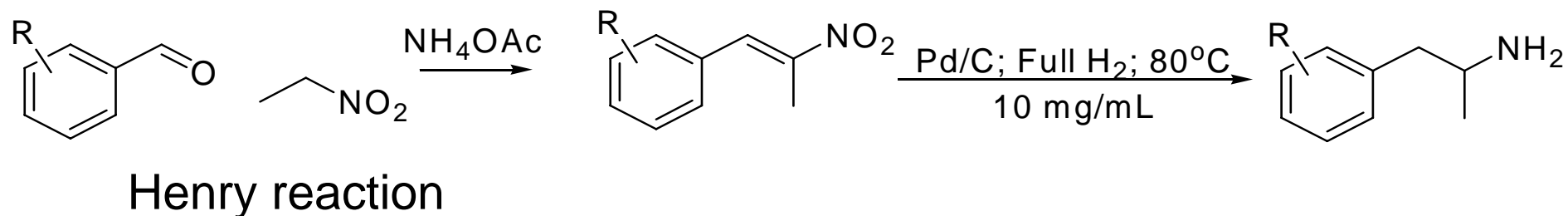
Crude LCMS (Phenol)

Crude LCMS of phenol library



High-Throughput Organic Synthesis

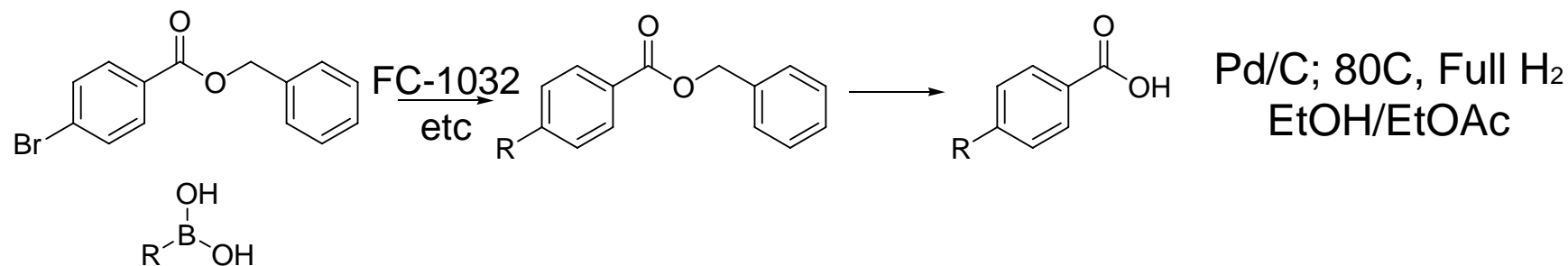
Nitro reductions- phenylethylamines



Note: few literature precedent for catalytic reduction of nitro olefins;
Most common conditions = $\text{LiAlH}_4/\text{THF}$ reflux!

For microwave promoted Henry reactions:
Varma et. al. *Tett. Letters*, **1997**, 5131

Benzyl ester deprotection of Suzuki libraries

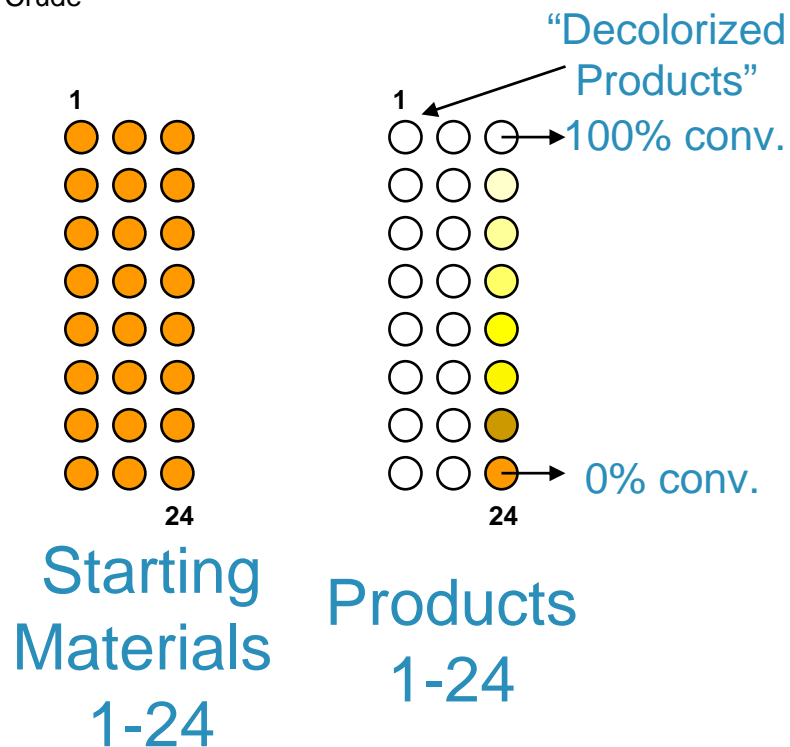
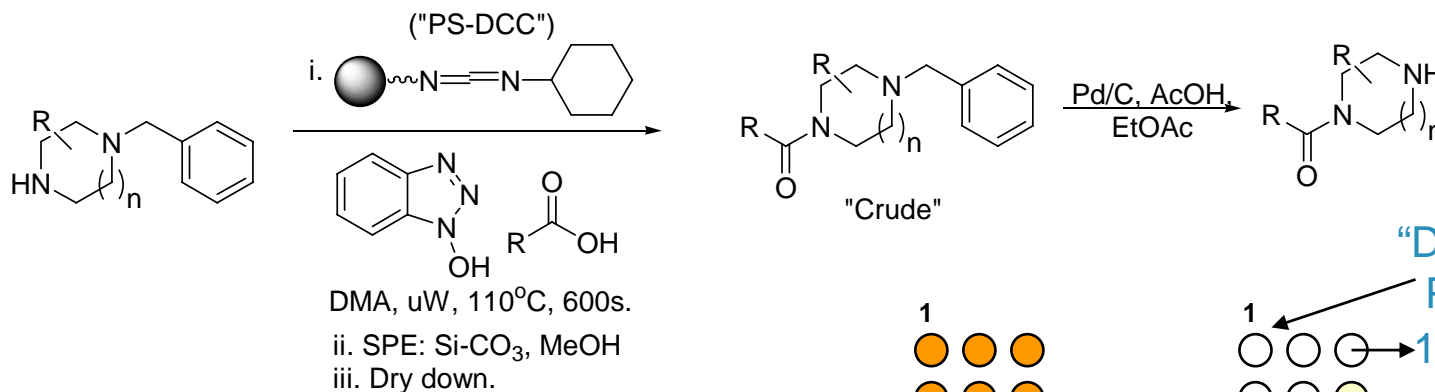


Library 1; from 48 monomers:
Standard synthesis with SPE
48 Suzuki products isolated by HPLC
Catalyst loses activity ~ #35
Desired product observed
33 biphenyl acids registered,
10% overall yield

Library 2:
Standard synthesis with SPE
Each intermediate dried down, re-dissolved
Catalyst deactivated ~# 15, 2 more runs
33 biphenyl acids registered,
20% overall yield

High-Throughput Organic Synthesis

Crude acylation libraries- catalyst poisoning



High-Throughput Organic Synthesis

Crude acylation libraries- catalyst poisoning

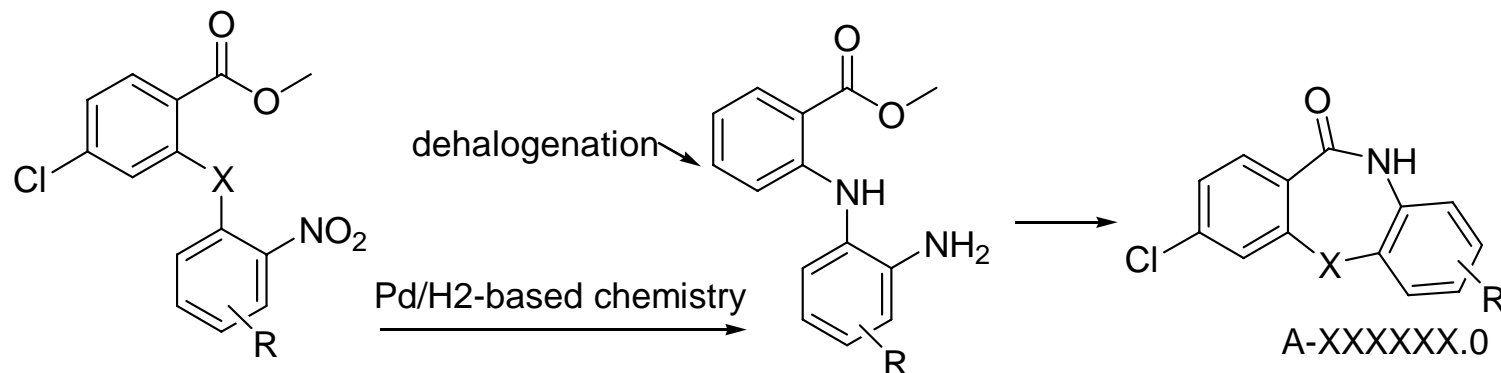
- Yellow impurities formed during acylation reaction/work up
- “Fines” from SPE also cause blockage of apparatus
- Yellow impurity adsorbed onto Pd/C catalyst (decolorized products)
- Catalyst rendered inactive

Currently under investigation

- Prepare HPLC guard column with activated carbon packing
- Prepare syringe filters with activated carbon membrane

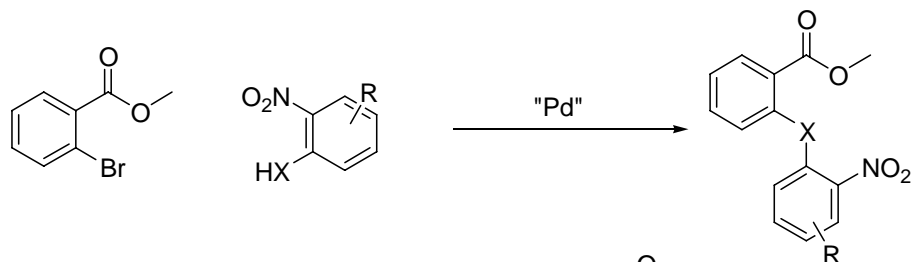
Nitro reductions: anilines

Stoichiometric quantities of tin required



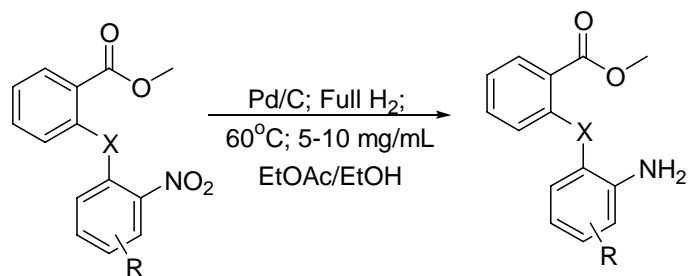
High-Throughput Organic Synthesis

Model library



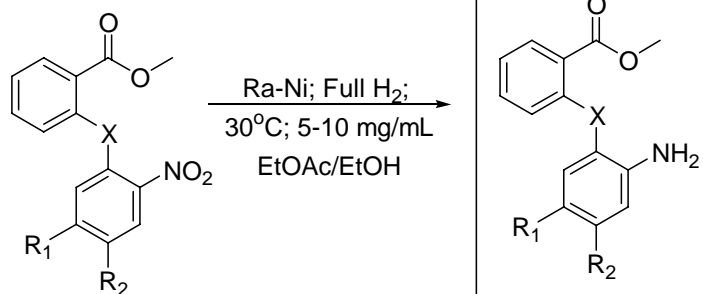
8 examples;
30-52% (ave 39%)

Literature procedure (thermal)
Converted to microwave

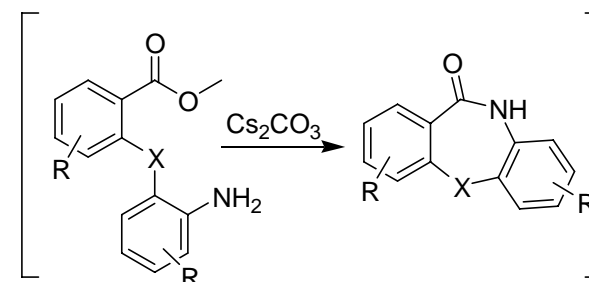


6 examples;
95%-Quant.

R = Cl, dehalogenation

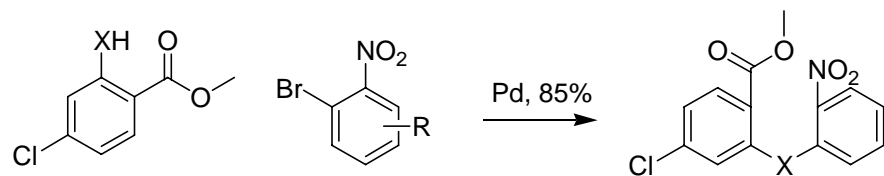


R₁ = Cl, R₂ = H, Quant.
R₁ = H, R₂ = Cl, Quant

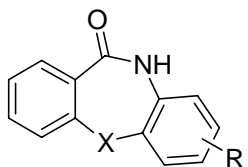
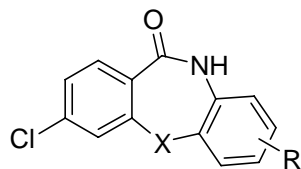


High-Throughput Organic Synthesis

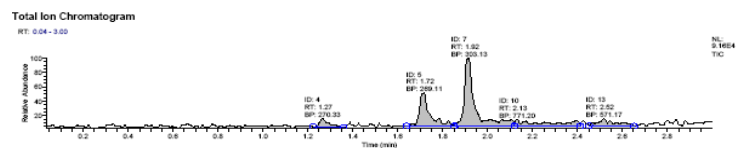
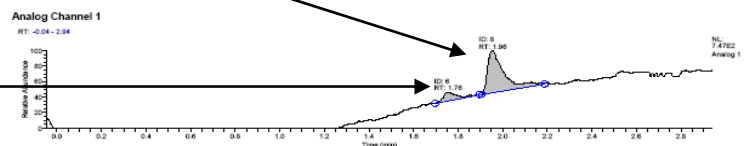
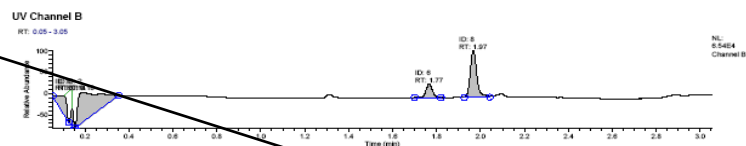
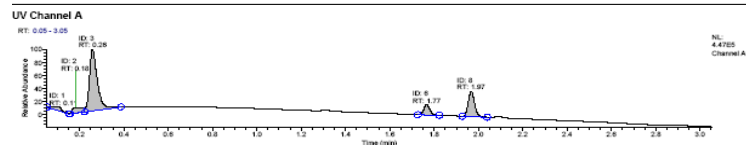
Synthesis of A-xxxxx.0



i. Ra/Ni; 20°C, cont H₂
EtOAc. ii. Cs₂CO₃



Acquisition Date: 08/08/2006 12:50:23 Abbott Laboratories HTP Group TFA method - Navigator 5 (AP-9B)
User: Bruce Clapham Mass: 302 UV Channel A = 220nm
Sample: S6731-54 (MS Number = m98675) Vial: 78 UV Channel B = 254nm
File: C:\XCalibur\Data\080810400_123416.raw Analog = ELSD



Sample drydown- Biotage V-10

- This instrument is to the speedvac, what the microwave was to the heater shaker!



High-Throughput Organic Synthesis

Summary:

- LIMS support of library login and enumeration
- LIMS support monomer storage, ordering; on- and off-site
- Automated hydrogenation; deprotection of libraries prepared using robust microwave chemistry

Acknowledgements- Abbott Advanced Technology Division



HTOS

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Phil Searle

Keithney Glass

Tomas Galicia

Jenny Garton

Anita McGreal

Automation Engineering

Jeff Pan

Tom Nemcek

Dave Blanchard

Stan Kantor

Dave Dingle

Structural Chemistry

Darlene Hepp

Jan Waters

David Whittern

Steve Spanton

Management

Daryl Sauer

Tom Sowin

Steve Djuric

Jim Summers