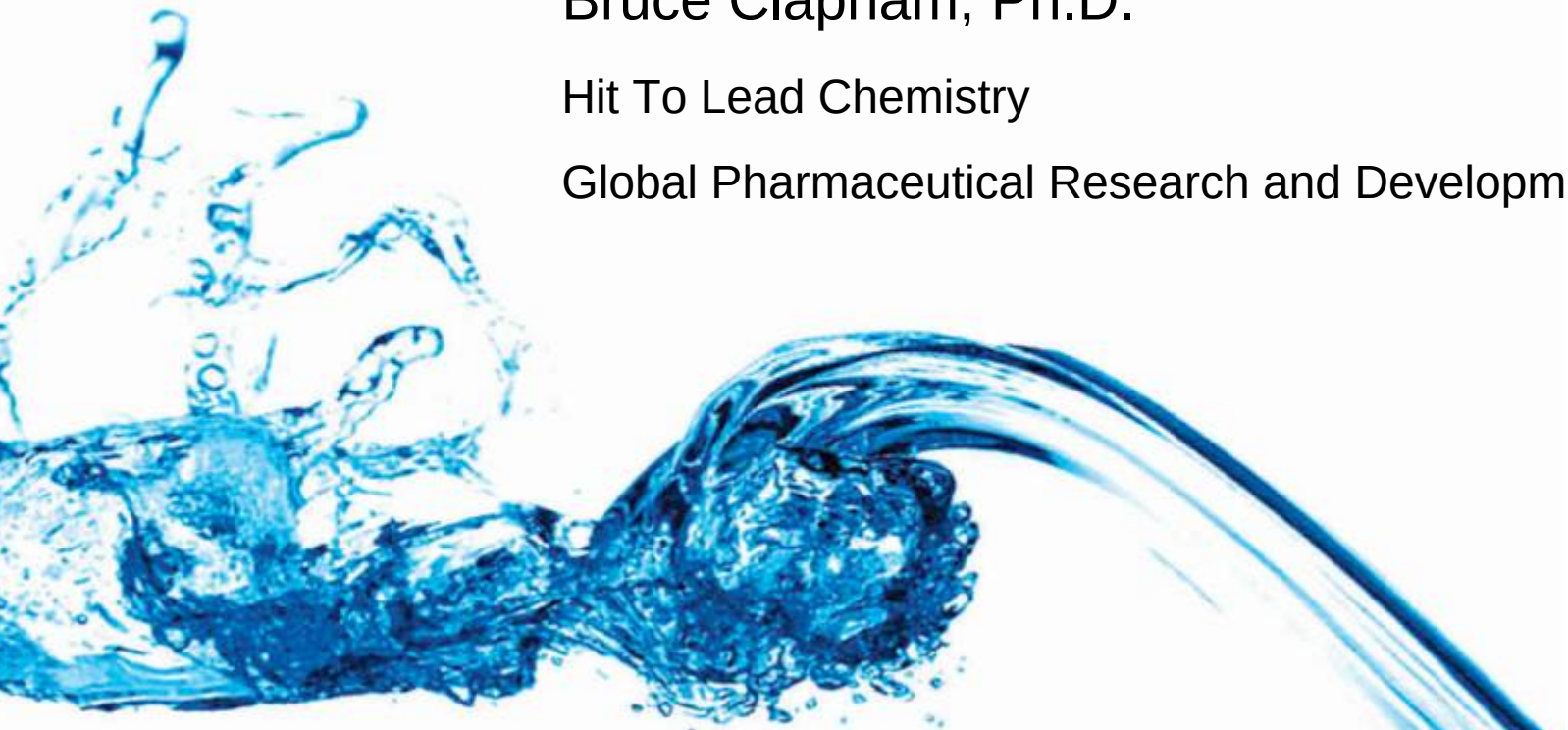
Integrating Microwave Synthesis with Emerging Chemical Technologies.

Biotage Summer Program, Richmond July 21-23

Bruce Clapham, Ph.D.

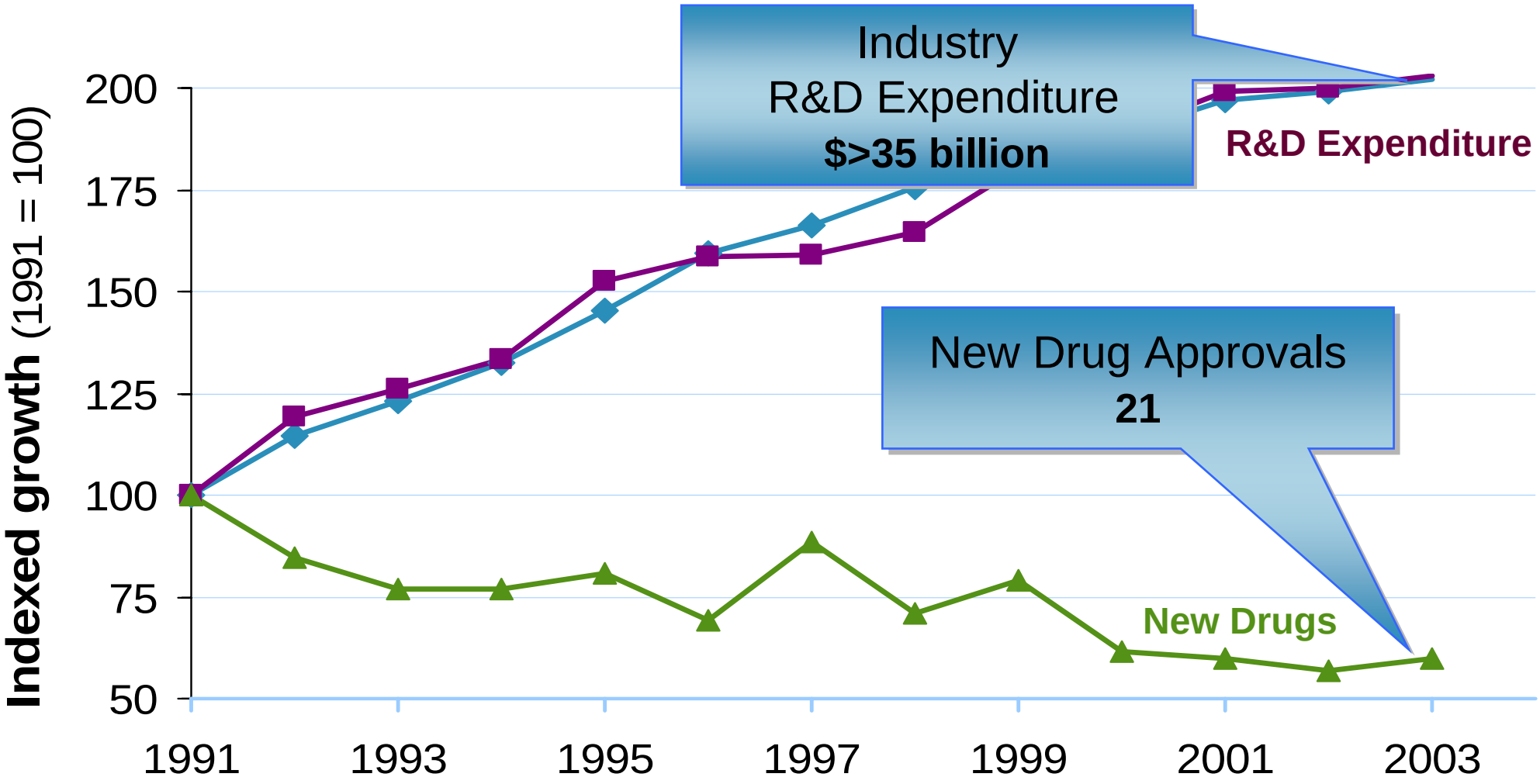
Hit To Lead Chemistry

Global Pharmaceutical Research and Development

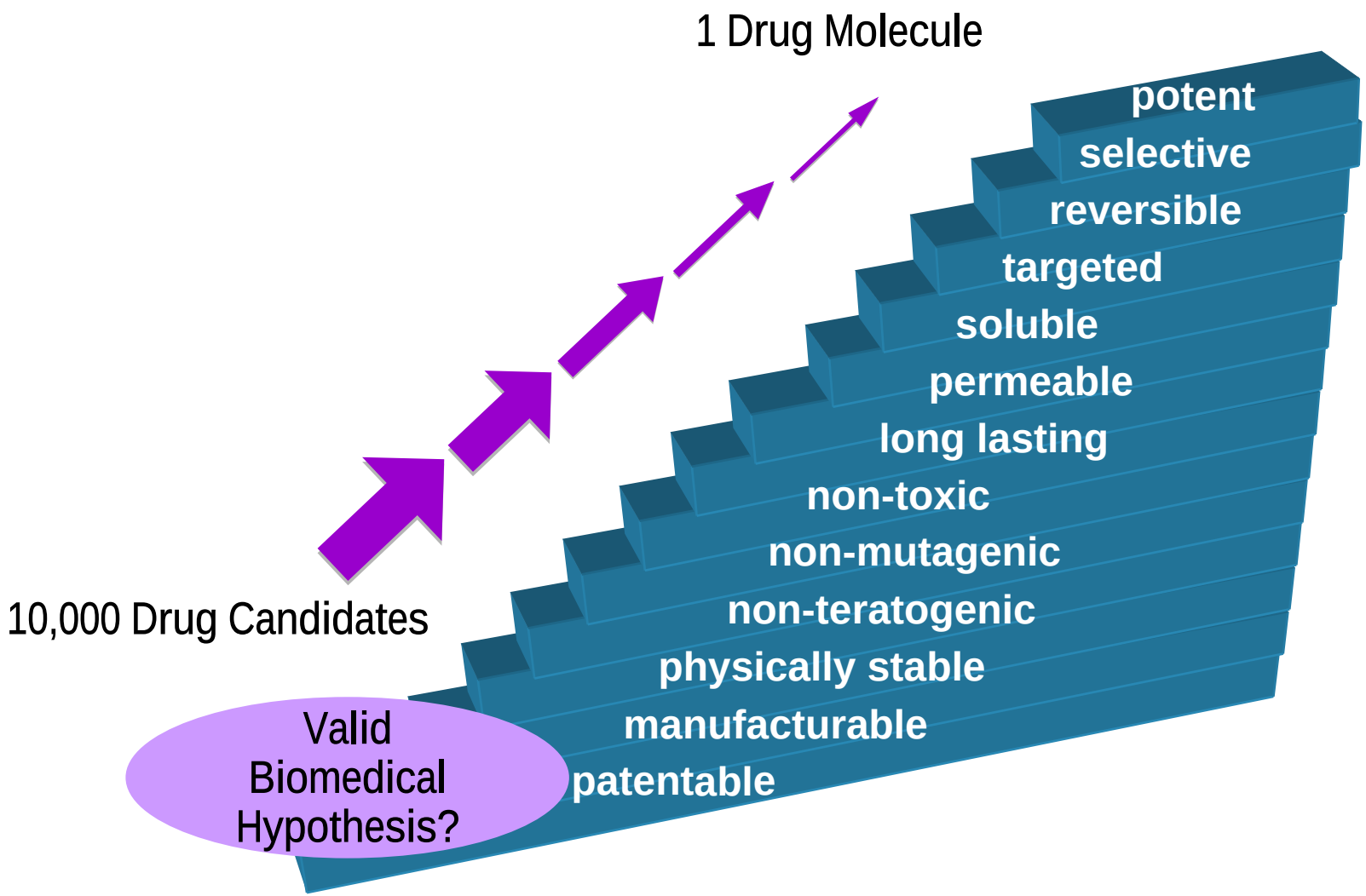


Abbott
A Promise for Life

Rising Research Costs, Fewer Drugs



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



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

Overview of HTOS Libraries

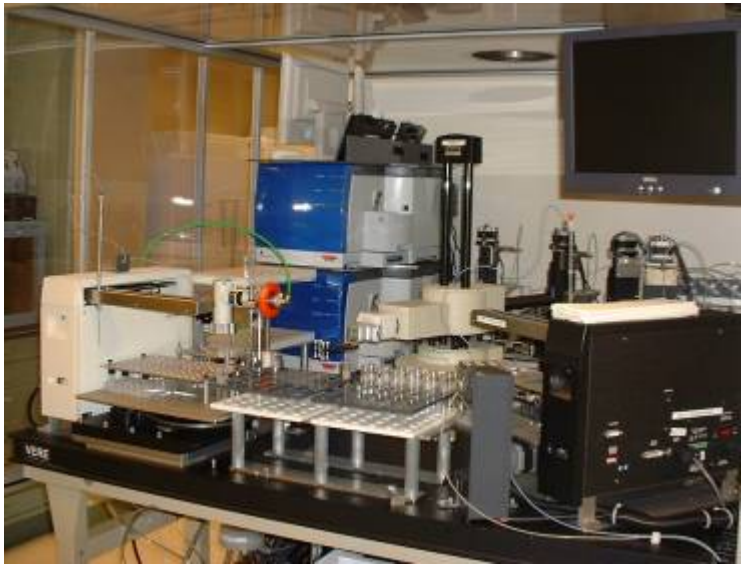
Library Characteristics

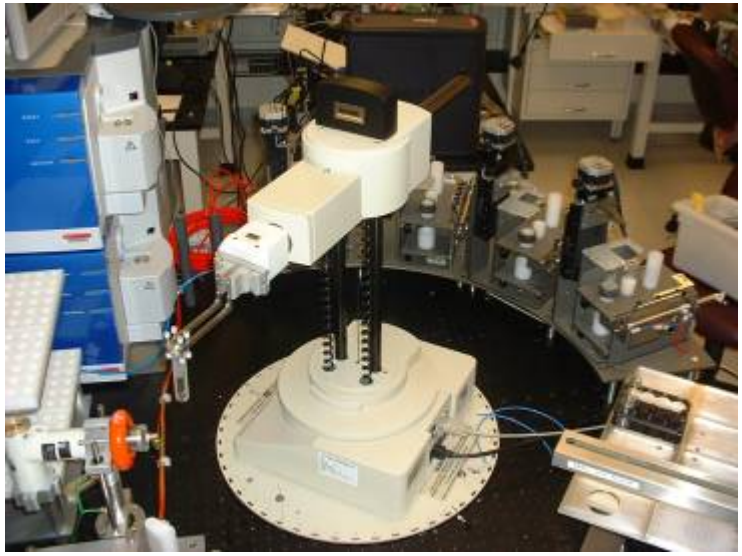
- Solution Phase
- Focused Chemical Space
- 24-96 Member Arrays
- 20-50 mg Scale
- Minimal Development
- High Purities and Yields
- Fully Characterized Products
- File Enhancement
- Hit to Lead
- Lead Optimization

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

In our lab, microwave is not the bottleneck!





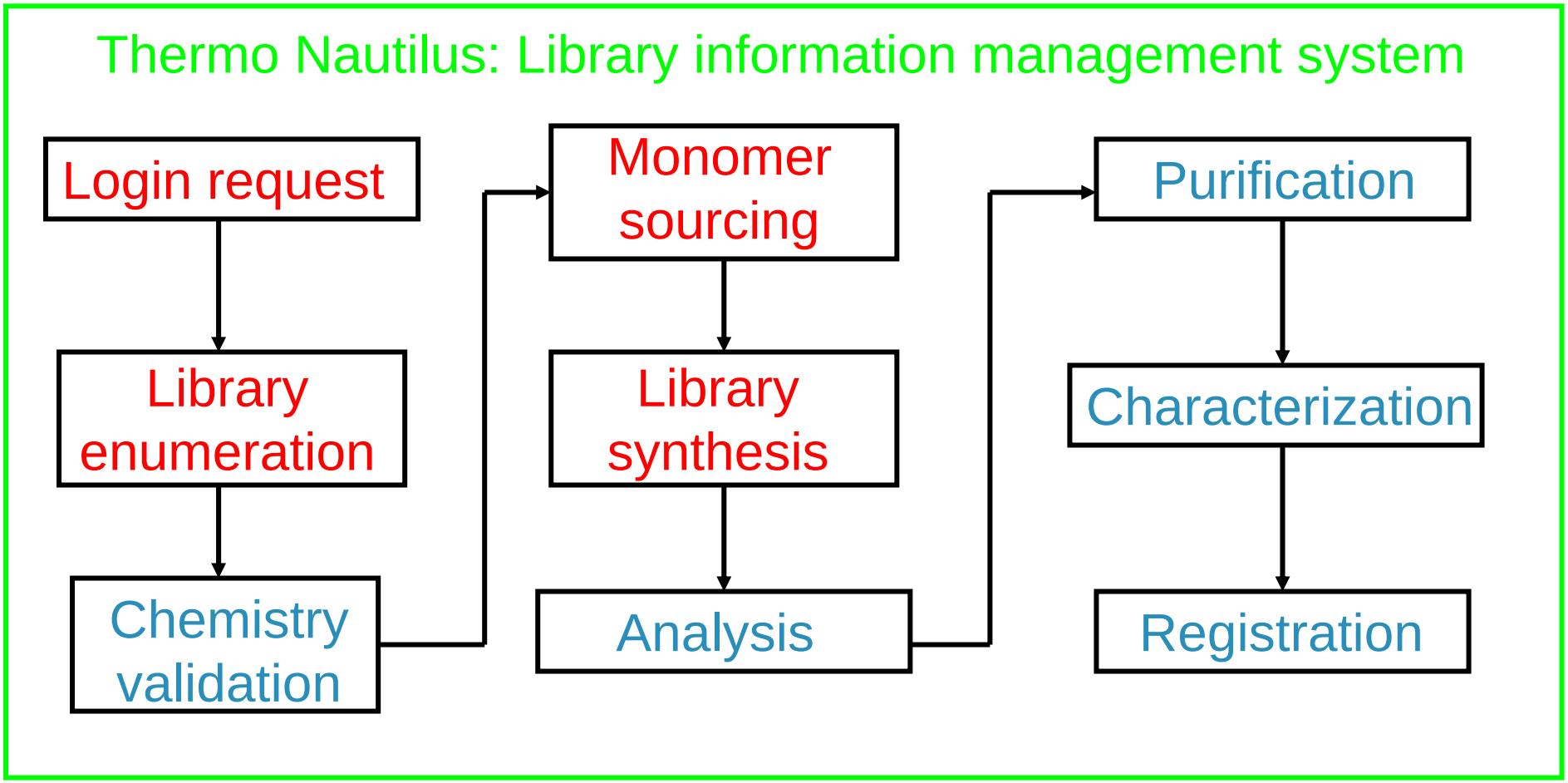
So what is today's talk about?

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

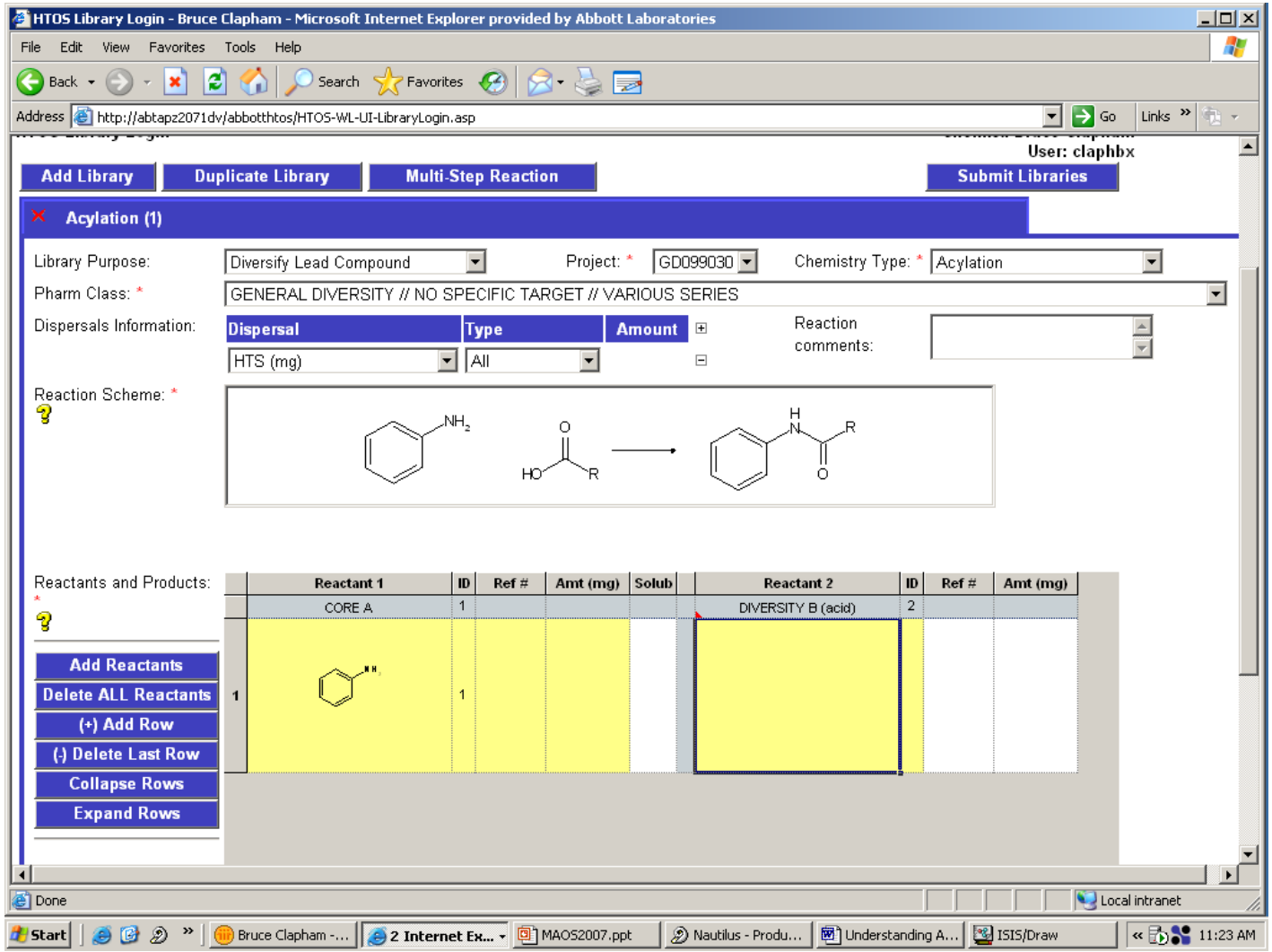
- *Improving efficiencies before samples reach the microwave:*
- Address issues with library login, enumeration
- Interface cheminformatics tool; synthesis "selected" compounds
- Provide chemists with standardized monomer sets
- Automated monomer storage, inventory control and re-stocking
- Seamless 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)

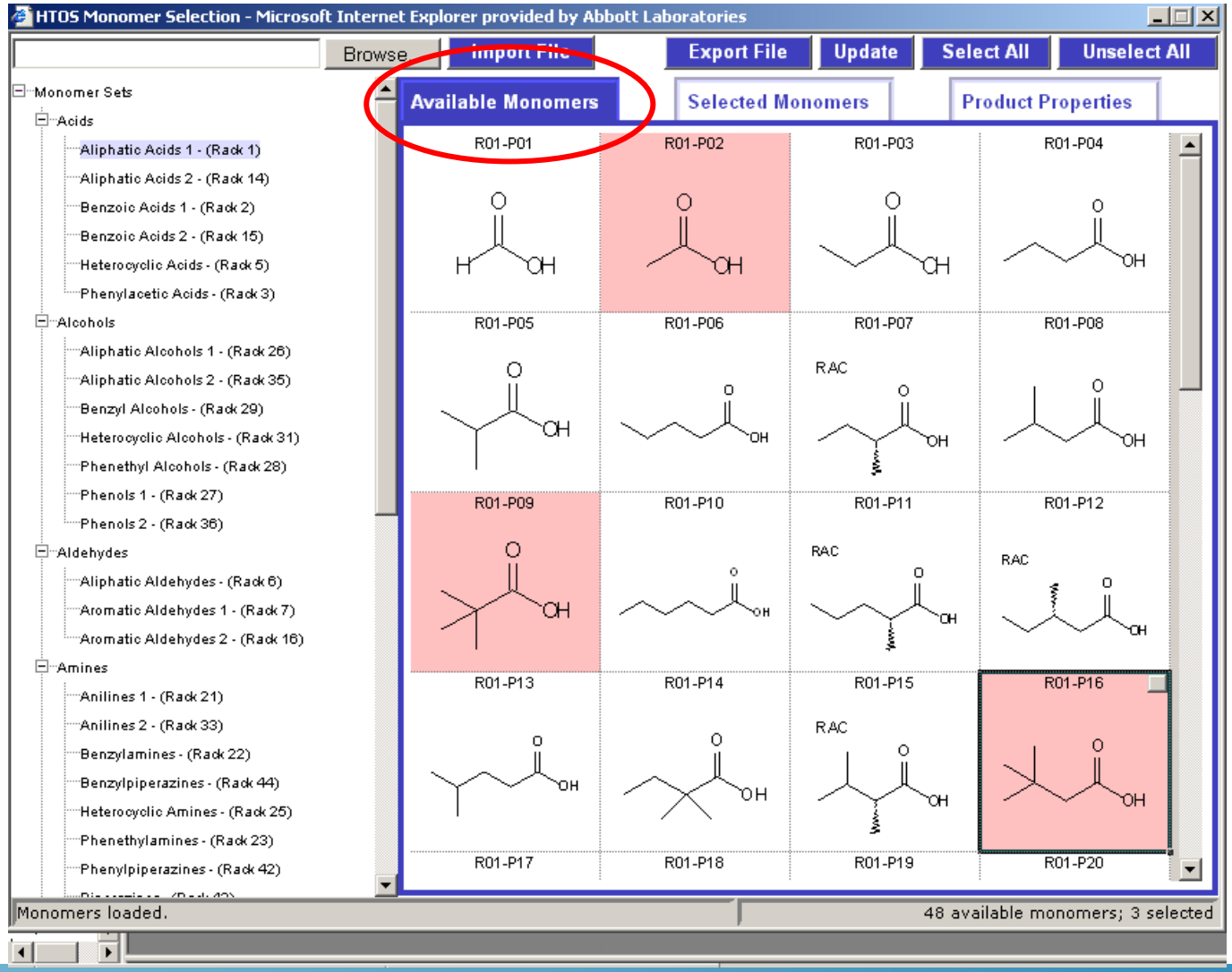
Simplified library production workflow:



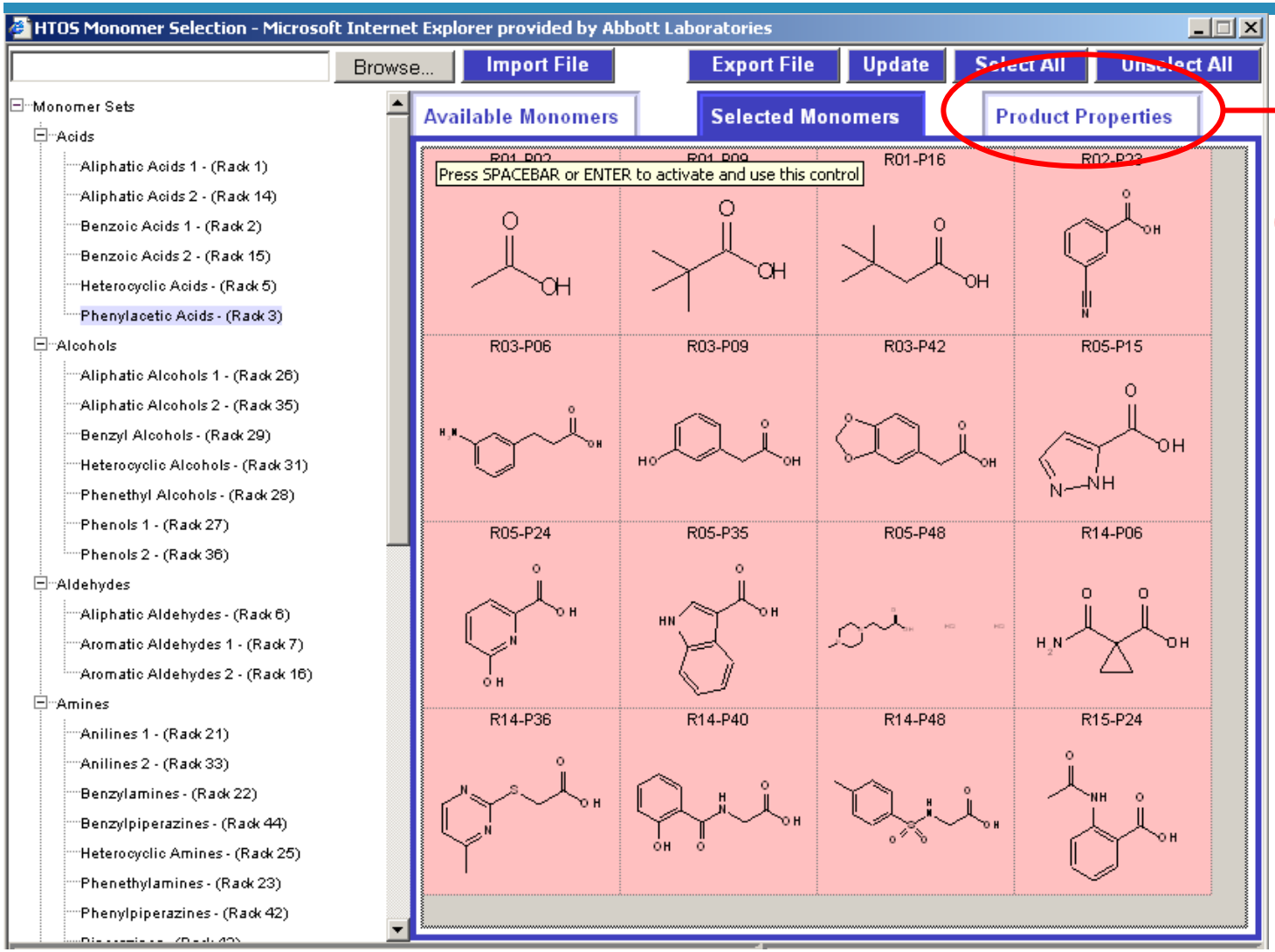
Web based library login portal (Client)



Monomer selection (Client)

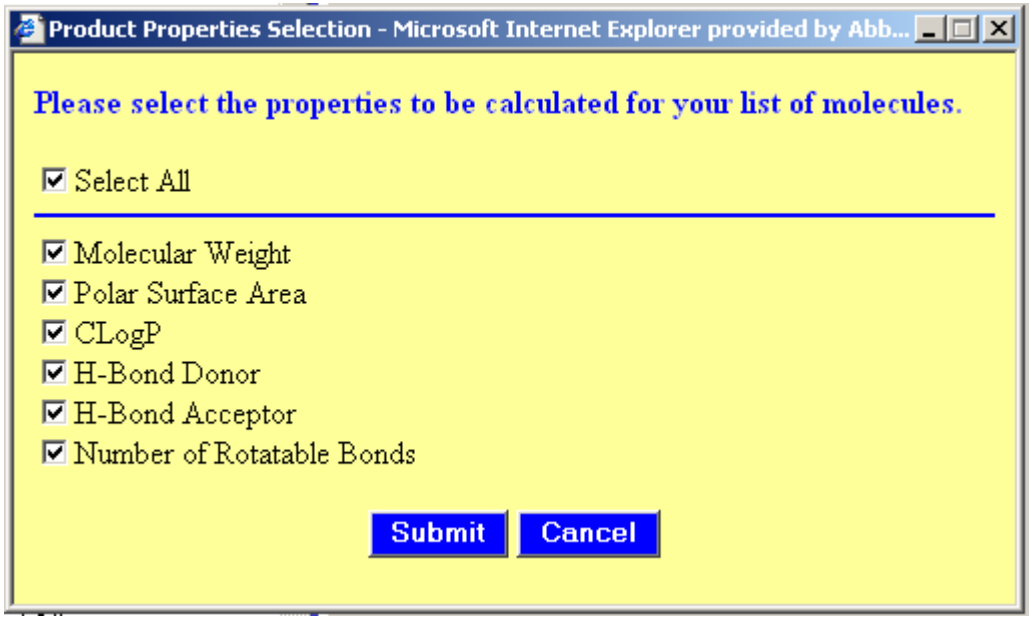


Review selected monomers (Client)

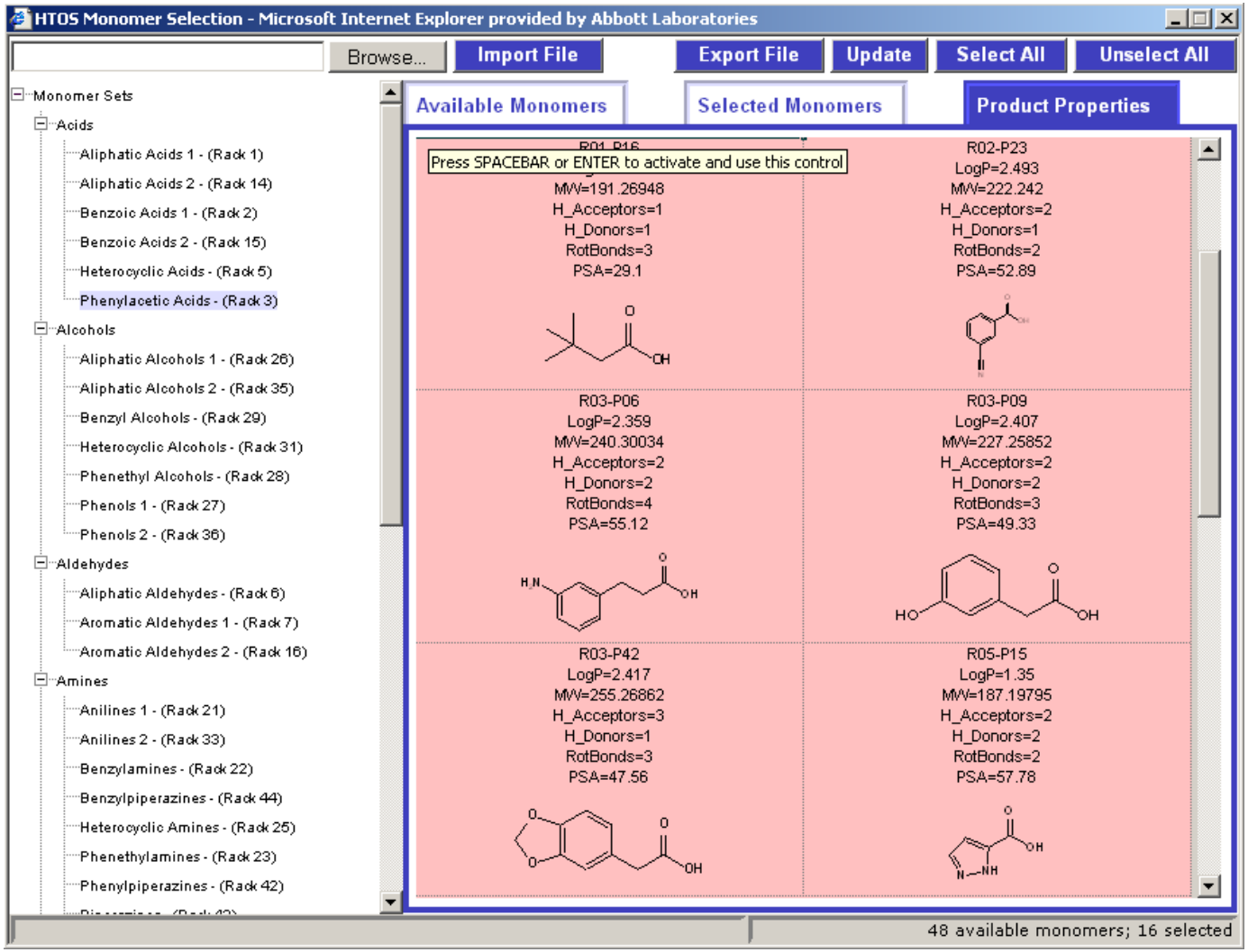


Pipeline pilot Interface (Cheminformactics Tool)

Pipeline pilot interface (Client)



Calculated properties of enumerated product (Client)



Version 1:
(Enumerated products not shown)

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

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

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)

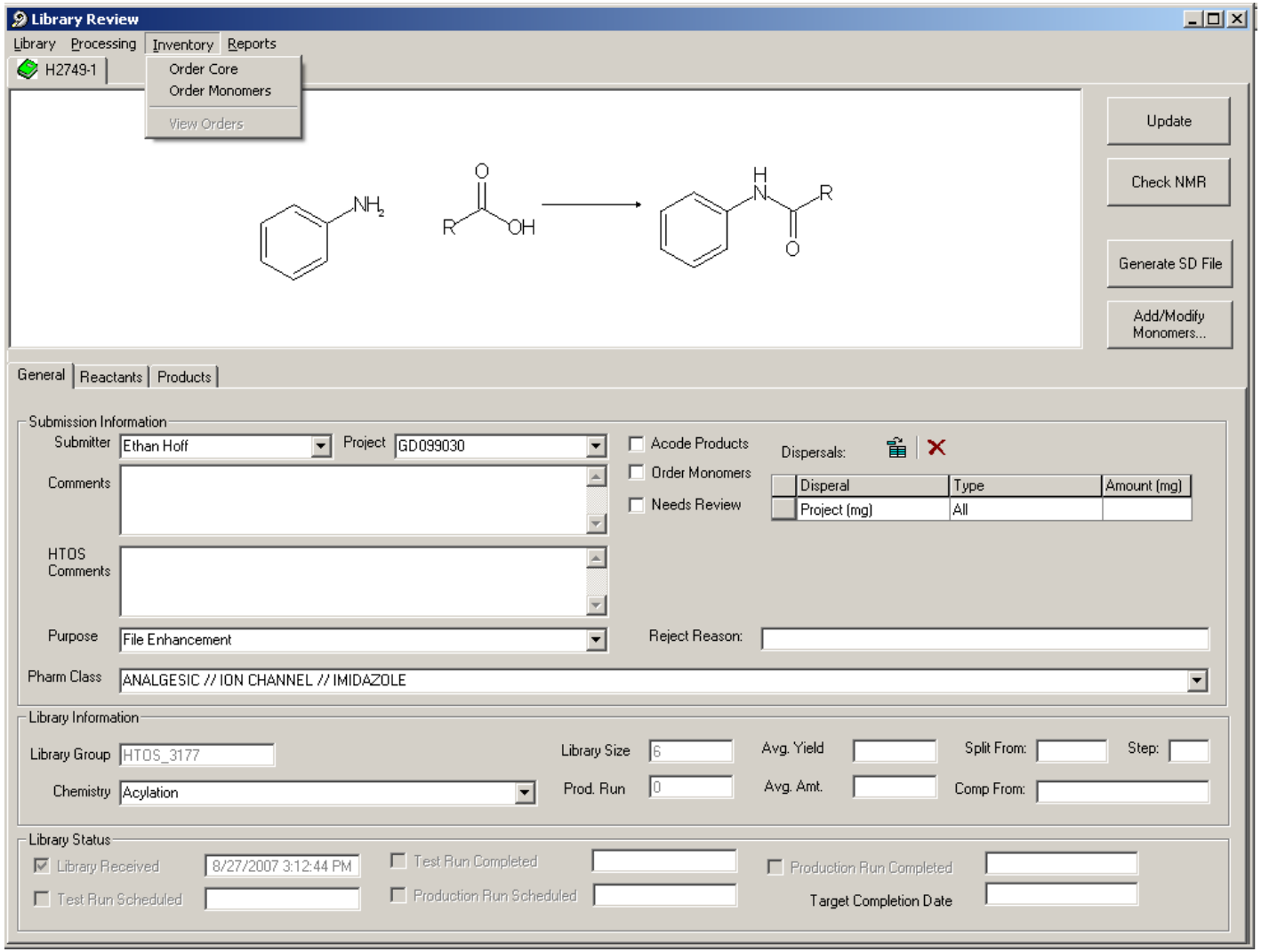
- Predominantly supplied by Aldrich Discovery CPR
- All monomers validated for chemistry, long term availability
- > 1500 individual monomers stored at Abbott, ~10 copies
- All supplied in 4mL vial, 0.6 mmol quantity
- Bar coded vial, septa caps

- “On Demand”- reactives, available from Discovery CPR < 5 days
- Custom monomer orders from Discovery CPR
- Abbott LIMS interface with Aldrich for seamless ordering

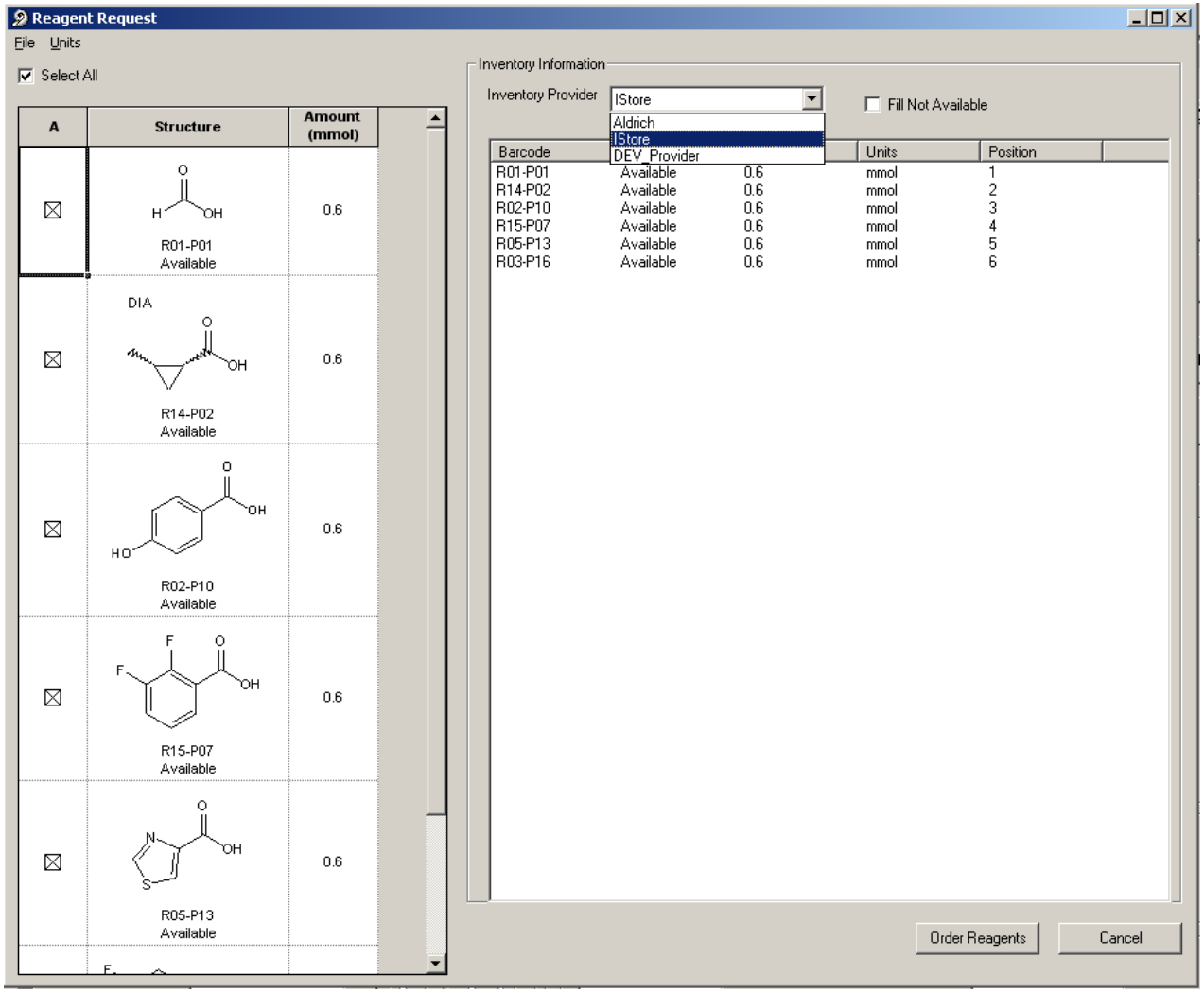
How do we store and manage those 15,000 vials?

- Old sample repository room converted into monomer “I-Store”
- Monomer requests filled by Robot into 24 well Falicon 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



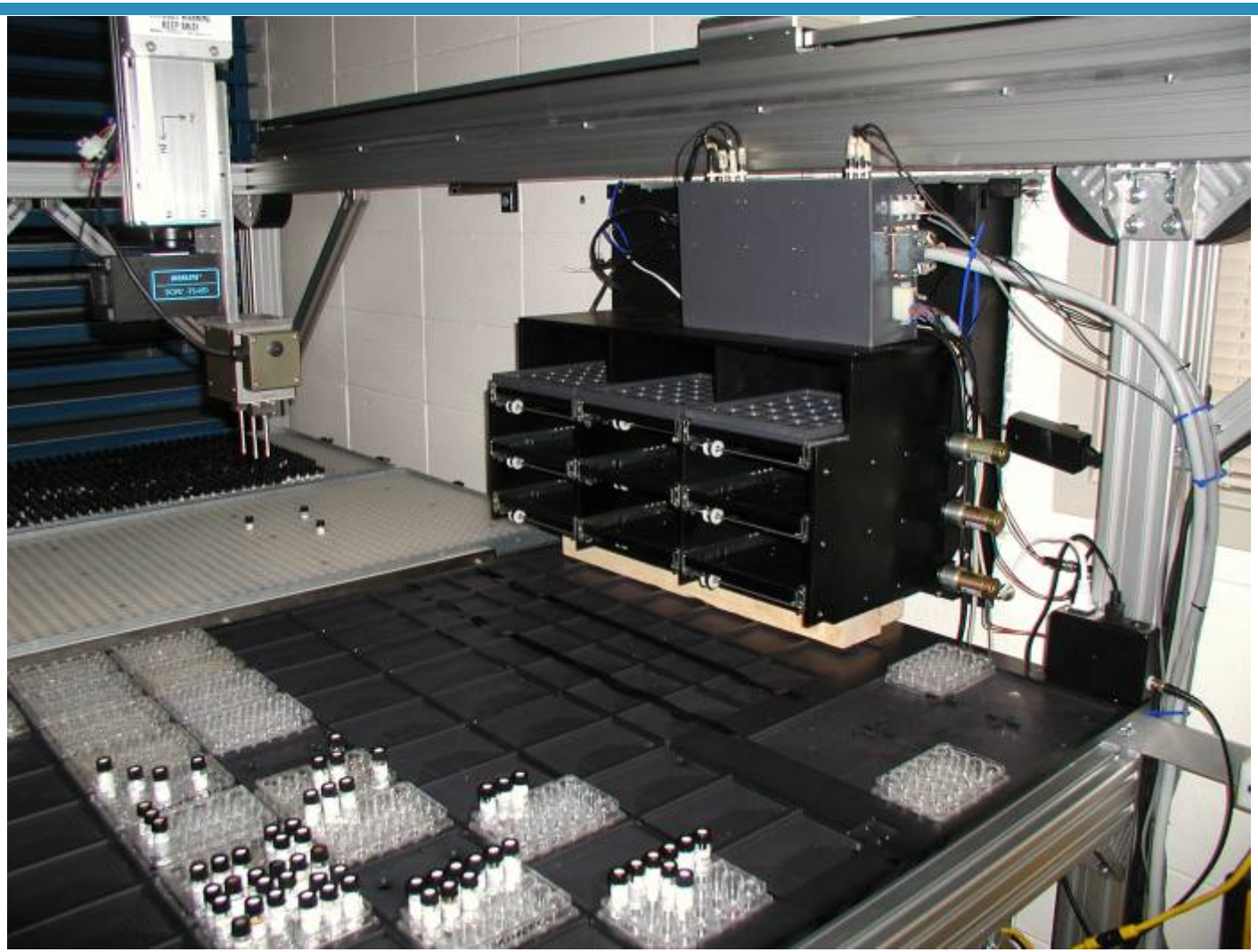
I-store vendor (HTOS)



Sample repository converted to “I-Store”

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

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

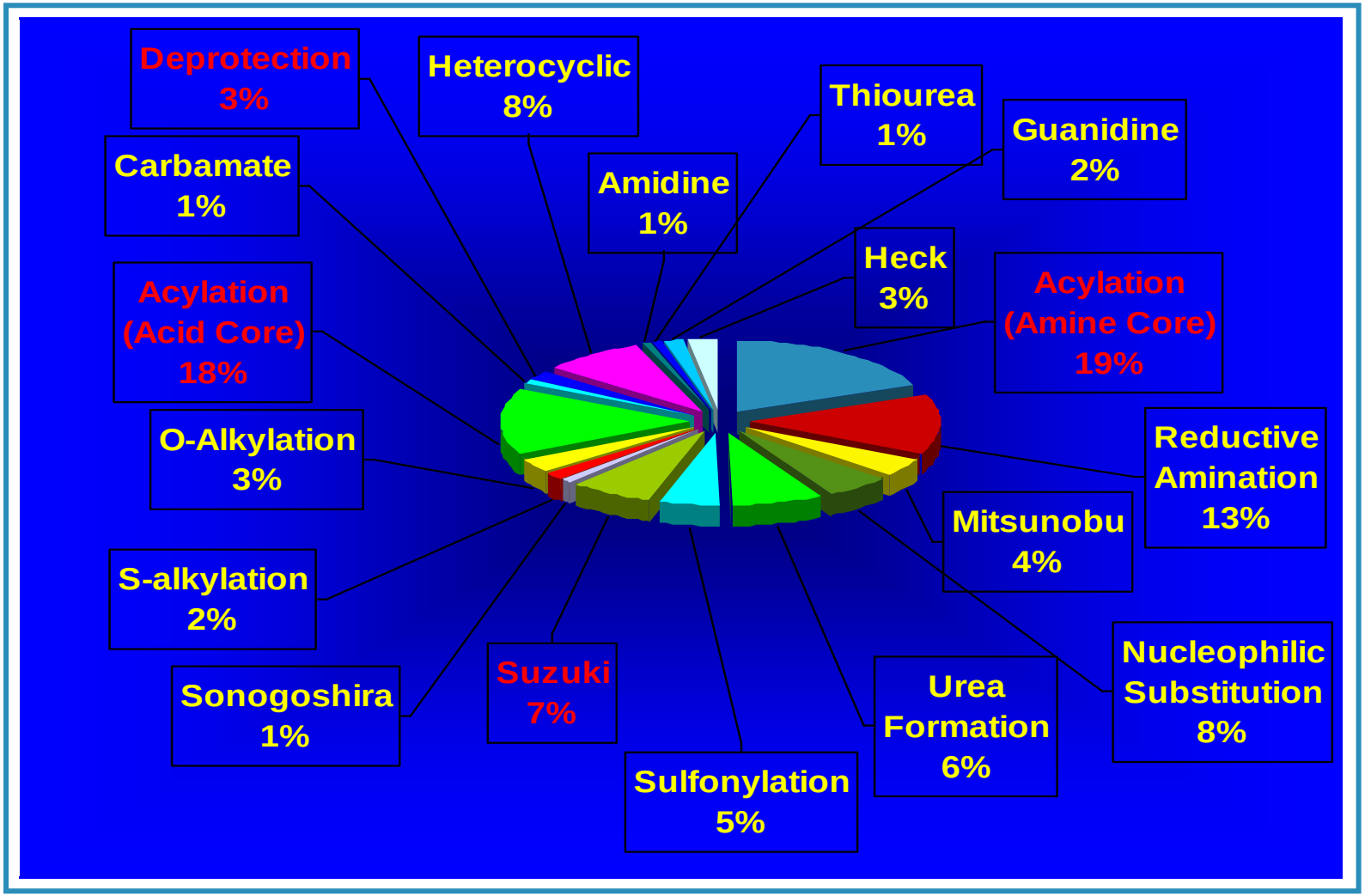


I-Store (Shop window)

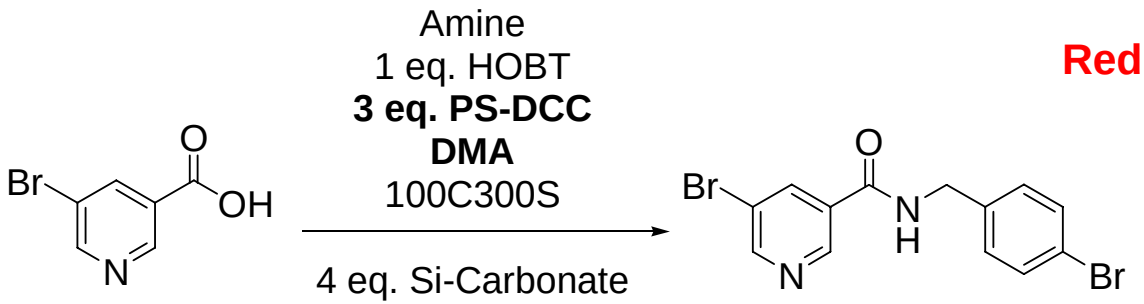
Chemist receiving monomers

Chemist receiving monomers

HTOS Reaction Repertoire

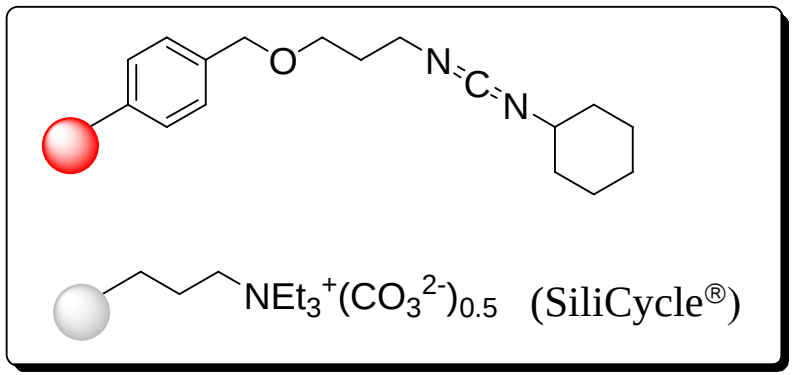


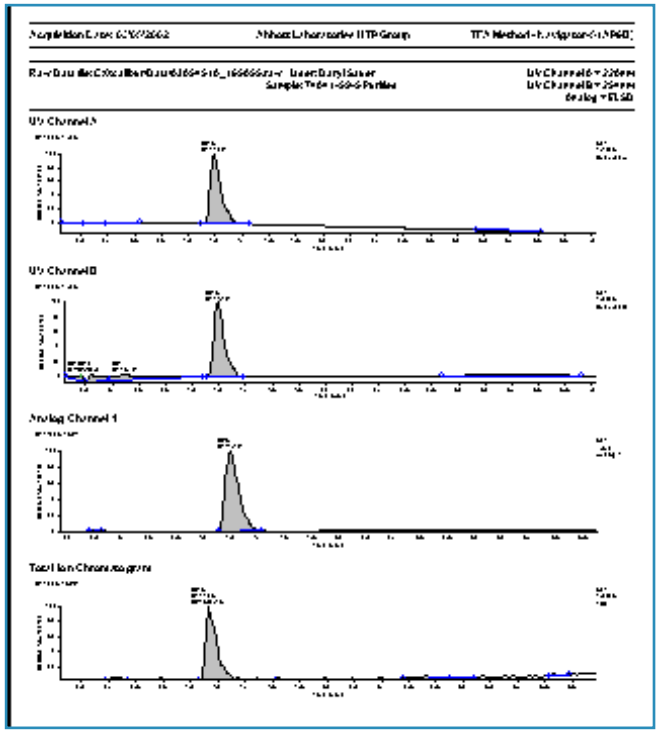
Highly efficient microwave acylation procedure



Reduces an 16 hour process to <15 minutes

95% Yield
98% Pure

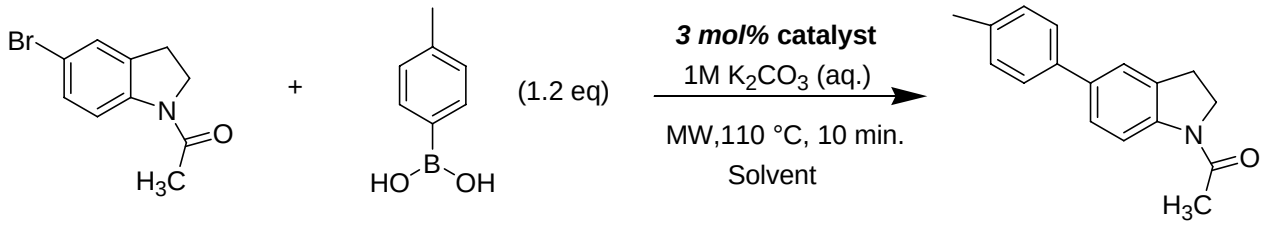




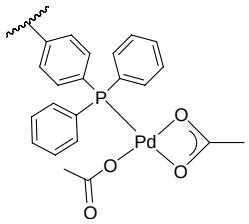
Initial Microwave Experiments
- HOBt adduct precluded use of DCM
- DCC not stable at 150C
- DMA derived by-products > 120C
- No by-products with NMP

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

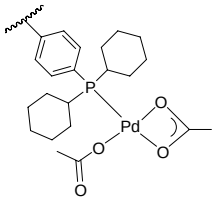
Highly efficient microwave Suzuki coupling



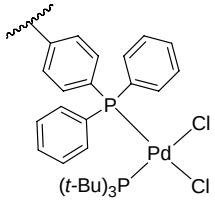
Entry	Catalyst	Solvent	Conversion
1	PS-PPh_3-Pd	DME/EtOH (1:1)	81%
2	FC1001	EtOH	97%
3	FC1007	EtOH	100%
4	FC 1032	EtOH	100%
5	$PdCl_2(PPh_3)_2$	DME/EtOH (1:1)	88%



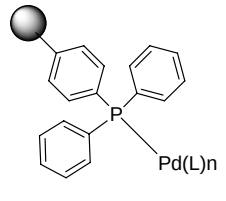
FC 1001



FC 1007



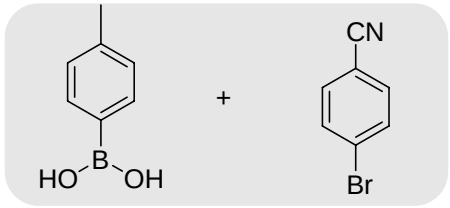
FC 1032

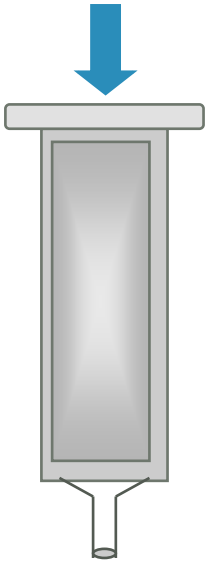


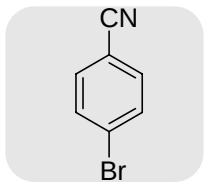
PS-PPh_3-Pd

Wang, Y.; Sauer, D, R. *Org. Lett.* **2004,** *6*, 2793-96

Si-Carbonate — Effective Scavenger For Boronic Acids

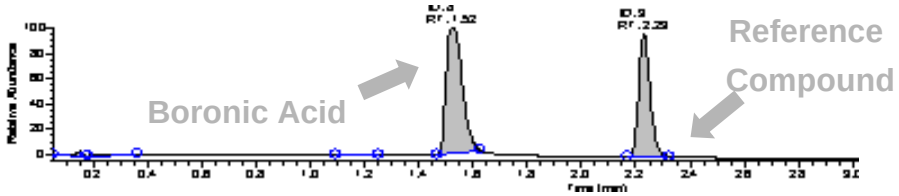




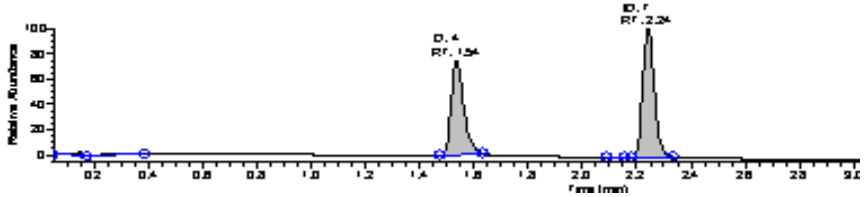


(Reference Compound)

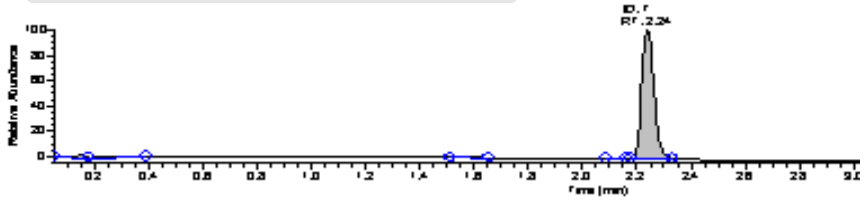
1 equiv. Si-Carbonate



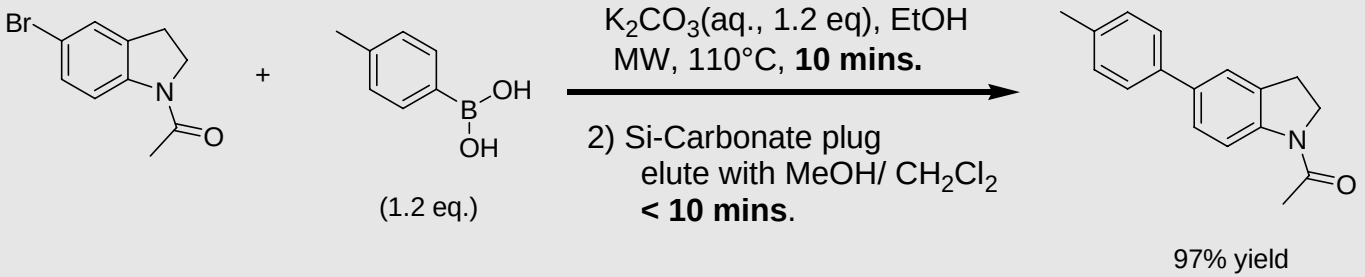
3 equiv. Si-Carbonate



10 equiv. Si-Carbonate



Vessel Rupture Due to Precipitated Pd Virtually Eliminated

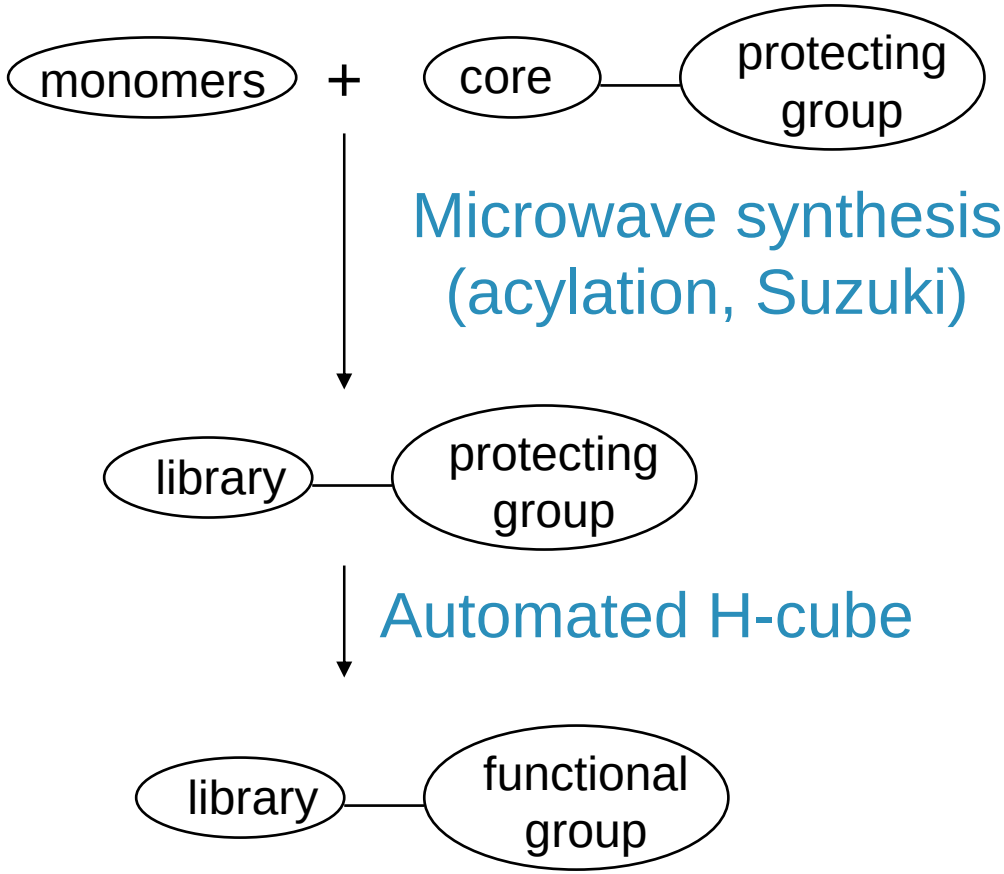


With FibreCat 1007

With $PdCl_2(PPh_3)_2$

Hydrogenation/Hydrogenolysis of microwave products

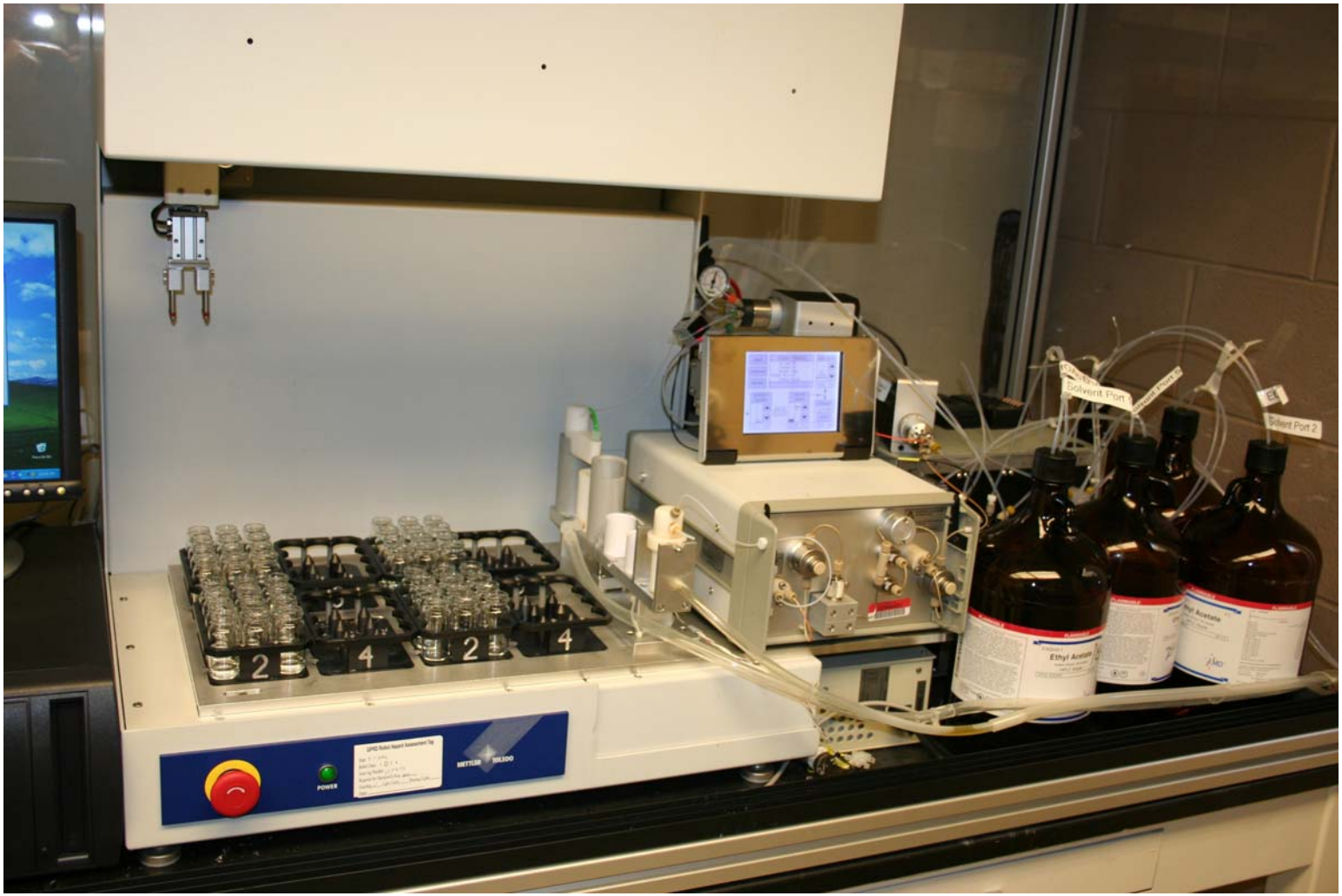
Monomers:
Aryl halides
Boronic acids
Amines
Acids



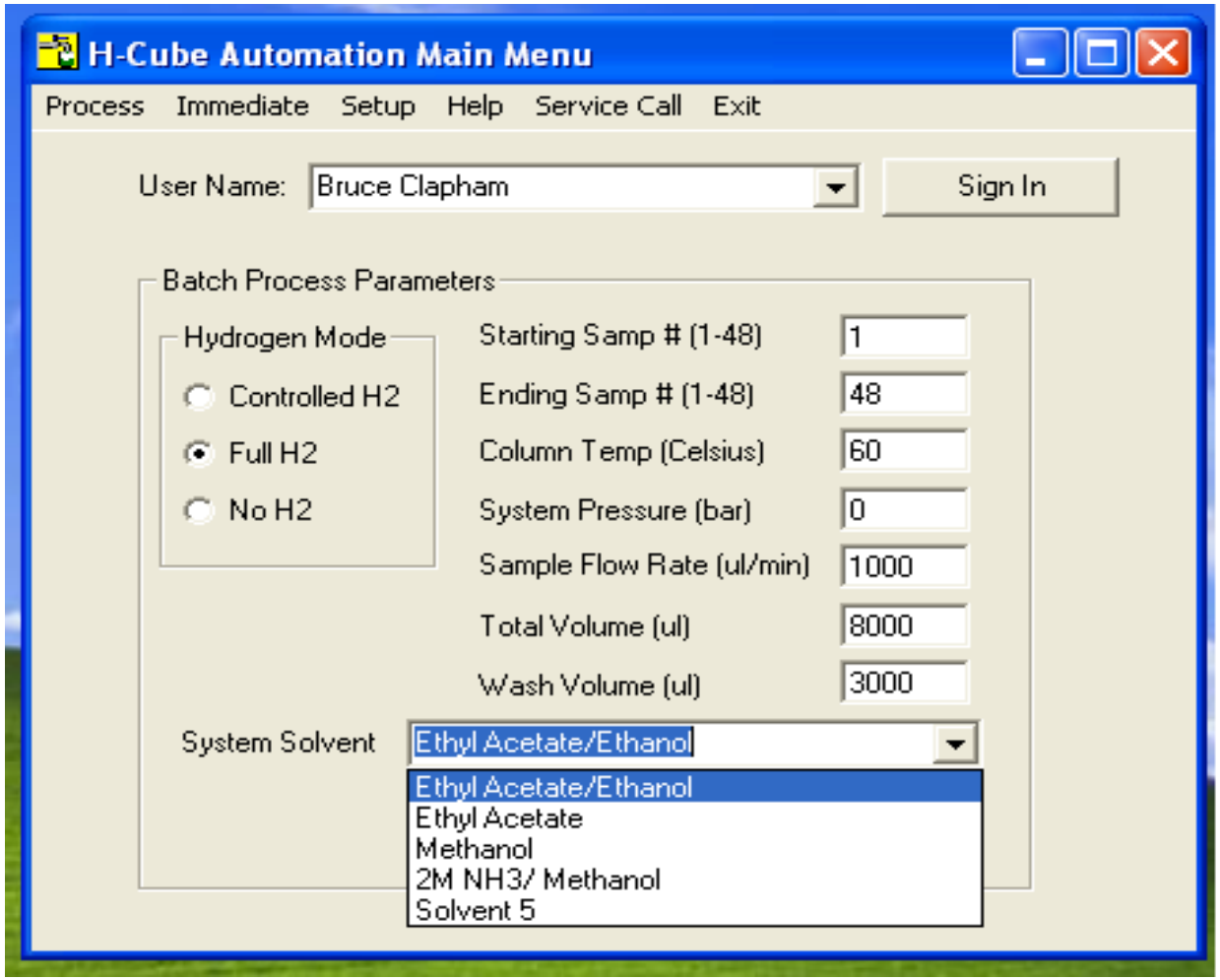
Protecting groups:
Benzyl carbamate (CBZ)
Benzyl amine
Benzyl ester
Benzyl ether

Functional groups:
Amines
Acids
Alcohols
Phenols

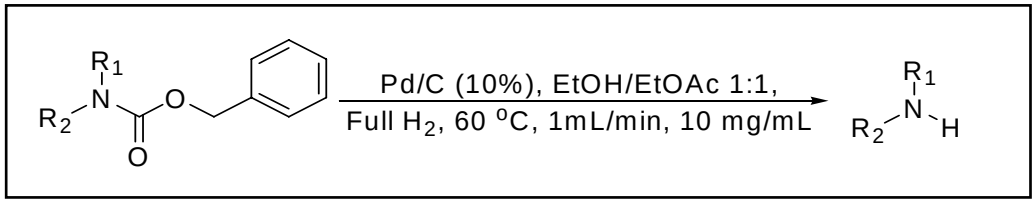
Automated H-Cube platform

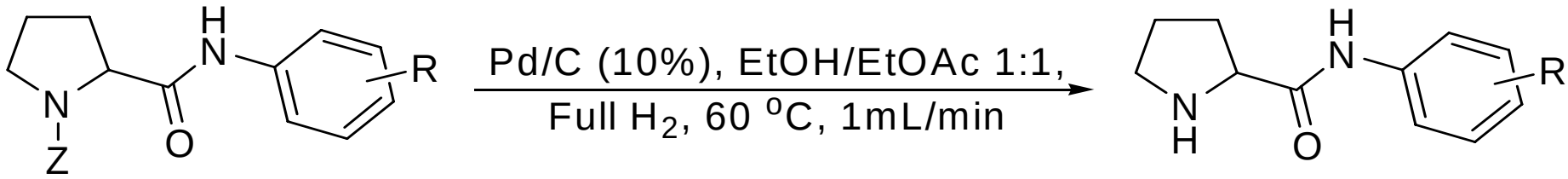


PC interface operation modes



CBZ deprotection:





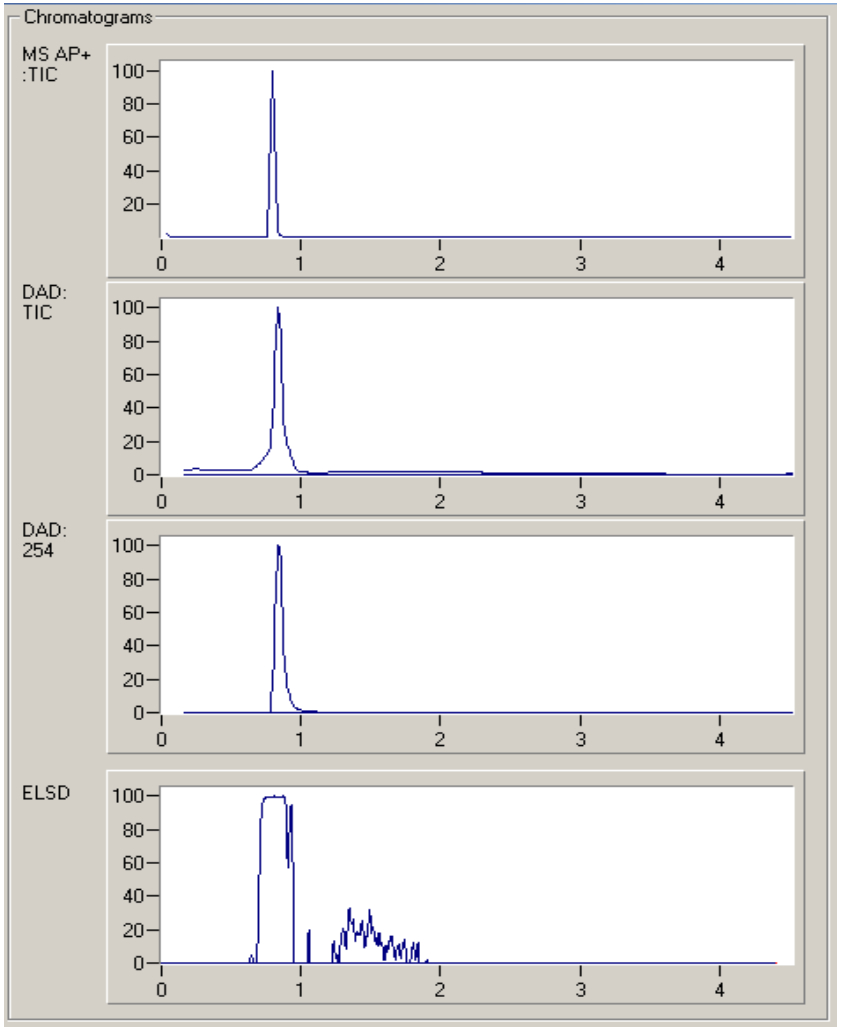
35 Amides
(Purified by HPLC)

27 from 35 reactions worked

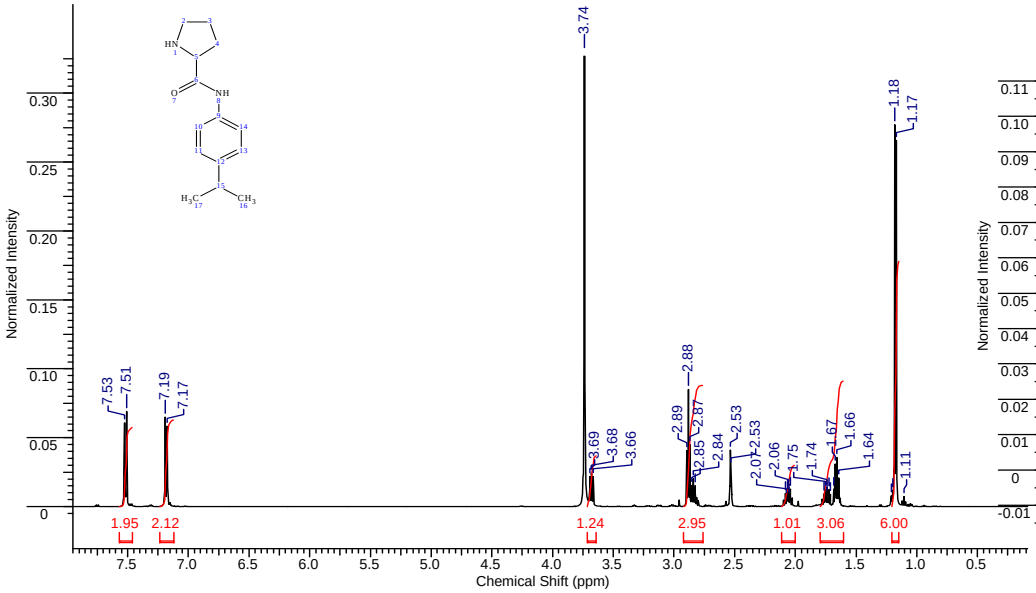
Most products >95% pure, 95% yield

Failures: dehalogenation of aryl halides

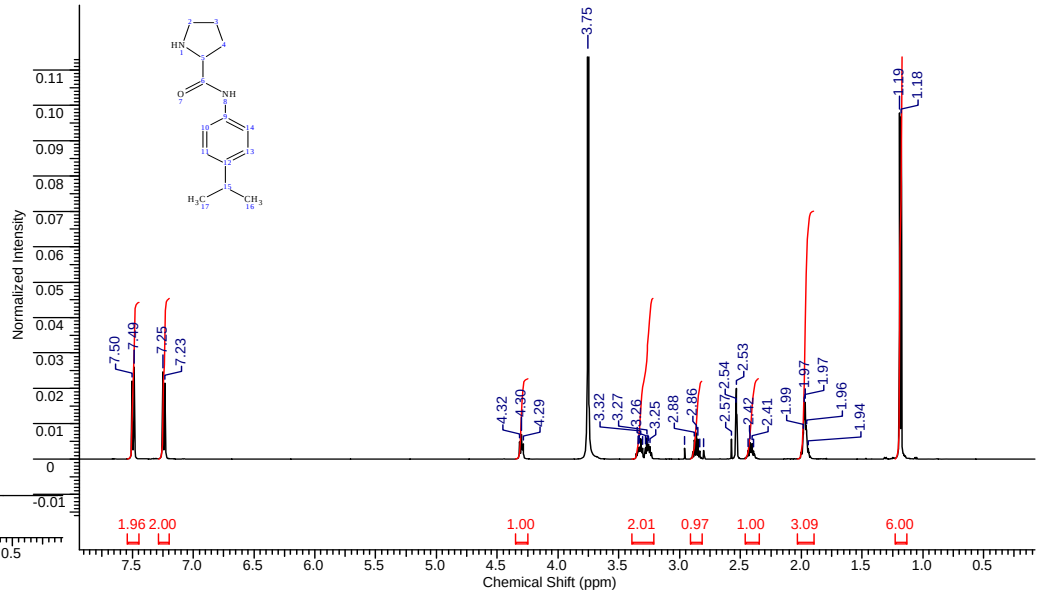
LCMS of Crude CBZ-deprotected product



NMR of Crude vs purified product



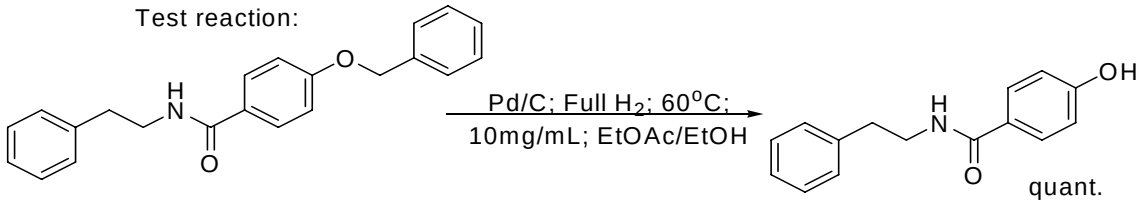
Crude (freebase)



Purified (TFA salt)

Benzyl ether deprotections:

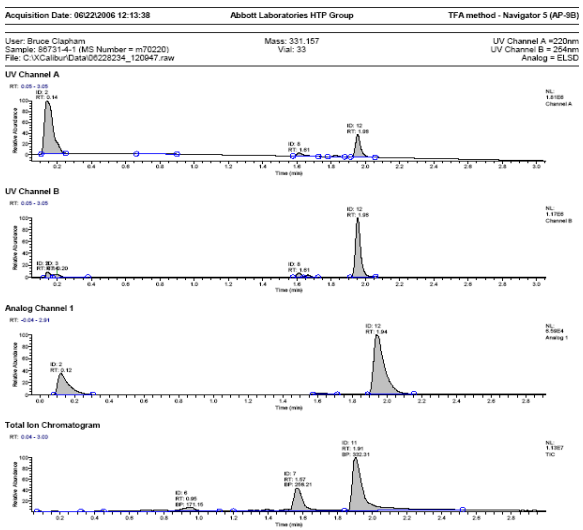
Test reaction:



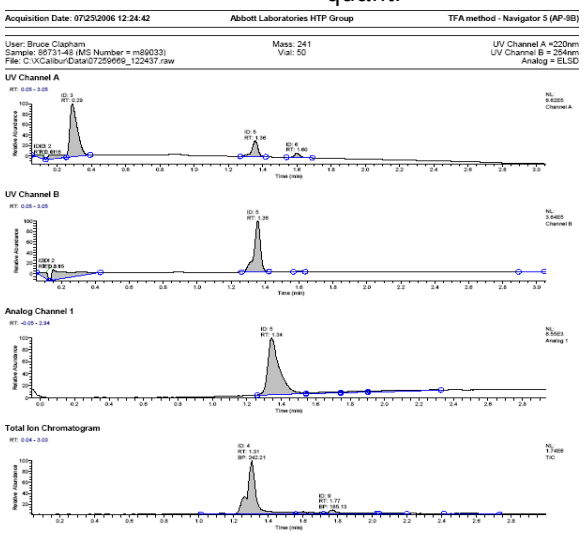
44 from 48
(Purified by HPLC)

44 from 44- 90%

to quant.

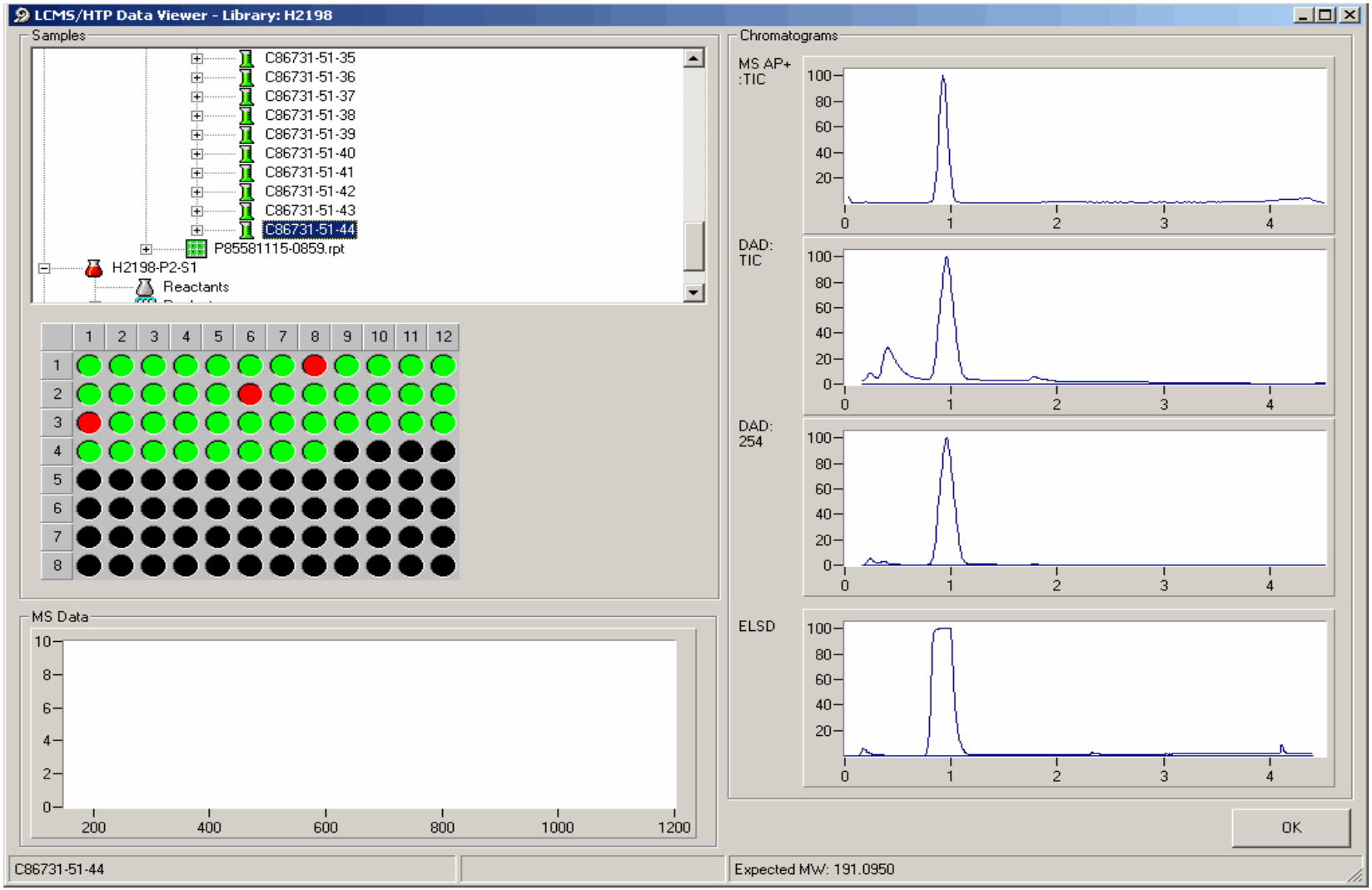


Ref LCMS (Ether)

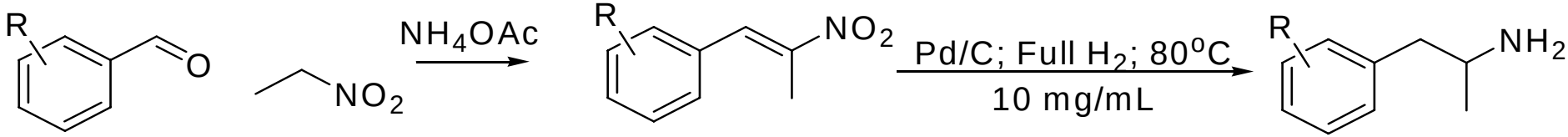


Crude LCMS (Phenol)

Crude LCMS of phenol library



Nitro reductions- phenylethylamines

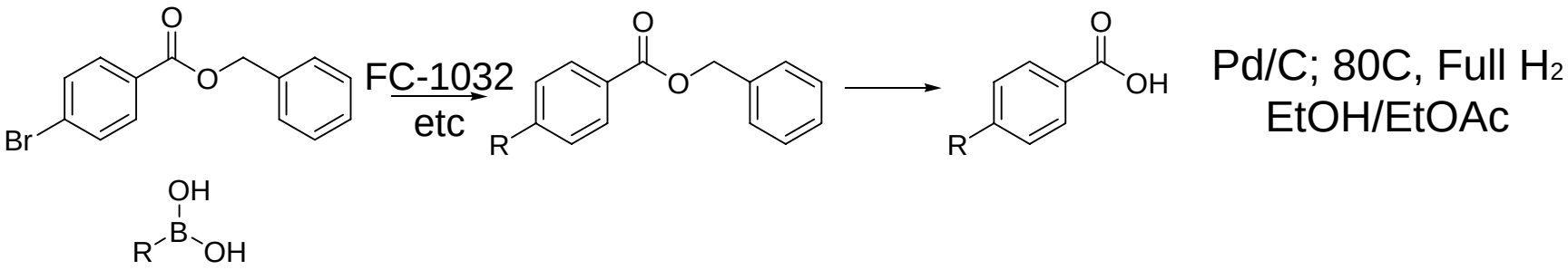


Henry reaction

Note: few literature precedent for catalytic reduction of nitro olefins;
Most common conditions = $LiAlH_4$/THF reflux!

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

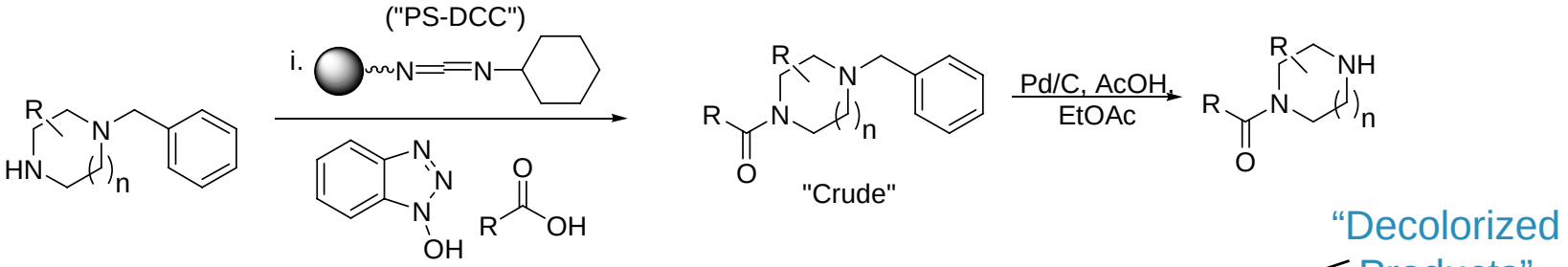
Benzyl ester deprotection of Suzuki libraries

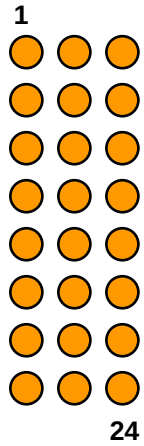


Library 1; from 48 monomers:
Standard synthesis with SPE
48 Suzuki products isolated by HPLC
Catalyst loses activity ~ #35
Desired product observed
33 biphenyl acids registered,
10% overall yield

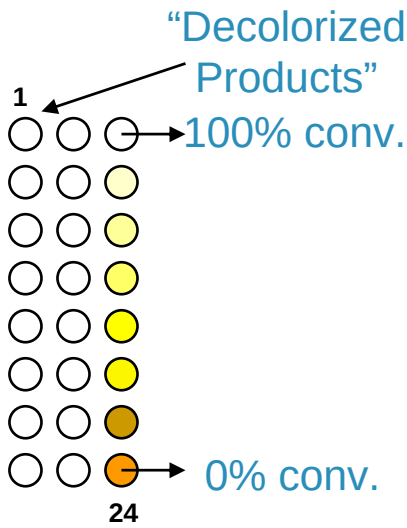
Library 2:
Standard synthesis with SPE
Each intermediate dried down, re-dissolved
Catalyst deactivated ~# 15, 2 more runs
33 biphenyl acids registered,
20% overall yield

Crude acylation libraries- catalyst poisoning





Starting Materials 1-24



Products 1-24

Crude acylation libraries- catalyst poisoning

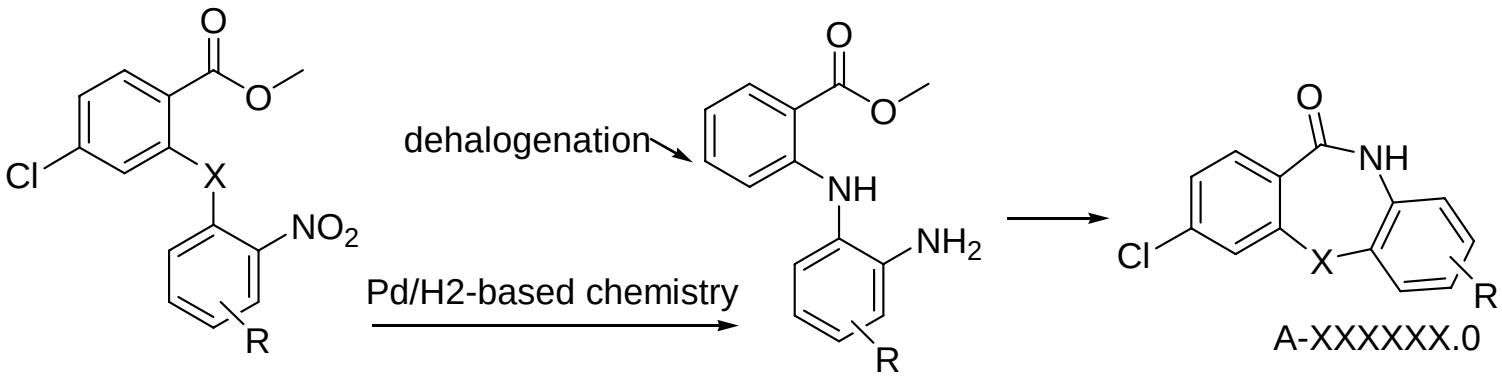
- Yellow impurities formed during acylation reaction/work up
- “Fines” from SPE also cause blockage of apparatus
- Yellow impurity adsorbed onto Pd/C catalyst (decolorized products)
- Catalyst rendered inactive

Currently under investigation

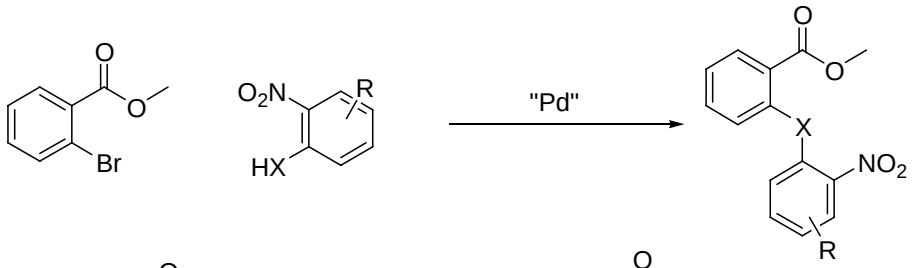
- Prepare HPLC guard column with activated carbon packing
- Prepare syringe filters with activated carbon membrane

Nitro reductions: anilines

Stoichometric quantities of tin required

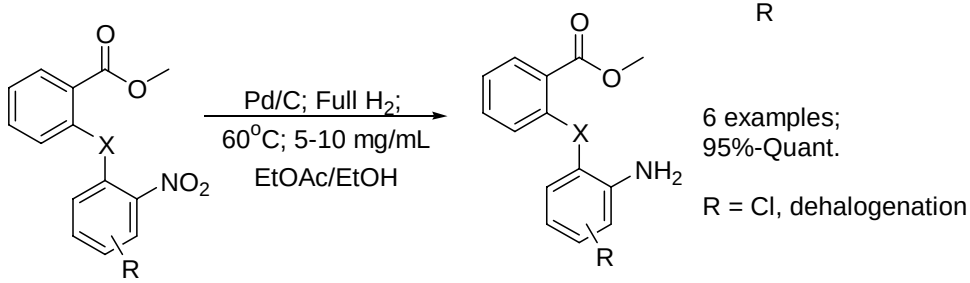


Model library



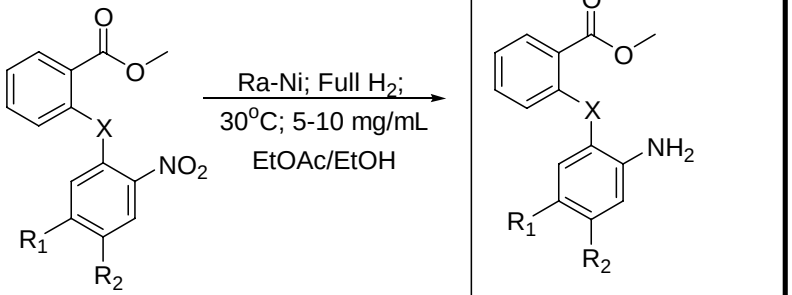
8 examples;
30-52% (ave 39%)

Literature procedure (thermal)
Converted to microwave

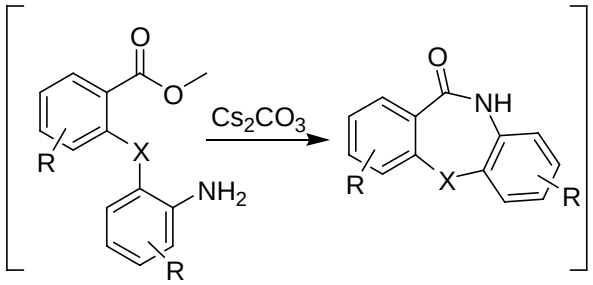


6 examples;
95%-Quant.

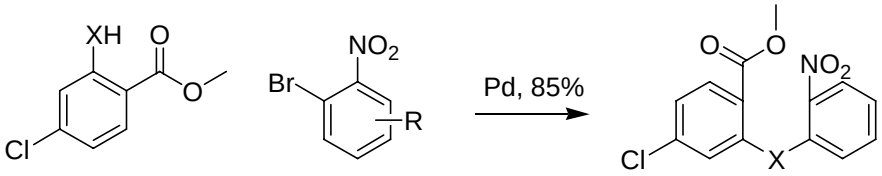
R = Cl, dehalogenation

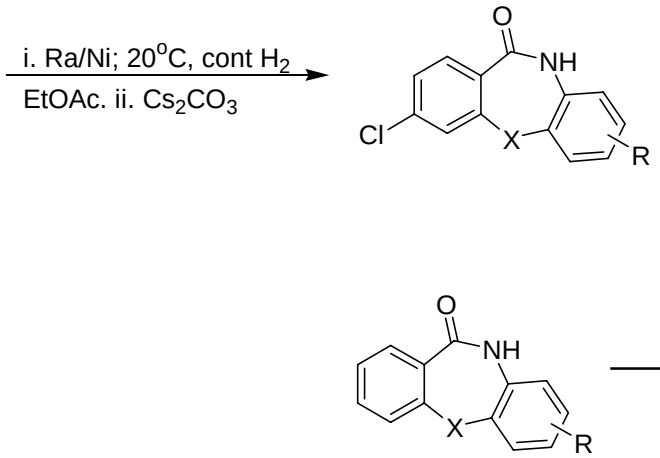


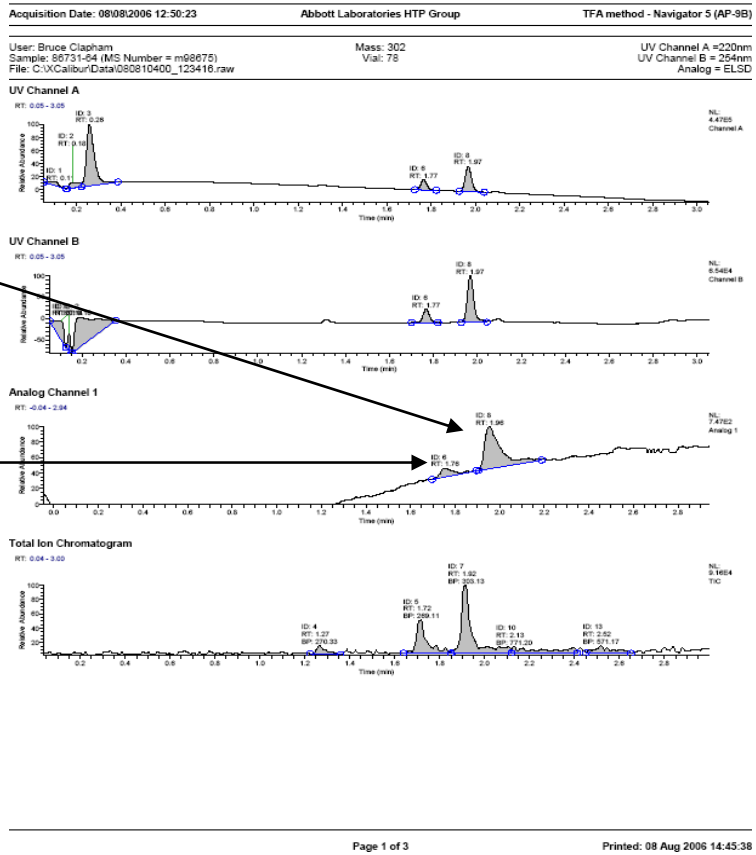
R1 = Cl, R2 = H, Quant.
R1 = H, R2 = Cl, Quant



Synthesis of A-xxxxxx.0







Sample drydown- Biotage V-10

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

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 chemstry

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